FY12-19, HP-12-19, POX-MVA-006

A randomized, open-label Phase III non-inferiority trial to compare indicators of efficacy for MVA-BN® smallpox vaccine to ACAM2000® in 18-42 year old healthy vaccinia naïve subjects

Clinical Trial Protocol Edition 8

29 September 2016

NCT 01913353

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1 General Information

1.1 Principal Investigator Signature Page

Herewith I agree that I have read and fully understand this protocol:

A randomized, open-label Phase III non-inferiority trial to compare indicators of efficacy for MVA BN® smallpox vaccine to ACAM2000® in 18-42 year old healthy vaccinia-naïve subjects

This protocol describes all the information necessary to conduct the trial. I agree that I will conduct the trial according to the instructions given within this protocol. Furthermore, I agree that I will conduct this trial according to International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the 2013 version of the Declaration of Helsinki, the Belmont Report, as well as applicable local legal and regulatory requirements in the respective countries. I agree that all information revealed in this protocol is handled strictly confidentially.

Additionally, I will permit trial related monitoring, audits, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review and regulatory inspections, providing direct access to source data/documents.

Principal Investigator _____ (b) (1) (A)

1.2 Sponsor Signature Page

By signing the protocol:

A randomized, open-label Phase III non-inferiority trial to compare indicators of efficacy for MVA BN® smallpox vaccine to ACAM2000® in 18-42 year old healthy vaccinia-naïve subjects

The undersigned parties agree that the protocol was written according to international ethical and scientific quality standards (ICH GCP), in compliance with the 2013 version of the Declaration of Helsinki, the Belmont Report, and applicable local legal and regulatory requirements in the respective countries.

Coordinating Author	(b) (1) (A)
Medical Monitor	
Manager QC Development	
Biostatistician	
GCP/GVP Compliance Management	
Sr. VP Clinical Development	

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Coordinating Author	(b) (1) (A)
Medical Monitor	
Manager QC Development	
Biostatistician	
GCP/GVP Compliance Management	
Sr. VP Clinical Development	

1.3 Responsibilities

Trial Number	FY12-19, HP-12-19, POX-MVA-006
Title	A randomized, open-label Phase III non-inferiority trial to compare indicators of efficacy for MVA-BN® smallpox vaccine to ACAM2000® in 18-42 year old healthy vaccinia-naïve subjects.
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E-mail	(b) (1) (A) [redacted]
Independent Take Review Committee (ITRC) Chair Member	(b) (1) (A) [redacted]
Phone	(b) (1) (A) [redacted]
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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
ACV	Assay Cut-off Value
AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
Alk Phos	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body Mass Index
BN	Bavarian Nordic
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CrCl	Creatinine Clearance
CRA	Clinical Research Associate
CRF(s)	Case Report Form(s)
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
DHA	Defense Health Agency (formerly MILVAX)
DMID	Division of Microbiology and Infectious Diseases
DS	Drug Safety
DSMB	Data Safety Monitoring Board
DoD	United States Department of Defense
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked Immunosorbent Assay
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
HBsAg	Hepatitis B Virus Surface Antigen
HCG	Human Choriogonadotropin
HCV	Hepatitis C Virus
HDL	High-density Lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus

HQ USAMRMC	Headquarters US Army Medical Research and Materiel Command
ICD	Informed Consent Document
ICH	International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITRC	Independent Take Review Committee
LDL	Low-density Lipoprotein
LLN	Lower Limit of Normal
LV	Left Ventricular
MedDRA	Medical Dictionary for Regulatory Activities
MILVAX	Military Vaccine Agency
MMWR	Morbidity and Mortality Weekly Report
MLA	Maximum Lesion Area
MLD	Maximum Lesion Diameter
MP	Medical Product
MPXV	Monkeypox Virus
MVA	Modified Vaccinia Ankara Strain
MVA-BN®	Modified Vaccinia Ankara – Bavarian Nordic
NHP	Non-human Primates
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NYCBH	New York City Board of Health
ODM	Operational Data Modeling
OHU&E	Office of Human Use and Ethics
PHI	Protected Health Information
PI	Principal Investigator
PPS	Per Protocol Set
PRNT	Plaque Reduction Neutralization Test
PV	Pharmacovigilance
RA	Regulatory Affairs
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
s.c.	Subcutaneous
SCR	Screening Visit
SD	Standard Deviation
SIN	Subject Identification Number
SOP	Standard Operating Procedure
$TCID_{50}$	Tissue Culture Infectious Dose 50%
ULN	Upper Limit of Normal
USA	United States of America
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
USAMRMC	United States Army Medical Research and Materiel Command

V	Visit
VACV	Vaccinia Virus
VAERS	Vaccine Adverse Event Reporting System
VHC	Vaccine Healthcare Centers (in USA)
VIG	Vaccinia Immunoglobulin
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WBC	White Blood Cell Count
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

Definitions

Full Take:
A full take is a successful primary take according to Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP) (Morbidity and Mortality Weekly Report [MMWR] June 22, 2001).

Formation of a major cutaneous reaction at the ACAM2000® vaccination site:

- The inoculation site becomes reddened and pruritic 3 to 4 days after vaccination.
- A vesicle surrounded by a red areola then forms, which becomes umbilicated (collapsed center) and then pustular by days 7 to 11 after vaccination.
- The pustule begins to dry; the redness subsides; and the lesion becomes crusted between the second and third week, the scab falls off, leaving a permanent scar that at first is pink in color but eventually becomes flesh colored.

Absent Take:
An absent take is considered to be the absence of a cutaneous reaction i.e. consistent with a full or partial take, at the ACAM2000® vaccination site.

Attenuation:
After revaccination, skin reactions at the ACAM2000® vaccination site are often less pronounced and there is more rapid progression and healing than those after primary vaccination. For the purposes of this Clinical Trial Protocol (CTP), attenuation is considered to be when the takes observed in Group 1 subjects (MVA-BN® recipients vaccinated with ACAM2000®) are determined to be diminished full takes based on the median of the individual measured parameter of Maximum Lesion Areas in Group 1 subjects, in comparison to the median of Maximum Lesion Areas of takes in Group 2 subjects (ACAM2000® recipients).

Maximum Lesion Area:
The Maximum Lesion Area (MLA) is defined as the maximum of two measurements: the lesion area measured on day 6-8 (after scarification) or the lesion area measured on day 13-15 (after scarification). If one of the lesion areas is missing, then the MLA will not be calculated.

Lesion:
Lesion measurements (area and diameter) referred to in this CTP will include signs (after scarification) of pustule, vesicle, pus, ulcer or scab but will not include extended symptoms of induration or erythema.

Peak Visit:
For the purposes of this CTP, the Peak Visit is the visit with the highest expected antibody titers.

For MVA-BN® the peak responses are considered to be at Day 42 after the first MVA-BN® vaccination (as described in the MVA-BN® Investigator's Brochure) when the subject has received two (2) MVA-BN® vaccinations according to the standard vaccination schedule. For ACAM2000® the peak responses are considered to be at Day 28 post vaccination (Group 2) in order to be in alignment with published data for conventional smallpox vaccines reaching a peak four weeks post vaccination (Frey, 2003; Belshe, 2004; Kennedy, 2004, Frey, 2007), which is also in full agreement with the data published for ACAM2000® (ACAM2000 Vaccines and Related Biological Products Advisory Committee [VRBPAC] Briefing Document, April 2007).

1.4 Protocol Synopsis

Title	A randomized, open-label Phase III non-inferiority trial to compare indicators of efficacy for MVA-BN® smallpox vaccine to ACAM2000® in 18-42 year old healthy vaccinia-naïve subjects.
Clinical phase	Phase III
Sponsor	Bavarian Nordic A/S Hejreskovvej 10A, 3490 Kvistgård, Denmark
Principal Investigator	(b) (1) (A) [redacted]
Vaccination dose, schedule and administration route	One 0.5 ml standard dose Modified Vaccinia Ankara – Bavarian Nordic (MVA-BN®) liquid-frozen vaccine contains a nominal titer of $1x10^8$ tissue culture infectious dose 50% ($TCID_{50}$) MVA-BN®. MVA-BN® vaccine will be administered as a subcutaneous (s.c.) injection preferably in the non-dominant upper arm. As per the prescribing information: One dose of reconstituted ACAM2000® vaccine consists of $2.5\text{-}12.5x10^5$ plaque forming units of live vaccinia virus (VACV). A droplet (0.0025 ml) vaccine is picked up with a bifurcated needle and is administered by the percutaneous route (scarification) using 15 jabs of that bifurcated needle. Group 1: Two vaccinations each of 0.5 ml MVA-BN® vaccine will be administered 4 weeks apart (Day 0 and Day 28) followed by a single vaccination of ACAM2000® vaccine 4 weeks after the second MVA-BN® vaccination (Day 56). Group 2: A single vaccination of ACAM2000® vaccine will be administered at Day 0.
Trial duration	Up to 22 weeks for Group 1 and up to 14 weeks for Group 2, plus

	follow-up (FU), (remote correspondence e.g. a phone call or email) 6 months after the last vaccination. If the remote correspondence reveals a medical need or any underlying condition that requires further examinations, the subject will be called in for a physical visit.
Trial Population	Volunteers from military personnel only.
Sample size	Up to 750 subjects may be screened to be able to vaccinate 440 eligible vaccinia-naïve subjects (220 per group) in order to achieve at least 175 subjects per group in the Per Protocol Set (PPS).
Co-Primary objectives	To demonstrate the efficacy of MVA-BN® by assessing non-inferiority of MVA-BN® compared to ACAM2000® in terms of vaccinia-specific Plaque Reduction Neutralization Test (PRNT) antibody response at the Peak Visits (Day 42 for Group 1 and Day 28 for Group 2) and by showing that vaccination with MVA-BN® prior to administration of ACAM2000® results in an attenuation of take in terms of MLA.
Secondary objectives	To assess non-inferiority of MVA-BN® compared to ACAM2000® in terms of vaccinia-specific Enzyme-linked Immunosorbent Assay (ELISA) antibody response at the Peak Visits. To assess seroconversion rates of MVA-BN® compared to ACAM2000® at the Peak Visits. To assess immune response dynamics in terms of antibody responses. To assess the effect on the ACAM2000® vaccination take following MVA-BN® priming. To assess and compare safety and reactogenicity of vaccinations with MVA-BN® and ACAM2000® given alone or ACAM2000® given after MVA-BN® priming.
Co-Primary endpoints	PRNT GMT at the Peak Visits Maximum Lesion Area (MLA) in mm² after scarification with ACAM2000®

Secondary endpoints	**Immunogenicity** GMTs at the Peak Visits and individual peak measured by vaccinia-specific ELISA. GMTs at the individual peak measured by vaccinia-specific PRNT. GMTs at all antibody blood sample time points measured by vaccinia-specific PRNT and vaccinia-specific ELISA. PRNT seroconversion rates at Peak Visits defined as the percentage of initially seronegative subjects with appearance of antibody titers equal or greater than the Assay Cut-off Value (ACV) in a vaccinia-specific PRNT. ELISA seroconversion rates at Peak Visits defined as the percentage of initially seronegative subjects with appearance of antibody titers equal or greater than the ACV in a vaccinia-specific ELISA. **Efficacy** Investigator assessed Maximum Lesion Diameter (MLD) in mm after scarification with ACAM2000® Investigator assessed Lesion diameter in mm at Day 6-8 after scarification with ACAM2000® Investigator assessed Lesion diameter in mm at Day 13-15 after scarification with ACAM2000® The individual take will be classified as either full or partial or absent take by a blinded ITRC. Lesion area in mm² at day 6-8 after scarification with ACAM2000® Lesion area in mm² at day 13-15 after scarification with ACAM2000® (The correct measurement of the lesion area will be confirmed by a blinded ITRC).

Safety and Reactogenicity

Occurrence, relationship to vaccine and intensity of any Serious Adverse Event (SAE).

Occurrence of any cardiac sign or symptom indicating a case of myo-/pericarditis, i.e. Adverse Events of Special Interest (AESIs).

Occurrence of any Grade 3 or 4 Adverse Events (AEs) possibly, probably or definitely related to vaccine within 28 days after each vaccination.

Occurrence, relationship to vaccine and intensity of any non-serious AEs within 28 days after each vaccination.

Occurrence of solicited general AEs (body temperature, headache, myalgia, chills, nausea, fatigue, malaise, swollen lymph nodes), within 15 days after each vaccination (days 0-14): Intensity, duration and relationship to vaccination.

Occurrence of solicited local AEs (pain, redness (erythema), swelling, induration, itching (pruritus), and vaccination site appearance (normal/healed, red spot, bump, reddish blister, whitish blister, scab, ulcer/crater, warmth, swollen >3in, red streaks, drainage) (within 15 days after each vaccination (days 0-14): Intensity and duration.

Daily measurement of lesion size, erythema and induration based on physical appearance of vaccination site as documented in the memory aid.

- major lesion diameter (mm) each day
- major erythema diameter (mm) each day
- major induration diameter (mm) each day

If the shape of the lesion, erythema (excludes lymphangitis) and induration observed is not round but rather asymmetrical then the largest (or major) cross-sectional measurement would be recorded.

Trial design	Open label, randomized, blinded immune analysis

	Group 1: 220 vaccinia-naïve subjects receiving two (2) standard doses of MVA-BN®, s.c., 4 weeks apart followed by one dose of ACAM2000® via scarification 4 weeks after the second MVA-BN® vaccination. Group 2: 220 vaccinia-naïve subjects receiving one (1) dose of ACAM2000® via scarification.
Inclusion criteria	1. Healthy male and female subjects, 18-42 years of age at date of informed consent signature 2. The subject has read, signed and dated the Informed Consent, having been advised of the risks and benefits of the trial in a language understood by the subject and prior to performance of any trial specific procedure 3. Acceptable medical history by screening evaluation and physical examination 4. Body Mass Index (BMI) ≥ 18.5 and < 35 5. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at Screening and a negative urine or serum pregnancy test within 24 hours prior to each vaccination 6. WOCBP must have used an acceptable method of contraception for 28 days prior to the first vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for 28 days after the last vaccination. A woman is considered of childbearing potential unless post-menopausal (defined as ≥ 12 months without a menstrual period) or surgically sterilized. (Acceptable contraception methods are restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products) 7. Human Immunodeficiency Virus (HIV) antibody negative, hepatitis B surface antigen negative and negative antibody test to hepatitis C virus 8. White blood cells ≥ 2,500/mm^3 and < 11,000/mm^3 9. Hemoglobin within normal limits 10. Platelets ≥ lower normal limits 11. Adequate renal function defined as a calculated Creatinine Clearance (CrCl) > 60 ml/min as estimated by the Cockcroft-Gault equation: ○ For men: (140 – age in years) x (body weight in kg) ÷ (serum

creatinine in mg/dl x 72) = CrCl (ml/min)
- For women: multiply the result by 0.85 = CrCl (ml/min)

12. Adequate hepatic function in the absence of other evidence of significant liver disease defined as:
- Total bilirubin ≤ 1.5 x Upper Limit Normal (ULN)
- Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) ≤ 1.5 x ULN
- Alkaline Phosphatase (Alk Phos) ≤ 1.5 x ULN

13. Troponin I < 2 x ULN
14. Electrocardiogram (ECG) without clinically significant findings, e.g. without atrioventricular or intraventricular conditions or blocks such as incomplete/complete left or complete right bundle branch block, second or third degree atrioventricular block, two premature ventricular contractions in a row, ST elevation consistent with ischemia, atrial or ventricular arrhythmia
- QTc prolongations > 500 ms which do not require clinical intervention should be discussed with the Medical Monitor before vaccination
- Following conditions can be included, if they do not require clinical intervention:
  - First degree atrioventricular block, PR interval prolongation, premature atrial contractions, occasional premature ventricular contractions, sinus bradycardia, right or left axis deviation, non-specific ST and T wave changes.

Further guidance is provided in Appendix VI.

Exclusion criteria

1. Pregnant or breast-feeding women
2. Typical vaccinia scar
3. Known or suspected history of smallpox vaccination defined as visible vaccination scar or documentation of smallpox vaccination or as reported by the subject
4. History of vaccination with any poxvirus-based vaccine
5. History of any serious medical condition, which in the opinion of the investigator would compromise the safety of the subject
6. History of or active immunodeficiency or immunosuppression caused by acquired or congenital diseases or caused by ongoing treatments such as chronic (> 14 days) high-dose corticosteroids (e.g. > 5 mg prednisone [or equivalent] per day administered systemically, i.e. parenterally or orally), chronic or planned treatment with steroid eye drops or ointment at time of screening

or radiation, or immunosuppressive drugs; low-dose corticosteroid topical products and nasal sprays used sporadically, i.e. pro re nata (according to circumstances) are permissible

7. Having had radiation or X-ray treatment (not routine X-rays) within the last 3 months
8. Post organ and bone-marrow transplant subjects whether or not receiving chronic immunosuppressive therapy
9. Recent surgery (including dental or eye) within 4 weeks prior to trial vaccination
10. History of or active autoimmune disease. Persons with vitiligo or hypothyroid disease taking thyroid hormone replacement are not excluded
11. Uncontrolled serious infection, i.e. not responding to antimicrobial therapy
12. History of malignancy, other than squamous cell or basal cell skin cancer, unless there has been surgical excision considered to have achieved cure. Subjects with history of skin cancer must not be vaccinated at the previous site of cancer
13. History of keloid formation
14. History or clinical manifestation of severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders
15. History of coronary heart disease, myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, uncontrolled high blood pressure, significant arrhythmia with or without corrective/ablative surgery, or any other heart condition under the care of a doctor
16. Chest pain (that is diagnosed as cardiac related) or trouble breathing on exertion
17. Ten percent or greater risk of developing a myocardial infarction or coronary death within the next 10 years, e.g. using the National Heart, Lung and Blood Institute's Risk Assessment Tool: http://cvdrisk.nhlbi.nih.gov/calculator.asp
    NOTE: This criterion applies only to subjects 20 years of age and older
18. History of an immediate family member (father, mother, brother, or sister) who has had onset of ischemic heart disease before the age of 50 years
19. Clinically significant psychological disorder not adequately controlled by medical treatment
20. Active or history of chronic alcohol abuse and/or intravenous and/or nasal drug abuse (within the past 6 months)

21. History of anaphylaxis or any severe allergic reaction or serious adverse reaction to a vaccine
22. Eczema of any degree or history of eczema
23. People with active atopic dermatitis (AD) [characterized by pruritus, eczematous lesions, xerosis (dry skin), and lichenification (thickening of the skin and an increase in skin markings] or with a history of AD
24. People with chronic exfoliative skin disorders/conditions
25. People with active current Varicella zoster, Herpes zoster, impetigo, uncontrolled acne, Darier's disease, recent tattoos or skin piercing (until it is healed, but not at least 4 weeks prior to trial vaccination), or any acute skin disorders of large magnitude, e.g., laceration requiring sutures
26. People with a tattoo that covers the vaccination injection area (preventing assessment of the area and interfering with a vaccination site photograph)
27. Having received any vaccinations or planned vaccinations with a live vaccine (except trial vaccine) within 28 days prior to or after trial vaccination
28. Having received any vaccinations or planned vaccinations with a killed vaccine within 14 days prior to or after trial vaccination
29. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from three months prior to administration of the vaccine and ending at trial conclusion
30. Use of any investigational or non-registered drug or vaccine other than the trial vaccines within 28 days preceding the first dose of the trial vaccine or planned administration of such a drug /vaccine during the trial period
31. Blood donation for the duration of the trial
32. Acute disease (illness with or without a fever)
33. Temperature ≥ 100.4°F (38.0°C)
34. Known household contacts with, or occupational exposure (other than minimal contact) to any of the following:
    - Pregnant women
    - Children <12 months of age
    - People with eczema or a history of eczema
    - People with active AD or history of AD
    - People with chronic exfoliative skin disorders/conditions
    - People with active Varicella zoster, Herpes zoster, impetigo, uncontrolled acne, Darier's disease or any acute skin disorders of large magnitude, e.g., laceration requiring sutures, burn with areas greater than 2×2 cm

- People with active or recent immunodeficiency disease or use of immunosuppressive medications, for example: have or take medication for HIV, Acquired Immune Deficiency Syndrome (AIDS), leukemia, lymphoma, or chronic liver problem, have or take medication for Crohn's disease, lupus, arthritis, or other immune disease; have had radiation or X-ray treatment (not routine X-rays) within the last 3 months; have ever had a bone-marrow or organ transplant (or take medication for that); or have another problem that requires steroids, prednisone or a cancer drug for treatment
- People having had eye surgery within the last 4 weeks

35. Known allergy to MVA-BN® vaccine or any of its constituents, e.g. tris(hydroxymethyl)-amino methane, including known allergy to egg or aminoglycoside (gentamycin)
36. Known allergies to ACAM2000® and its diluents including polymyxin B sulfate, neomycin sulfate, and phenol
37. Known allergies to vaccinia immunoglobulin (VIG) including thimerosal or previous allergic reaction to immunoglobulins
38. Known allergies to cidofovir, sulfa drugs, Tecovirimat (ST246) or probenecid
39. Trial personnel

Statistical considerations	The following statistical considerations were applied for the trial with GMTs measured by PRNT as co-primary endpoint for non-inferiority testing (assuming have a log-normal distribution): Using PRNT titers on the $\log_{10}$ scale: Delta=0.301 Sigma=0.866 Alpha=0.05 N=175 (per group) Power=90.0% With GMTs measured by PRNT as a co-primary endpoint, a sample size of 175 subjects per group provides a power of 90%. To account for dropouts from the PPS, 440 subjects will be vaccinated (220 subjects per group). The efficacy co-primary analysis is based on the ratio of the median of

the MLA of subjects in Group 1 divided by the median in Group 2 after scarification with ACAM2000®.

This is tested using a one-sided 97.5% Hodges-Lehmann confidence interval of 1 minus the ratio in medians of the MLA. If the lower confidence limit of the ratio is greater than a pre-specified percentage ($\lambda = 40\%$) then the co-primary endpoint will have been met.

Calculations based on the POX-MVA-002 data show that this sample size will give sufficient power (>90% power).

The overall power for meeting both primary endpoints is therefore greater than 80% (since $0.9 \times 0.9 > 0.8$).

1.5 Trial Procedure Schedule

Trial Procedure Schedule – Group 1

Visit (V)	SCR	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	Remote FU
Day / V +… d	-70- -1	0	V1 +6-8	V1 +13-15	V1 +27-29	V4 +6-8	V4 +13-15	V1 +55-57	V7 +6-8	V7 +13-15	V7 +27-29	Last Vaccination +182-210
Week	-10- -1	0	1	2	4	5	6	8	9	10	12	34-38
Procedures												
Informed consent	X											
Check inclusion / exclusion criteria	X	X										
Medical/Surgical History	X											
Check vaccination history and absence of vaccination scar	X											
Complete physical exam[1]	X											
Targeted physical exam[1]		X	(X)	X	X	(X)	X	X	(X)	X	X	(X)
Evaluation of vital signs	X	X	X	X	X	X	X	X	X	X	X	(X)
Recording of Baseline signs and symptoms	X	X										
Check cardiac risk factors	X											
ECG[2]	X			X			(X)			X		
Questions on cardiac signs and symptoms		X		X	X		X	X		X	X	
Review of prior/concomitant medications	X	X		X	X		X	X		X	X	(X)
Counseling[3]	X	X	X	X	X	X	X	X	X	X	X	
Examination of vaccination site		X	X	X	X	X	X	X	X	X	X	
Photo of vaccination site									X	X		
Bandage application / change[4]								X	X	X	X	
Assessment of axillary and supraclavicular lymphadenopathy		X	X	X	X	X	X	X	X	X	X	
SAE/AE/AESI recording		X	X	X	X	X	X	X	X	X	X	X[5]

Trial Procedure Schedule – Group 1 continued

Visit (V)	SCR	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	Remote FU
Day / V +… d	-70- -1	0	V1 +6-8	V1 +13-15	V1 +27-29	V4 +6-8	V4 +13-15	V1 +55-57	V7 +6-8	V7 +13-15	V7 +27-29	Last Vaccination +182-210
Week	-10- -1	0	1	2	4	5	6	8	9	10	12	34-38
Vaccination												
Randomization		X										
Vaccine administration		X			X			X				
Subject Observation (at least 30 minutes)		X			X			X				
Handout of memory aid[6]		X			X			X		X[7]		
Review of memory aid			X	X		X	X		X	X	X[7]	
Collection of memory aid[6]				X			X			X	X[7]	
Labs												
Pregnancy test[8]	X	X			X			X			X	
Safety lab[2] (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium)	X			X			X			X		(X)
Total, HDL and LDL cholesterol	X											
Hepatitis serology (HBsAg / Anti-HCV)	X											
HIV	X											
Troponin I testing[2]	X			X						X		
Blood draw for antibody analysis		X	X	X	X		X	X			X	
Blood volume												
Blood volume drawn per visit (ml)[9]	22	21	16	26	21		26	21		10	21	(10)
Cumulative blood volume drawn (ml)[9]	22	43	59	85	106		132	153		163	184	(194)

( ) Only indicated in case of medical need or any underlying condition that requires further examinations.

1 For more information on the physical examinations, please refer to Section 8.2.3

2 Additional safety measures can be taken at any other trial visits or at unscheduled visits, if clinically indicated.

3 Counseling on avoidance of pregnancy and HIV infection and specifically after the ACAM2000® vaccination counseling on the avoidance of contact spread. At Visit 10 counseling for avoidance of pregnancy is not required.

4 After ACAM2000® administration subjects should change their own dressings as instructed by the administering clinic (leave the bandage on for the 1st 48 hours, then change every day or when bandage becomes wet) using the Care Kits provided by site staff until the vaccination site scab falls off, as this will keep the vaccination site intact and will minimize softening. Salves or ointments must not be applied to the vaccination site. Measurements of the vaccination site are to be taken until bandage not required.

5 Follow-up on ongoing AEs, AESIs, SAEs and recording of new SAEs/AESIs.

6 The memory aid should be completed daily for 15 days (day of vaccination and the following 14 days). If symptoms persist at 14 days post vaccination, temperature/symptom should be recorded until resolution or Visit 10.

7 If lesion at vaccination site has not healed at Day 14, measurements of lesion size, erythema and induration should be recorded on a memory aid extension each day until healed or Visit 10.

8 WOCBP only. At Screening Visit, a serum test must be performed. At all other visits, either a serum or urine pregnancy test will be performed.

9 Approximate volumes of single blood draws: Safety lab including all tests: 22 ml at SCR (incl. serum for pregnancy test) and 10 ml at regular visits, 5 ml for serum pregnancy test and 16 ml for antibody analysis.

Trial Procedure Schedule – Group 2

Visit (V)	SCR	V1	V2	V3	V4	V5	V6	Remote FU
Day / V +… d	-70- -1	0	V1 +6-8	V1 +13-15	V1 +27-29	V1 +41-43	V1 +55-57	Last Vaccination +182-210
Week	-10- -1	0	1	2	4	6	8	26-30
Procedures								
Informed consent	X							
Check inclusion / exclusion criteria	X	X						
Medical/Surgical History	X							
Check vaccination history and absence of vaccination scar	X							
Complete physical exam[1]	X							
Targeted physical exam[1]		X	(X)	X	X			(X)
Evaluation of vital signs	X	X	X	X	X			(X)
Recording of Baseline signs and symptoms	X	X						
Check cardiac risk factors	X							
ECG[2]	X			X				
Questions on cardiac signs and symptoms		X		X	X			
Review of prior/concomitant medications	X	X		X	X			(X)
Counseling[3]	X	X	X	X	X			
Examination of vaccination site		X	X	X	X			
Photo of vaccination site			X	X				
Bandage application / change[4]		X	X	X	X			
Assessment of axillary and supraclavicular lymphadenopathy		X	X	X	X			
SAE/AE/AESI recording		X	X	X	X			X[5]

Trial Procedure Schedule – Group 2 continued

Visit (V)	SCR	V1	V2	V3	V4	V5	V6	Remote FU
Day / V +… d	-70- -1	0	V1 +6-8	V1 +13-15	V1 +27-29	V1 +41-43	V1 +55-57	Last Vaccination +182-210
Week	-10- -1	0	1	2	4	6	8	26-30
Vaccination								
Randomization		X						
Vaccine administration		X						
Subject Observation (at least 30 minutes)		X						
Handout of memory aid[6]		X		X[7]				
Review of memory aid			X	X	X[7]			
Collection of memory aid[6]				X	X[7]			
Labs								
Pregnancy test[8]	X	X			X			
Safety lab[2] (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium)	X			X				(X)
Total, HDL and LDL cholesterol	X							
Hepatitis serology (HBsAg / Anti-HCV)	X							
HIV	X							
Troponin I testing[2]	X			X				
Blood draw for antibody analysis		X	X	X	X	X	X	
Blood volume								
Blood volume drawn per visit (ml)[9]	22	21	16	26	21	16	16	(10)
Cumulative blood volume drawn (ml)[9]	22	43	59	85	106	122	138	(148)

( ) Only indicated in case of medical need or any underlying condition that requires further examinations.

1 For more information on the physical examinations, please refer to Section 8.2.3.

2 Additional safety measures can be taken at any other trial visits or at unscheduled visits, if clinically indicated.

3 Counseling on avoidance of pregnancy and HIV infection and specifically after the ACAM2000® vaccination counseling on the avoidance of contact spread. At Visit 4 counseling for avoidance of pregnancy is not required.

4 After ACAM2000® administration subjects should change their own dressings as instructed by the administering clinic (leave the bandage on for the 1st 48 hours, then change every day or when bandage becomes wet) using the Care Kits provided by site staff until the vaccination site scab falls off, as this will keep the vaccination site intact and will minimize softening. Salves or ointments must not be applied to the vaccination site. Measurements of the vaccination site are to be taken until bandage not required.

5 Follow-up on ongoing AEs, AESIs, SAEs and recording of new SAEs/AESIs.

6 The memory aid should be completed daily for 15 days (day of vaccination and the following 14 days). If symptoms persist 14 days post vaccination, temperature/symptom should be recorded until resolution or Visit 4.

7 If lesion at vaccination site has not healed at Day 14, measurements of lesion size, erythema and induration should be recorded on a memory aid extension each day until healed or Visit 4.

8 WOCBP only. At Screening Visit, a serum test must be performed. At all other visits, either a serum or urine pregnancy test will be performed.

9 Approximate volumes of single blood draws: Safety lab including all tests: 22 ml at SCR (incl. serum for pregnancy test) and 10 ml at regular visits, 5 ml for serum pregnancy test and 16 ml for antibody analysis.

2 Background Information and Scientific Rationale

2.1 Introduction

Despite the fact that the World Health Organization (WHO) officially declared successful global eradication of smallpox in 1980, the existence of variola stockpiles and the threat of bioterrorism demands to maintain immunity to smallpox through vaccination. After the events of September 11th, 2001, concern over the use of bioweapons as agents of terrorism increased (McCurdy, 2004). As mass vaccination programs halted more than 30 years ago, it is estimated that the majority of the world population has no existing immunity to smallpox, and as such, the release of this highly contagious virus would have devastating effects. As a consequence, there is an urgent need for a safe and efficacious vaccine to protect the public against smallpox.

Bavarian Nordic A/S (BN), an international biopharmaceutical company, is developing a proprietary strain of Modified Vaccinia Ankara (MVA [MVA BN®, trade name IMVAMUNE® outside the European Union {EU} invented name IMVANEX® in the EU]) for use as a vaccine protecting against smallpox infection. For IMVANEX® a marketing authorization under exceptional circumstances was granted in July 2013. BN filed a New Drug Submission with Health Canada in 2011 under the invented name IMVAMUNE®. A marketing authorization for IMVAMUNE® was granted in November 2013.

2.2 First Generation Smallpox Vaccines

The original smallpox vaccines were based on a number of different VACV strains, e.g. Lister-Elstree recommended by the WHO and used primarily in Europe or the New York City Board of Health (NYCBH, Dryvax®) strain used in the United States of America (USA). While these proved to be highly effective immunizing agents making the eradication of smallpox possible, they also showed considerable side effects. Besides local reactions with scab development and scarring, general symptoms observed frequently after smallpox vaccination have been pyrexia, weakness, muscular pain, headache, swelling and soreness of local lymph nodes and rashes. Apart from less dramatic and transient side effects like erythematous or urticarial rashes, severe and potentially fatal cutaneous complications of VACV vaccination include eczema vaccinatum and progressive vaccinia. Most feared are complications of the central nervous system, especially post-vaccinal encephalitis, which lead to death in 15-25% of cases and in 25% to neurologic sequelae (Goldstein, 1975; Lane, 1969; Lane, 1970). Even though some countries such as the USA excluded high-risk individuals from vaccination, an average of seven persons a year still died from complications due to smallpox vaccination during the eradication campaign (McElwain, 1972).

Traditionally, successful vaccination with a smallpox vaccine was assessed based on the formation of a vesicle (“take”) at the inoculation site seven to nine days after vaccination. Recent

clinical trials using Dryvax® confirmed a success rate by vesicle formation in vaccinia-naïve volunteers of 95 to 99% (Frey, 2002; ACAM2000 VRBPAC Briefing Document, 2007).

In an individual previously exposed to a smallpox vaccine, successful revaccination is confirmed when a pustular lesion is present or an area of definite induration or congestion surrounding a central lesion (i.e. scab or ulcer) is observed upon examination 6-8 days after revaccination (MMWR, June 22, 2001). However, revaccination may lead to skin reactions that are less pronounced with more rapid progression and healing than those after primary vaccination or a lesion may even be absent (Frey, 2003). Still, these individuals are considered to be fully protected, i.e. the occurrence of a partial take or the absence of a take in previously vaccinated individuals does not require any additional vaccination (ACAM2000 prescribing information, Appendix IVc; Section 17.7). In an earlier clinical trial comparing MVA-BN® and Dryvax®, priming with MVA-BN® either prevented take development or resulted in a diminished take coupled with an accelerated healing time following scarification with Dryvax® (Frey, 2007). The attenuation of the take following vaccination due either to a prior vaccination and/or infection with Variola virus has historically been a measure of a protection against smallpox (Fenner, 1988).

2.3 Second Generation Smallpox Vaccines

Second generation smallpox vaccines are derived from first generation VACV strains by plaque purification and manufactured in cell cultures according to current Good Manufacturing Practice standards (Monath, 2004). Vaccination of individuals with these vaccines is performed in the same way as with first generation smallpox vaccines, namely by intradermal administration (scarification) of a single dose.

ACAM2000® is based on the Dryvax® NYCBH strain (Monath, 2004). In preparation of a Biologics License Application at the US Food and Drug Administration (FDA), two pivotal Phase III clinical trials were conducted enrolling either vaccinia-naïve or vaccinia-experienced populations. The trials were designed to compare the safety, tolerability and efficacy of ACAM2000® to Dryvax®. In total, the ratio of individuals in these trials receiving ACAM2000® and Dryvax® was 3:1 (ACAM2000 VRBPAC Briefing Document, 2007).

Safety information available from these trials suggests that the non-serious adverse reactions were typical for vaccines administered by injection or scarification. The majority (99% and 97% respectively) of subjects experienced at least one treatment-emergent AE after vaccination. The AEs most commonly reported fell into four distinct categories: reactions at the vaccination site, lymphadenitis, constitutional “flu-like” symptoms and minor gastrointestinal symptoms. Of special interest, however, were a total of 10 serious cases of myo-/pericarditis that were reported within the ACAM2000® development program. In a vaccinia-naïve population of 1,675 subjects, these events occurred in seven subjects treated with ACAM2000® (5.73 events per thousand vaccinations) and in three subjects having received Dryvax® (10.38 events per thousand vaccinations) for a combined calculated incidence of 5.97 cases of myo-/pericarditis per thousand

vaccinations (95% confidence interval of 2.87 to 10.95 cases per thousand). These figures represent quite a high rate of potentially life-threatening serious AE following vaccination with a prophylactic vaccine.

Vaccine efficacy data were collected to demonstrate non-inferiority compared to Dryvax® based on the efficacy parameters of major cutaneous reaction ("take") rates and neutralizing antibody titers by PRNT in both trials. Enrolling vaccinia-naïve subjects in one of the two trials, non-inferiority against Dryvax® could be shown for take rates, but not for antibody titers. On the contrary, for the trial population of vaccinia-experienced subjects enrolled in the second Phase III trial, non-inferiority against Dryvax® could be determined for neutralizing antibody titers, but not for take rates. Taken together, two of the four targeted efficacy measures were met in these trials.

Based on the safety and efficacy data collected in these pivotal Phase III trials, the FDA approved ACAM2000® in September 2007 for use in vaccinia-naïve, as well as vaccinia-experienced healthy populations, issuing a black box warning on the prescribing information (Appendix IVc; Section 17.7) for the special risks of this conventional second generation smallpox vaccine. In Section 2.4 of the prescribing information entitled "Instructions for Interpreting Vaccination Response", it states that formation of a major cutaneous reaction at day 6 to 8 is evidence of a successful take and acquisition of protective immunity. It additionally states that prior vaccination may modify the cutaneous response upon revaccination such that the absence of a cutaneous response does not necessarily indicate vaccination failure.

2.4 Origin and Characteristics of MVA-BN®

VACV is considered the best known member of the poxvirus family and the prototype live viral smallpox vaccine. VACV replicates in the cytoplasm of the host cell, its deoxyribonucleic acid does not integrate into the host cell genome and it is non-oncogenic.

Modified Vaccinia Ankara (MVA) was derived from the serial passage of Chorioallantois Vaccinia Ankara, a VACV strain used during the smallpox eradication program. During this passaging, MVA suffered a multitude of mutations within its genome, including six major deletions, resulting in the loss of 15% (31kbp) of original genetic information (Antoine, 1998). The deletions affected a number of virulence and host range genes (Antoine, 1998; Rosel, 1986; Meyer, 1991) and as a consequence, MVA exhibits a severely restricted host range in most mammalian cell types (Sutter, 1992; Carroll, 1997; Blanchard, 1998; Drexler, 1998). Although MVA exhibits a strongly attenuated replication in these cell types, its genes are efficiently transcribed with the block in viral replication being at the level of virus assembly and egress (Sutter, 1992; Carroll, 1997).

MVA-BN® has been derived from MVA-572 and is a highly attenuated, purified live vaccine produced under serum-free conditions in chicken embryo fibroblast cells. In contrast to the first and second generation smallpox vaccines MVA-BN® is not administered by scarification. The standard route and schedule of MVA-BN® are two subcutaneous injections administered four

weeks apart. Since MVA-BN® is non-replicating in human cells (Mayr, 1975) and is administered via the subcutaneous route, it does not form vesicles ("takes").

For further details on MVA-BN®, please refer to the relevant sections in the Investigator's Brochure.

2.5 Summary of Nonclinical Studies with MVA-BN®

An extensive nonclinical development program has demonstrated the safety, efficacy and bio-equivalence of MVA-BN® compared to other traditional smallpox vaccines.

The studies conducted demonstrated the superior attenuation profile of MVA-BN® compared to conventional smallpox vaccines (e.g. ACAM2000®, Dryvax®) as well as to other MVA strains. In contrast to other strains, MVA-BN® does not replicate in any of the human cell lines tested (Chaplin, 2002) and is not lethal for severely immune compromised animals (Suter, 2009). Repeated administrations (s.c. or intra-muscular) of MVA-BN® at doses up to $4.9x10^8$ $TCID_{50}$ resulted in injection site irritations and some lymphoid changes; however, these effects were minimal and reversible and are therefore not considered to be dose-limiting.

Three developmental toxicity studies in rats and rabbits demonstrated that none of the tested doses of MVA-BN® ($1x10^7$ $TCID_{50}$ or $1x10^8$ $TCID_{50}$) were teratogenic or caused intrauterine toxicity to the fetuses. In a peri- and postnatal study in rats MVA-BN® did not have any effect on the dams or the intrauterine development of the embryos. Furthermore, it did not have any effect on the lactating females or their developing offspring.

Non-clinical studies on immunogenicity and efficacy demonstrated that MVA-BN® smallpox vaccine induces a comparable immune response (antibody and T cells) as conventional smallpox vaccines (ACAM2000®, Dryvax® and Elstree) in both mice and non-human primates (NHP) (Stittelaar, 2005). A linear correlation between vaccine dose and antibody responses (total and neutralizing antibodies) induced by MVA-BN® could be demonstrated in mice and NHP (and in human subjects). This correlation translated into a vaccine dose related protection of NHP from lethal challenge with monkeypox virus (MPXV), indicating that antibodies are good predictive correlates for protection, reasonably likely to predict clinical efficacy. Indeed, the correlation of the fit between PRNT titers (induced by MVA-BN®) and the probability of survival from a lethal MPXV challenge was 0.9992, demonstrating a highly significant correlation between neutralizing antibodies and protection ($p = 0.00076$). Similarly, the correlation of the fit between ELISA titers (induced by MVA-BN®) and the probability of survival from a lethal MPXV challenge was 0.9966, demonstrating a highly significant correlation between total antibodies and protection ($p = 0.00336$).

For more detailed information on preclinical data please refer to the respective sections of the Investigator's Brochure.

2.6 Clinical Profile of MVA-BN®

To date, 19 clinical trials (13 sponsored by BN, thereof eight (9) under Investigational New Drug (IND) 11596; one (1) under Investigational New Drug (IND) 15316, six (6) sponsored by the Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) under IND 11229 evaluating the safety and immunogenicity of MVA-BN® have been completed. Currently two (2) clinical trials are ongoing (sponsored by BN) under IND 11596.. As of July 31, 2016, 7,542 subjects have been vaccinated with MVA-BN® in the completed clinical trials, including risk groups with contraindications to conventional smallpox vaccines, such as HIV infected patients and patients with AD.

2.6.1 Safety Overview of MVA-BN®

In all completed and ongoing clinical trials, vaccinations with MVA-BN® have shown to be generally safe and well tolerated. No cases of death, assessed as being even possibly related, have been reported for a subject in a clinical trial using MVA-BN®.

Serious Suspected Adverse Drug Reactions

A total of seven (7 out of 7,758 vaccinated subjects = 0.09 %) serious suspected Adverse Drug Reactions (ADRs) have been reported for MVA-BN® so far (see Table 2). All of them have been thoroughly reviewed by BN and the trial specific Data Safety Monitoring Board (DSMB), who concluded that the continued use of MVA-BN® in a clinical setting presented no special risks to the subjects. In the NIH sponsored trial POX-MVA-036, the Safety Monitoring Committee (SMC) had put the trial on a temporary hold and had requested further information, following the receipt of a possibly related SAE of throat tightness and further hypersensitivity symptoms (see Table 2) along with three further non-serious cases of rashes/hives (two of which were reported as possibly related). BN assessed reactions as “possibly related” for which no medical cause or medical etiology is known to date and thus a relationship to the vaccine cannot be ruled out technically. No pattern regarding serious suspected ADRs could be detected. This trial had resumed recruiting in January 2014, after a review of all available safety and quality data by the SMC.

Adverse Drug Reactions

Suspected ADRs were reported in completed clinical trials (see Table 1):

Table 1 Suspected Adverse Drug Reactions Reported in Completed Clinical Trials*

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Infections and Infestations	-	-	Nasopharyngitis Upper respiratory tract infection	Sinusitis Conjunctivitis Influenza Gastroenteritis Oral Herpes Viral Infection
Blood and Lymphatic System Disorders	-	-	Lymphadenopathy	-
Metabolism and Nutrition Disorders	-	Appetite disorder	-	-
Psychiatric Disorders	-	-	Sleep disorder	-
Nervous System Disorders	Headache	-	Dizziness Paraesthesia	Migraine Dysgeusia Peripheral sensory neuropathy Somnolence
Ear and Labyrinth Disorders	-	-	-	Vertigo Ear pain
Cardiac Disorders	-	-	-	Tachycardia
Respiratory, Thoracic and Mediastinal Disorders	-	-	Pharyngolaryngeal pain Rhinitis Cough	-
Gastrointestinal Disorders	Nausea	-	Diarrhoea Vomiting Dry mouth	Abdominal Pain Aphthous stomatitis
Skin and Subcutaneous Tissue Disorders	-	-	Rash Pruritus Dermatitis Urticaria	Skin discolouration Ecchymosis Hyperhidrosis Night sweats Subcutaneous Nodule Angioedema
Musculoskeletal and Connective Tissue Disorders	Myalgia	Arthralgia Pain in extremity	Musculoskeletal stiffness Back pain Neck pain	Muscle spasms Musculoskeletal pain Muscular weakness
General Disorders and Administration Site Conditions	Injection site pain Injection site erythema Injection site swelling Injection	Injection site oedema Injection site discolouration Injection site nodule Injection site haematoma Chills Malaise	Injection site warmth Injection site haemorrhage Injection site irritation Injection site rash Underarm swelling Flushing Chest pain	Injection site exfoliation Injection site inflammation Injection site paraesthesia Injection site reaction Injection site dryness

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
	site induration Injection site pruritus Fatigue	Axillary pain		Injection site vesicles Oedema peripheral Injection site anesthesia Injection site movement impairment Injection site papule Asthenia Influenza like illness
Investigations	-	Body temperature increased Pyrexia	Troponin I increased Hepatic enzyme increased White blood cell count decreased Mean platelet volume decreased	White blood cell count increased
Injury, Poisoning and Procedural Complications	-	-	-	Contusion

* POX-MVA-001, -002, -004, -005, -007, -008, -009, -010, -011, -013, -023, -024, -027, -028, -029, -030, HIV-NEF-004 and HIV-POL-002; 7 subjects in POX-MVA-009 received Dryvax® either on the same day or within 7 days after MVA-BN® administration and were therefore not included to avoid a potential bias in the adverse event reporting.

Looking only at the events that were reported by at least 1% of the subjects, the majority of ADRs represented local vaccination site reactions as well as common systemic reactions typical for modern injectable vaccines and were classified as being mild to moderate. Overall, the ADRs reported to date following multiple administrations with MVA-BN® in healthy or various special populations, be it vaccinia-experienced or vaccinia-naïve, are comparable in frequency and have not identified any particular safety risks for the vaccine.

The current Investigator's Brochure provides more details on frequencies of suspected ADRs according to System of Organ Class and Preferred Term reported in completed clinical trials and a comparison of suspected ADRs reported by ≥1% of immunocompromised subjects vaccinated with MVA-BN®.

Cardiac Signs and Symptoms

Based on earlier observations with first and second generation smallpox vaccines (see Sections 2.2 and 2.3), particular attention has been placed on monitoring for cardiac signs and symptoms in all recent smallpox vaccine clinical trials.

Ongoing evaluation of health outcomes among Armed Forces personnel indicates individuals vaccinated with conventional smallpox vaccine are at higher risk for myocarditis and/or pericarditis than those not vaccinated. Suspected cases of myocarditis and/or pericarditis have been observed in healthy adult primary vaccinees at an approximate rate of 5.73 per 1,000 receiving ACAM2000®. This finding includes cases of acute symptomatic or asymptomatic myocarditis or pericarditis or both.

Despite close cardiac monitoring, no confirmed cases of myo-/pericarditis have been observed in any completed MVA-BN® trials. In a recently completed Phase III trial, a case of chest pain in a 32-year-old female subject was observed. This chest pain was described as worse when lying down and improving when sitting in an upright position, thereby meeting the case definition of a 'possible case of acute pericarditis' according to the criteria stated in the trial protocol. All cardiologist examinations, including repeated ECGs, troponin testing and echocardiography showed normal results, not confirming a pericarditis. Physical examination did not show auscultatory signs of a pericardial rub. The subject was in a good physical condition, including exercise tolerability. In summary, the sponsor assessment in this case was concluded as unlikely related, as it remained unclear whether a diagnosis of pericarditis can be finally confirmed in this subject considering the diagnosis of 'possible acute pericarditis' was purely based on the clinical observation (chest pain being worse when lying down). As possible alternative risk factor, viral serology examinations for this subject revealed a positive titer for Coxsackie B virus in temporal relation to the reported chest pain in this subject, which may be considered as contributory factor for the medical condition.

Table 2 Serious Suspected ADRs (SAEs Assessed by the Investigator to be at Least Possibly Related to MVA-BN®)

Trial	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	Investigator Assessment	BN Opinion
POX-MVA-005	30/Male	70 days after 2nd vaccination	Sarcoidosis	Stable and asymptomatic	Urinary tract infection with Chlamydia trachomatis at time of first symptoms (arthralgia)	Possibly related	Possibly related
POX-MVA-005	31/Female	26 months after 2nd vaccination	Crohn's disease	Stable and asymptomatic under therapy	Abnormal lab results (elevated alkaline phosphatase, absolute neutrophils and platelet counts) at screening for 2-year follow-up study POX-MVA-023 (excluded)	Possibly related	Possibly related
POX-MVA-008	28/Female	8 days after 2nd vaccination	Transitory ocular muscle paresis	Resolved without sequelae	No relevant medical history	Probably related	Possibly related
POX-MVA-010	30/Female	133 days after 2nd vaccination	Congestive heart failure due to cardiomyopathy	Stable under cardiac medications	Surgery for ventricular septal defect as child. HIV infection. Concomitant (denied, therefore previously unknown to BN) participation in a Growth-Hormone Releasing Hormone study; event also assessed as possibly related to Growth-Hormone Releasing Hormone	Possibly related	Unlikely related
POX-MVA-011	39/Female	1 day after 2nd vaccination	Simple pneumonia and pleurisy	Resolved without sequelae	HIV infection (CD4 count four weeks prior to second vaccination was 299 cells/µl). History of chronic obstructive pulmonary disease. Acute sinusitis and nasal congestion due to swimmer's ear which triggered hospital admittance.	Possibly related	Unlikely related

Trial	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	Investigator Assessment	BN Opinion
POX-MVA-036	27/Female	0 days after 2nd vaccination	Throat tightness and other hypersensitivity symptoms such as hives, pruritus, tender vaccination site, swollen axilla, angioedema of forearms	Resolved without sequelae	The subject received her second dose of MVA-BN® 21 days after the first dose and after 2 hours developed symptoms such as skin reactions and throat tightness which was responsive to epinephrine treatment. She had no wheezing and was not hypotensive. Symptoms subsided after several days under prednisone and diphenhydramine treatment. She has a family history of allergies and a medical history of shingles. She has received multiple vaccines before but never had previous hives or other problems with vaccines.	Possibly related	Possibly related
POX-MVA-036	30/Male	117 days after 1st vaccination	Non ST segment elevation myocardial infarction	Resolved without sequelae	Positive family history for cardiovascular diseases (both grandfathers had myocardial infarctions in their 50ies, father had blood clots), as well as overweight with a BMI above 33. A few days before event onset, subject returned from a trip to India with diarrhoea and was started on ciprofloxacine treatment (which per US prescribing information is associated with angina pectoris	Possibly related	Unlikely related

Trial	Age/ Gender	Days After Vaccination	Event	Outcome	Underlying Diseases/ Circumstances	Investigator Assessment	BN Opinion
					and myocardial infarction). He showed chest pain and increased troponin I, but no ST segment changes in the ECG and no coronary artery disease in cardiac catheterization. A post-infectious myocarditis (published case reports exist for campylobacter, shigella, salmonella) was considered as alternative etiology for the reported event.		

2.6.2 Immunogenicity Overview of MVA-BN®

In three Phase I and II dose finding trials MVA-BN® was tested for safety and immunogenicity among healthy volunteers (Vollmar, 2006; Frey, 2007; Von Krempelhuber, 2010; Zitzmann-Roth, 2015). Across these trials a linear dose relationship was observed between the vaccine doses for both ELISA and PRNT titers. Maximum ELISA seroconversion rates and peak titers were reached two weeks after the second vaccination, with 100% seroconversion after the second dose for all dose groups receiving at least $2x10^7$ $TCID_{50}$ of MVA-BN® or higher. Statistical analysis indicated lower doses to be inferior to a nominal titer of $1x10^8$ $TCID_{50}$ tested throughout all dose ranging studies. This highest dose tested achieved ELISA seroconversion rates between 81 and 100% already after the first dose. For the PRNT, the same trend was observed with 71-96% seroconversion rates two weeks after the second MVA-BN® administration in all groups receiving the highest dose.

The early onset of seroconversion and the higher titers of total and neutralizing antibodies combined with an excellent safety profile qualified the highest dose as the most suitable human dose. Therefore, based on the results of these dose ranging studies, coupled with the animal immunogenicity and efficacy studies, the final optimal (standard) dose and schedule for the general population was decided to be two doses of MVA-BN® with a nominal titer of $1x10^8$ $TCID_{50}$ administered (s.c.) four weeks apart.

Although antibody responses measured by ELISA in HIV infected subjects tend to be lower compared to GMT in healthy (Greenberg, 2013; Overton, 2015) and AD subjects four weeks after the first and second vaccinations with MVA-BN®, GMTs measured by PRNT were comparable in HIV infected compared to healthy and AD populations (von Sonnenburg, 2014; Greenberg, 2015). The ability of the second MVA-BN® vaccination to significantly boost the immune response in immunocompromised populations to high titer levels is as robust as in the healthy population.

In NIH sponsored trials POX-MVA-002 (DMID 02-017; Frey, 2007) and POX-MVA-009 (DMID 06-0012, Frey, 2013) the immune responses induced by MVA-BN® were compared to Dryvax®. In total 97.8% of subjects vaccinated with a single administration of the standard dose of MVA-BN® seroconverted by ELISA either at Day 14 or Day 28 post vaccination (29/29 in POX-MVA-002 and 61/63 in POX-MVA-009). 100% of subjects in the Dryvax® group had seroconverted 28 days after scarification (13/13 and 8/8 respectively). A second vaccination with MVA-BN® significantly increased the titers measured two weeks later so that the GMTs two weeks after the second vaccination with MVA-BN® were comparable to those four weeks after a single vaccination with Dryvax®. Furthermore, the majority of study participants (n=54) received MVA-BN® prior to challenge (vaccination) with Dryvax®. In these subjects, MVA-BN® priming (even at lower doses, i.e. $2x10^7$ $TCID_{50}$) resulted in a significant reduction of viral replication at the site of Dryvax® inoculation and either prevented take development or resulted in a diminished take coupled with an accelerated healing time; factors which are associated with people previously vaccinated with traditional smallpox vaccines or infected with variola virus. Partial

attenuation of primary takes in some vaccinia-experienced individuals receiving vaccination has also been well documented in previous studies (Stickl, 1974; Cherry, 1977; McIntosh, 1977; Orr, 2004).

Analysis of sera derived from MVA-BN® vaccinees compared to sera from Dryvax® recipients demonstrated that subjects vaccinated with MVA-BN® had a significantly higher in vitro Variola virus neutralization capacity (titer) compared to subjects vaccinated with Dryvax® (Damon, 2009). This result supports a comparable efficacy afforded by MVA-BN® and conventional smallpox vaccines against smallpox in people.

In addition, MVA-BN® and Dryvax® induced similar levels of T cell immunity with most subjects having detectable T cell responses 26-30 days following vaccinations. Data on cellular immune responses, analyzed in various trials using intracellular cytokine staining for detection of vaccinia-specific Interferon -γ producing CD4+/CD8+ T cells showed a strong dose-dependency. In vaccinia-experienced subjects, MVA-BN® was able to stimulate the memory T and B cell responses induced by a previous smallpox vaccination with conventional vaccines.

Additional detailed information on the clinical development of MVA-BN® is provided in the Investigator's Brochure.

2.7 Rationale

The efficacy of MVA-BN® cannot be demonstrated in traditional pivotal human Phase III efficacy trials since Variola challenge studies in humans are unethical and the world-wide eradication of smallpox makes field trials impossible. During the global smallpox vaccination campaigns, the development of a major cutaneous reaction following scarification (pock or "take") was used as a surrogate parameter of clinical efficacy, i.e. protection against smallpox following vaccination was reported upon the formation of a vaccinia take, which occurred one week post vaccination with a traditional smallpox vaccine (Fenner, 1988). This is also confirmed by the ACAM2000® prescribing information that states "formation of a major cutaneous reaction by day 6-8 is evidence of a successful 'take' and acquisition of protective immunity" and the take rate was used as surrogate parameter for approval of this vaccine.

Since MVA-BN® does not induce a take due to its high attenuation, inability to replicate in humans and route of administration, demonstration of the protective efficacy of MVA-BN® needs to be built on alternative strategies. This phase III trial therefore aims to demonstrate efficacy of MVA-BN® by comparing indicators of efficacy to the US licensed smallpox vaccine ACAM2000®. The first important component of BN's strategy to demonstrate efficacy of MVA-BN® in this Phase III trial is to compare the neutralizing antibody response induced by MVA-BN® to that of the conventional, US licensed smallpox vaccine ACAM2000®. Immunogenicity results obtained in preclinical studies have demonstrated that MVA-BN® induces equivalent immune responses (total antibodies, neutralizing antibodies and T cells) and efficacy in mice and NHP (Stittelaar, 2005) when compared to conventional smallpox vaccines, such as ACAM2000®

and Dryvax®. Furthermore, a linear correlation between vaccine dose and antibody responses (total and neutralizing antibodies) induced by MVA-BN® could be demonstrated in mice and NHP (and in human subjects). This correlation translated into a vaccine dose related protection of NHP from lethal challenge with MPXV, indicating that antibodies are good predictive correlates for protection, reasonably likely to predict clinical efficacy.

A NIH / DMID sponsored Phase I trial (POX-MVA-002 / DMID 02-017; Frey, 2007) allowed for a direct comparison of immune responses induced by either MVA-BN® or Dryvax® alone and results demonstrated that the peak and long-term immune responses (ELISA and PRNT) induced by MVA-BN® were comparable to those induced by Dryvax® in healthy vaccinia-naïve subjects. Furthermore, a retrospective study demonstrated the non-inferiority of total (ELISA) and neutralizing antibodies (PRNT) induced in healthy vaccinia-naïve subjects after vaccination with MVA-BN® drawn from three (3) BN clinical studies (POX-MVA-005, POX-MVA-008 and POX-MVA-011) compared to responses obtained from five (5) NIH / DMID sponsored studies with Dryvax®/Wetvax (Aventis Pasteur Smallpox Vaccine [APSV]). All sera were analyzed using the same validated ELISA and PRNT assays, allowing a retrospective comparison of immune responses induced by MVA-BN® and the two first generation smallpox vaccines (Bavarian Nordic Scientific Report; Sept 2011).

In conclusion, assessing non-inferiority of MVA-BN® compared to ACAM2000® in terms of vaccinia-specific Plaque Reduction Neutralization Test (PRNT) antibody response at the Peak Visits (Day 42 for Group 1 and Day 28 for Group 2) was selected to demonstrate the efficacy of MVA-BN®.

However, only very few subjects have seroconverted by Day 8 post vaccination with Dryvax® (Frey, 2003; Kennedy, 2004). Therefore, protection afforded by traditional smallpox vaccines would appear to occur in the absence of detectable antibodies. Therefore the second component of the strategy to demonstrate the protective efficacy of MVA-BN® is to evaluate in subjects immunized with MVA-BN® the absence and/or the attenuation of the take after subsequent scarification with ACAM2000®. This absence and/or the attenuation of the take has historically been associated with pre-existing immunity against smallpox infections, acquired either by previous vaccination(s) using conventional smallpox vaccines or a prior smallpox infection (Fenner, 1988). A significant reduction of the lesion size in vaccinia-experienced subjects following re-vaccination with traditional smallpox vaccines was also shown in controlled clinical trials. Vaccinia-experienced participants presented with significantly smaller skin lesions (Frey, 2003) or a reduced mean diameter of the peak lesion size (Parrino, 2007) after vaccination with Dryvax® compared to the full take observed in vaccinia-naïve individuals. In the above mentioned Phase I trial (POX-MVA-002 / DMID 02 017), MVA-BN® (even at lower doses, i.e. $2x10^7$ $TCID_{50}$/ml) given prior to vaccination with Dryvax® reduced viral replication at the site of Dryvax® inoculation, resulting in a significantly diminished skin response (i.e. take), as well as an accelerated healing time, suggesting that immune responses induced by MVA-BN® were protective against vaccinia replication. Taken together, this experience strongly suggests that

attenuation of the take in MVA-BN® recipients following vaccination with ACAM2000® can be considered to indicate induction of a strong vaccinia-specific immunity.

Therefore, the co-primary objective of the present trial is to demonstrate the efficacy of MVA-BN® by showing that vaccination with MVA-BN® prior to scarification with ACAM2000® results in an attenuation of take. In the clinical trial POX-MVA-002 a reduction of average lesion area was observed in pre-vaccinated subjects and noted as being clinically relevant (Frey, 2003). There is a high subject to subject variability in the timing and level of attenuation observed, and the calculation of whether a subject has an attenuation of take therefore needs be considered as a defined concept that is calculated per subject for the period following scarification with ACAM2000®.

The present trial will therefore define attenuation as when the takes observed in Group 1 subjects (MVA-BN® recipients vaccinated with ACAM2000®) are determined to be diminished full takes based on the median of the individual measured parameter of Maximum Lesion Areas in Group 1 subjects, in comparison to the median of Maximum Lesion Areas of takes in Group 2 subjects (ACAM2000® recipients).

Since these two components are considered important indicators of the protective efficacy of MVA-BN®, both will be co-primary endpoints of the present trial, i.e. to assess the non-inferiority of MVA-BN® compared to ACAM2000® based on the neutralizing antibody GMT 28 days after an ACAM2000® vaccination and on the neutralizing antibody GMT 42 days after the first MVA-BN® vaccination measured using a validated PRNT and to demonstrate the efficacy of MVA-BN® by showing that vaccination with MVA-BN® prior to scarification with ACAM2000® results in an attenuation of take. The day 28 time point was selected in order to be in alignment with published data for conventional smallpox vaccines reaching a peak four weeks post vaccination (Frey, 2003; Belshe, 2004; Kennedy, 2004; Frey, 2007), which is also in full agreement with the data published for ACAM2000® (ACAM2000 VRBPAC Briefing Document, 2007). The clinical trials conducted for MVA-BN® to date consistently show that the peak responses are observed at Day 42 after the first MVA-BN® vaccination (Investigator Brochure).

Further secondary objectives of the trial include a comparison of safety and reactogenicity of MVA-BN® and ACAM2000® vaccinations and the effect on the ACAM2000® vaccination take following MVA-BN® priming.

It is planned to have at least 175 healthy vaccinia-naïve subjects per group (assigned to the PPS) vaccinated with either MVA-BN® and ACAM2000® or ACAM2000® alone.

2.8 Trial Population

Male and female United States military personnel aged 18 to 42 years, who meet all the inclusion criteria and none of the exclusion criteria.

2.9 Risk/Benefit Assessment

2.9.1 Potential Risks

Blood drawing may cause local discomfort or bleeding under the skin from needle sticks, resulting in a localized hematoma that generally resolves within 1 to 2 weeks. A rare complication may be localized infection at the phlebotomy site or thrombophlebitis (swelling of a vein caused by a blood clot). This would be treated as medically indicated. Some subjects may feel lightheaded, queasy, or nauseated; have chills; develop a fast heartbeat; and/or faint during blood collection. These symptoms can be resolved by having the subject lie down and/or by stopping the procedure. To minimize risks, only qualified personnel will draw blood.

Preclinical data with MVA- BN® in rats and rabbits have revealed no special hazards for humans based on conventional studies of safety.

Based on the present clinical experience with MVA-BN® and MVA-based vaccines, adverse reactions to MVA- BN® in this trial setting are expected to be comparable to adverse reactions previously reported for MVA-BN® and/or those typically seen with other modern vaccines. Main risks involve the development of local reactions at the vaccination site, e.g. erythema, pain, swelling and induration.

As with all injected vaccines, there is a risk of an allergic reaction or an anaphylactic event. Clinical trial site staff will watch subjects for at least 30 minutes after each vaccination and in case a severe allergic reaction should occur, appropriate medical treatment and supervision will be readily available.

Serious complications that may follow either primary ACAM2000® vaccination or revaccination include: myocarditis and/or pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum and blindness (ocular vaccinia), and fetal death in pregnant women. For risks associated with ACAM2000® please see the prescribing information (Appendix IVc; Section 17.7) and the medication guide (Appendix IVa; Section 17.5).

MVA-BN® is replication incompetent in human cells and consequently has a favorable safety and tolerability profile. It is essentially impossible that MVA-BN® could induce the severe side effects listed above associated with replication competent vaccinia viruses. Apart from the favorable safety profile with regard to severe reactions, the available clinical experience with MVA-BN® shows that it is in general well tolerated, for example with regard to local reactions.

2.9.2 Benefits

Based on the current immunogenicity and efficacy data collected for MVA-BN® and ACAM2000® in preclinical and clinical studies, trial participants are expected to acquire protection against smallpox infection. Subjects will contribute significantly to the development of a safer smallpox vaccine, which is a benefit for society in view of a potential threat following deliberate release of smallpox virus.

Future analysis of the samples collected will not directly benefit the subject. BN may learn more about immune response to smallpox disease: prevention, treatment, or cure.

3 Objectives

3.1 Co-Primary Objectives

To demonstrate the efficacy of MVA-BN® by assessing non-inferiority of MVA-BN® compared to ACAM2000® in terms of vaccinia-specific PRNT antibody response at the Peak Visits (Day 42 for Group 1 and Day 28 for Group 2) and by showing that vaccination with MVA-BN® prior to scarification with ACAM2000® results in an attenuation of take in terms of MLA.

3.2 Secondary Objectives

To assess non-inferiority of MVA-BN® compared to ACAM2000® in terms of vaccinia-specific ELISA antibody response at the Peak Visits.

To assess seroconversion rates of MVA-BN® compared to ACAM2000® at the Peak Visits.

To assess immune response dynamics in terms of antibody responses.

To assess the effect on the ACAM2000® vaccination take following MVA-BN® priming.

To assess and compare safety and reactogenicity of vaccinations with MVA-BN® and ACAM2000®given alone or ACAM2000®given after MVA-BN® priming.

4 Trial Design

4.1 Experimental Design

This trial is a randomized, open-label Phase III non-inferiority trial to demonstrate efficacy for MVA-BN® compared to ACAM2000® in 18 to 42 year old healthy, vaccinia-naïve subjects.

Group 1

MVA-BN®, two standard doses s.c., 4 weeks apart followed by one dose of ACAM2000® via scarification 4 weeks after the second MVA-BN® vaccination.

Group 2

ACAM2000®, one dose via scarification, in accordance with US military smallpox vaccine program.

Subjects in Group 1 will participate in eleven physical trial visits, nine blood draws and one remote follow-up visit. Subjects in Group 2 will participate in seven physical trial visits, seven blood draws and one remote follow-up visit. For the schedule of the trial visits and the description of trial procedures, please refer to the trial procedure schedule and the following protocol sections.

4.2 Description of Trial Procedures

The trial procedures will be conducted according to the trial procedure schedule and as described in this CTP. Visits should be scheduled within the given time intervals. All blood tests are non-fasting.

4.2.1 Screening Phase

Screening Visit (SCR, Day -70 to -1)

The informed consent must be reviewed with and signed and dated by the subject prior to the initiation of any evaluations or procedures required by the protocol. All subjects must be thoroughly informed of all aspects of the trial (e.g. trial procedure schedule, required evaluations and procedures, risks and benefits) as described in the informed consent document.

After informed consent has been signed, subjects will enter a screening period of up to ten weeks before the first vaccination.

An extensive screening assessment will be performed during the screening period.

Screening Visit (Days -70 to -1)
The following tasks will be performed: • Subject to read, sign and date Informed Consent Document (ICD) • Check inclusion/exclusion criteria (which incorporates the criteria from the US Department of Defense [DoD] Smallpox Vaccine Screening Forms) • Obtain medical/surgical history • Check vaccination history and absence of smallpox vaccine scar • Complete physical examination / vital signs (temperature, pulse, respiratory rate and blood pressure, including auscultation of heart and lungs and measurement of body weight and height and examination of axillary and supraclavicular lymph nodes) • Evaluation of vital signs, BMI calculation and calculation for creatinine clearance • Recording of baseline signs and symptoms • Check cardiac risk factors, including immediate family (father, mother, brother or sister) risk factors, total cholesterol, high-density and low-density lipoprotein (HDL, LDL) and calculation of individual cardiac risk factor • Perform baseline ECG • Review of prior/concomitant medications • Counseling on avoidance of contact spread (specifically after ACAM2000® vaccination), HIV infection, and pregnancy: Review of acceptable contraceptive methods and recent menstrual history with WOCBP. • Blood draw (22 ml) for safety laboratory (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium) including total, HDL and LDL cholesterol, hepatitis serology (HBsAg, Anti-HCV), HIV, troponin I and serum pregnancy test

If a subject is screened and cannot be vaccinated because of a certain transient condition (e.g. abnormal lab value due to an acute condition or a missing lab evaluation due to mishandling of the sample), then the subject can be re-screened on one further occasion only and the respective tests should be repeated as a "partial" re-screening rather than a “full” re-screening. The re-screening visit must be within the 70 day window started by the first Screening Visit and the window -70 to 1 day before 1st vaccination must not be exceeded. A “partial” re-screening visit is indicated by completing only the respective re-screening sections of the Case Report Form (CRF).

If a subject could not be vaccinated due to other circumstances (e.g. intermediate closure of the trial group because of an interim safety analysis) and the 70 day period is over, a "full" re-screening assessment including re-consenting, physical examination, lab examination, ECG must be performed. The clock then re-starts at the re-screening visit with Day -70 before 1st vaccination. A "full" re-screening visit is indicated by completing all re-screening CRF pages.

4.2.2 Active Trial Phase

After successfully passing the screening evaluations, the eligible subjects will enter the active trial phase starting with Visit 1. At Visit 1 subjects will be assigned randomly to one of the two treatment groups (Groups 1 or 2) after re-confirmation of subject's eligibility. The active trial phase will continue until Visit 10 for Group 1 subjects and until Visit 4 for Group 2 subjects.

The procedures performed at the active trial phase visits are listed below. Blood draws and all other examinations listed above the vaccination procedure must always be performed prior to vaccination.

At Visit 1 / Day 0, subjects in Group 1 will receive the first of two s.c. vaccinations with one standard dose of MVA-BN® preferably in the non-dominant upper arm (deltoid region). Subjects in Group 2 will receive a single vaccination with ACAM2000®. One dose of reconstituted ACAM2000® vaccine consists of 2.5-12.5x10^5 plaque forming units of live VACV. A droplet (0.0025 ml) vaccine is picked up with a bifurcated needle and is administered by the percutaneous route (scarification) using 15 jabs of the bifurcated needle. Following vaccination subjects will be kept under close observation for at least 30 minutes, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of the vaccine. Only appropriately trained and qualified medical personnel according to DoD guidelines will administer the ACAM2000® vaccination. The DoD Smallpox Vaccination Training curriculum is an online course for Military Healthcare Personnel and can be found under the weblink: http://www.vaccines.mil/default.aspx?cnt=ImzU/SmallpoxTraining. ACAM2000® will be administered in the appropriate designated military site clinic and will be the responsibility of the administering military site clinic.

Further information on the ACAM2000® product can be found in Appendix IVc; Section 17.7: ACAM2000® Prescribing Information. Information on the medical management of adverse reactions after ACAM2000® vaccination can be found in Appendix V; Section 17.15: Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir.

Subjects receiving MVA-BN® may have the vaccination site covered with a BAND-AID® or equivalent as needed. Subjects receiving ACAM2000® will have the vaccination site covered with a semi-permeable bandage provided in a Care Kit (the contents of which will be defined in agreement with the trial site staff and will be the same for all ACAM2000® vaccinated subjects). The vaccination site must be kept covered for 30 days and/or until the site is healed. The vaccinee

should change the bandage as instructed by the administering clinic (leave the bandage on for the 1st 48 hours, then change every day or when bandage becomes wet) until the vaccination site scab falls off as this will keep the vaccination site intact and will minimize softening. Salves or ointments must not be applied to the vaccination site.

Any AEs that occur during or after vaccination will be recorded. All subjects will be asked to record, on a subject memory aid, daily maximum temperatures and solicited AEs for 15 days, beginning with the day of vaccination and report them to the research staff. If solicited AEs persist after 14 days post vaccination, daily symptoms and temperatures will continue to be measured each day until resolved or Visit 10 (Group 1) or Visit 4 (Group 2) respectively.

Visit 1 (Day 0)
Tasks to be performed prior to randomization and vaccination: • Re-check inclusion/exclusion criteria • Check of safety laboratory results obtained at Screening Visit • Targeted physical examination, including auscultation of heart and lungs, see Section 8.2.3 for more details • Evaluation of vital signs • Recording of baseline signs and symptoms • Questions on cardiac signs and symptoms • Review of prior/concomitant medications • Assessment of axillary and supraclavicular lymphadenopathy, see Section 8.2.3 for more details • Examination of the possible deltoid vaccination sites • Counseling on avoidance of contact spread (specifically after ACAM2000® vaccination), HIV infection and pregnancy • Urine or serum pregnancy test (5 ml, if applicable) • Blood draw (serum collection) for antibody analysis (16 ml) Blood draws and all other tasks mentioned above must always be performed prior to vaccination. If the subject is still eligible for participation in this trial, the subject will be randomized. The following tasks will be performed after randomization: • Vaccination: Group 1: administration of one (1) dose of MVA-BN® Group 2: administration of one (1) dose of ACAM2000® • Subject observation by clinical trial site staff for at least 30 minutes after vaccination

Visit 1 (Day 0)
• Examination of the vaccination site and/or the area around the bandage for skin reactions (approximately 30 minutes after vaccination) • Recording of immediate AEs/SAEs/AESIs • Handout of memory aid, ruler and thermometer • Bandage application and handout of clinical trial specific Care Kits to Group 2 subjects only • After ACAM2000® scarification subjects should change their own bandage as instructed by the administering clinic (leave the bandage on for the 1st 48 hours, then change every day or when bandage becomes wet) using the clinical trial specific Care Kits provided by site staff **Temporary deferral of vaccination:** If an acute illness is present at the time scheduled for the vaccination, the subject may be vaccinated at a later date within the foreseen time window. The vaccine can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection, or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4°F (< 38.0°C).

Visit 2 (Visit 1 + 6-8 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs (if clinically indicated); see Section 8.2.3 for more details • Evaluation of vital signs • Counseling on avoidance of contact spread (specifically after ACAM2000® vaccination), HIV infection and pregnancy • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Examination of vaccination site • Recording of AEs/SAEs/AESIs • Review of memory aid • Blood draw (serum collection) for antibody analysis (16 ml) Group 2 only: • Photo of vaccination site • Bandage application/change

Visit 3 (Visit 1 + 13-15 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Evaluation of vital signs • Perform ECG • Questions on cardiac signs and symptoms • Review of prior/concomitant medications • Counseling on avoidance of contact spread (specifically after ACAM2000® vaccination), HIV infection and pregnancy • Examination of the vaccination site • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Recording of AEs/SAEs/AESIs • Collection of the memory aid and review with subject • Blood draw for safety laboratory (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium, 10 ml) including troponin I testing • Blood draw (serum collection) for antibody analysis (16 ml) • If vaccination site has not yet fully healed then a memory aid extension would be handed out Group 2 only: • Photo of vaccination site • Bandage application/change

Visit 4 (Visit 1 + 27-29 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Evaluation of vital signs • Questions on cardiac signs and symptoms • Review of prior/concomitant medications • Counseling on avoidance of contact spread (specifically after ACAM2000® vaccination), HIV infection and pregnancy. **Group 2:** Counseling for avoidance of pregnancy not required. • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Examination of vaccination site • Urine or serum pregnancy test (5 ml, if applicable) • Recording of AEs/SAEs/AESIs • Blood draw (serum collection) for antibody analysis (16 ml) • If a memory aid extension had been provided at Visit 3 then a review of the memory aid extension should be conducted and the memory aid collected Group 1: Tasks mentioned above must always be performed or repeated prior to vaccination • Second administration of one (1) dose of MVA-BN® • Subject observation by clinical trial site staff for at least 30 minutes after vaccination • Handout of memory aid • Recording of immediate AEs/SAEs/AESIs **Temporary deferral of vaccination:** If an acute illness is present at the time scheduled for the vaccination, the subject may be vaccinated at a later date within the foreseen time window. The vaccine can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection, or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4°F (< 38.0°C).

Visit 4 (Visit 1 + 27-29 days)
Group 2: • If vaccination site has not yet fully healed then another memory aid extension would be handed out. • Bandage application/change

All subsequent visits are relevant for Group 1 subjects only.

Visit 5 (Group 1: Visit 4 + 6-8 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs (if clinically indicated); see Section 8.2.3 for more details • Evaluation of vital signs • Counseling on avoidance of HIV infection and pregnancy • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Recording of AEs/SAEs/AESIs • Examination of vaccination site • Review of memory aid

Visit 6 (Group 1: Visit 4 + 13-15 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Evaluation of vital signs • Perform ECG (if clinically indicated) • Questions on cardiac signs and symptoms • Review of prior/concomitant medications

Visit 6 (Group 1: Visit 4 + 13-15 days)
• Counseling on avoidance of HIV infection and pregnancy • Examination of the vaccination site • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Collection of the memory aid handed out at Visit 4 and review with subject • Recording of AEs/SAEs/AESIs • Blood draw (serum collection) for antibody analysis (16 ml) • Blood draw for safety laboratory (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium, 10 ml)

Visit 7 (Visit 1 + 55-57 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Evaluation of vital signs • Questions on cardiac signs and symptoms • Review of prior/concomitant medications • Counseling on avoidance of contact spread, HIV infection and pregnancy • Examination of vaccination site • Assessment of axillary and supraclavicular lymphadenopathy, see Section 8.2.3 for more details • Recording of AEs/SAEs/AESIs • Urine or serum pregnancy test (5 ml, if applicable) • Blood draw (serum collection) for antibody analysis (16 ml) • Check of safety laboratory results obtained at Visit 6 Tasks mentioned above must always be performed prior to vaccination. • Administration of one dose of ACAM2000®

Visit 7 (Visit 1 + 55-57 days)
The following tasks will be performed (or repeated) after vaccination: • Subject observation by clinical trial site staff for at least 30 minutes after vaccination • Handout of memory aid • Recording of immediate AEs/SAEs/AESIs • Examination of the vaccination site and/or the area around the bandage for skin reactions (approximately 30 minutes after vaccination) • Bandage application and handout of clinical trial specific Care Kits **Temporary deferral of vaccination:** If an acute illness is present at the time scheduled for the vaccination, the subject may be vaccinated at a later date within the foreseen time window. The vaccine can be administered to persons with a minor illness such as diarrhea, mild upper respiratory infection, or any other mild condition with or without low-grade febrile illness, i.e. oral temperature < 100.4°F (< 38.0°C).

Visit 8 (Visit 7 + 6-8 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs (if clinically indicated); see Section 8.2.3 for more details • Evaluation of vital signs • Counseling on avoidance of contact spread, HIV infection and pregnancy • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Recording of AEs/SAEs/AESIs • Examination of vaccination site • Photo of vaccination site • Bandage application/change • Review of memory aid

Visit 9 (Visit 7 + 13-15 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Evaluation of vital signs • Perform ECG • Questions on cardiac signs and symptoms • Review of prior/concomitant medications • Counseling on avoidance of contact spread, HIV infection and pregnancy • Examination of the vaccination site • Photo of vaccination site • Bandage application/change • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Recording of AEs/SAEs/AESIs • Collection of the memory aid handed out at Visit 7 and review with subject • If vaccination site has not yet fully healed then a memory aid extension would be handed out • Blood draw for safety laboratory (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium, 10ml) including troponin I testing

Visit 10 (Visit 7 + 27-29 days)
The following tasks will be performed • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Questions on cardiac signs and symptoms • Review of prior/concomitant medications • Counseling on avoidance of contact spread and HIV infection

Visit 10 (Visit 7 + 27-29 days)
• Examination of the vaccination site • Bandage application/change • Assessment of axillary and supraclavicular lymphadenopathy; see Section 8.2.3 for more details • Recording of AEs/SAEs/AESIs • Urine or serum pregnancy test (5 ml, if applicable) • Blood draw (serum collection) for antibody analysis (16 ml) • If a memory aid extension had been provided at Visit 9 then a review of memory aid extension should be conducted and the memory aid collected

4.2.3 Follow Up Phase

Visit 5 (Group 2: Visit 1 + 41-43 days)
The following tasks will be performed • Blood draw (serum collection) for antibody analysis (16 ml)

Visit 6 (Group 2: Visit 1 + 55-57 days)
The following tasks will be performed • Blood draw (serum collection) for antibody analysis (16 ml)

To monitor long-term safety, the clinical trial site will contact the subjects by remote correspondence (e.g. telephone or email) 6 months after the last trial vaccination to inquire whether SAEs and/or AESIs might have occurred since the last trial visit. In cases where a serious condition is detected, the trial subject will be asked to return for a physical examination and further work-up at the clinical trial site or (specifically in the case of deployed military subjects) at another medical unit as agreed upon by the Principal Investigator (PI).

Remote FU (Last vaccination + 182 – 210 days)
The following tasks will be performed: • FU on ongoing AEs, AESIs, SAEs and recording of new SAEs/AESIs In case a physical visit is deemed necessary, the following should be performed: • Targeted physical examination, including auscultation of heart and lungs; see Section 8.2.3 for more details • Review of prior / concomitant medications, (if related to an ongoing AE, AESIs, SAEs and new SAEs/AESIs) • Blood draw (10 ml) for safety laboratory (CBC with differential, total bilirubin, Alk Phos, AST, ALT, creatinine, sodium, potassium and calcium, if clinically indicated) • Other safety evaluation, if clinically indicated

4.2.4 Unscheduled Visits

If clinically indicated, additional visits may be necessary between scheduled visits. Unscheduled visits may be performed to repeat laboratory testing or physical exams due to a new development. Unscheduled visits may occur when subjects request assistance with or experience problems with bandage changes after ACAM2000® vaccination. In cases where the vaccination site has not fully healed at Visit 4 in Group 2 subjects and at Visit 10 in Group 1 subjects, then the subject would be asked to provide date that scab fell off. Examinations, performed at unscheduled visits will be documented in the source documents as well as on the respective CRF pages for unscheduled visits.

4.2.5 Withdrawal from Further Trial Vaccinations (Group 1)

The decision not to administer further trial vaccinations can be made by the PI as well as by the subject.

Criteria:

For Group 1 subjects the following criteria should be checked prior to administration of the second MVA-BN® vaccination at Visit 4 and the ACAM2000® vaccination at Visit 7.

If any are applicable, the subject should not receive any of these vaccinations:

- Any clinically significant cardiac sign and symptom.

  The detection of cardiac events indicative for cases of myo-/pericarditis are collected as AESI, defined as:

  - Any cardiac sign or symptom (e.g. chest pain, shortness of breath etc.) developed since the first vaccination
  - ECG abnormalities determined to be clinically significant by the investigating physician
  - Cardiac enzyme troponin I ≥ 2 x ULN (≥ Grade 2 according to the toxicity scale provided in Appendix I; Section 17.1)

Case definitions for acute myocarditis and pericarditis, as published by the Center of Disease Control and Prevention (CDC) (MMWR, May 30, 2003) are provided in Appendix III; Section 17.3, in order to:

- help Investigators to recognize possible events of acute myocarditis and/or pericarditis and
- distinguish from unspecific and isolated ECG abnormalities without or with unclear clinical significance.

- An AE that, in the opinion of the investigator, makes it unsafe for the subject to receive any further trial vaccination. In this case, the appropriate measures will be taken
- Anaphylactic reaction following the administration of any vaccine(s)
- Start of chronic administration (defined as more than 14 days) of > 5 mg prednisone (or equivalent) per day or any other immune-modifying drugs
- Administration of immunoglobulins and/or any blood products
- Clinical need for concomitant or ancillary therapy not permitted in the trial
- Use of any investigational or non-registered drug or vaccine other than the trial vaccine
- Any condition which contradicts administration of any further trial vaccination in the opinion of the investigator
- Pregnancy
- Subject refuses to receive any further vaccination

Procedure:

If the subject is withdrawn from further trial vaccinations the reason for this decision should be recorded. The procedures below should be followed:

If withdrawn after the 1st MVA-BN® vaccination

- All visits up to Visit 4 must be performed according to the trial procedure schedule.
- Visit 5 to Visit 10 will not be performed.
- The remote FU Visit has to be performed 182 to 210 days after Visit 1.

If withdrawn after the 2nd MVA-BN® vaccination

- All visits up to Visit 7 must be performed according to the trial procedure schedule
- Visit 8 to Visit 10 will not be performed
- The remote FU Visit has to be performed 182 to 210 days after Visit 4

4.2.6 Premature Discontinuation

The trial may be discontinued prematurely for a subject at any time. The decision to discontinue a subject prematurely can be made by the PI as well as by the subject. Reasons may include, but are not limited to, the following:

Criteria:

- Subject's request to discontinue prematurely
- Subject unwilling or unable to comply with trial requirements
- Any reason that, in the opinion of the investigator, precludes the subject's further participation in the trial

Procedure:

If a subject discontinues prematurely, the reason for this decision should be recorded. If the subject is unable or not willing to attend all planned visits, every attempt should be made to perform at least a concluding safety visit. For WOCBP a pregnancy test should be performed during this safety visit. If the subject is not willing to undergo any further trial procedure (withdrawal of consent), "withdrawal of consent" needs to be documented in writing as reason for premature discontinuation.

4.3 Trial Duration

The total duration of the trial for each subject including the screening period and remote FU will be up to 48 weeks. The duration of the trial as a whole is dependent on the recruitment period.

4.4 Data Safety Monitoring Board

The DSMB is an independent board that oversees the safety of subjects participating in the trial. The members of the DSMB are independent, i.e. not involved as investigators in any MVA-BN® trials and have no direct or indirect financial interests in BN or the Contract Research Organization (CRO) managing the trial. The primary responsibilities of the DSMB are to review periodically and to evaluate the accumulated trial data for participant safety, trial conduct and progress, and to make recommendations to BN and the PI(s) concerning the continuation, modification, or termination of the trial program. The DSMB considers trial specific data as well as relevant background knowledge about the disease, test agent, and subject population under trial. A separate charter describes in detail relevant operational procedures, communication pathways, roles and responsibilities of the DSMB.

In case an event occurs which fulfils the trial halting criteria, the DSMB will review the event in a timely manner and give a recommendation to BN and the PI(s) to halt, resume or terminate the trial participation of the affected subject and/or the trial as a whole.

4.5 Trial Halting Rules

A temporary halting or termination for the trial as a whole can be decided by the DSMB in the event of an occurrence of

- an SAE
- an unexpected Grade 3 or higher systemic reaction or lab toxicity (Appendix I; Section 17.1)

with an at least reasonable possibility of a causal relationship to the administration of MVA-BN®, i.e. the relationship cannot be ruled out.

Suspected cases of illnesses such as progressive vaccinia, eczema vaccinatum, and severe generalized vaccinia or inadvertent inoculation or other SAE observed after smallpox vaccination with ACAM2000® should be reported immediately following standard of practice. VIG and Cidofovir are available from CDC for treatment of AEs among smallpox vaccine recipients and their contacts under IND protocols.

Additionally, SAEs after ACAM2000® vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS). Reports can be submitted through a secure Internet-based system at https://vaers.hhs.gov/esub/step1. Printable VAERS forms are located online at

https://vaers.hhs.gov/resources/vaers_form.pdf, or postage-paid forms can be obtained by calling 800 822 7967 (toll-free). Submission of VAERS reports by Internet is encouraged to expedite processing and data entry. Completed forms can be faxed to 877 721 0366 (toll-free) or mailed to P.O. Box 1100, Rockville, MD 20894-1100. Additional information related to VAERS reporting can be obtained by calling 800 822 7967 or by e-mail at info@vaers.org.

These parameters are not all-inclusive. Other AEs could occur that would trigger a DSMB review. Any member of the DSMB, the PI and/or the BN Pharmacovigilance Officer could request a DSMB review based on any observation.

If an event fulfilling the trial halting criteria reaches the investigator's attention, the investigator has the responsibility to alert the responsible DS Department immediately (within 24 hours) and provide a comprehensive documentation of the event. Contact details of the responsible DS Department are provided in Section 8.3.1.

5 Selection of Subjects

The clinical trial site investigator or designee will keep a log of subjects screened for the trial according to the USAMRIID Standard Operating Procedure (SOP) (b) (1) (A) Clinical Trials Enrollment: Assignment of Subject Study Identification Numbers and Documentation of Subject Study Participation.

5.1 Recruitment Procedure

Subjects will be recruited from DoD personnel who are scheduled to receive their initial smallpox vaccination.
Recruitment strategies, including IRB approved advertisements, will be evaluated by the Sponsor. Prospective volunteers will be briefed by trial personnel on the nature of the trial and will be provided the appropriate approved consent document describing all aspects of the research trial and procedures. Prospective volunteers will be provided the opportunity to discuss the trial with trial personnel.

Up to 750 subjects may be screened in order to vaccinate 440 eligible healthy subjects (220 in each group) in order to obtain at least 175 subjects per group qualifying for the PPS. After signing the Informed Consent, subjects undergo screening procedures to check eligibility according to the inclusion/exclusion criteria (Section 1.4). In the event of a screening failure secondary to mild or limited acute illness or abnormal laboratory values, the subject may be re-screened after resolution of the event. Re-screening may require only an additional blood draw or may require a full re-screening evaluation, depending on the circumstances of and the time interval from the initial screening failure as described in Section 4.2.1.

5.2 Inclusion Criteria

1. Healthy male and female subjects, 18-42 years of age at date of informed consent signature
2. The subject has read, signed and dated the Informed Consent, having been advised of the risks and benefits of the trial in a language understood by the subject and prior to performance of any trial specific procedure
3. Acceptable medical history by screening evaluation and physical examination
4. BMI ≥ 18.5 and < 35
5. WOCBP must have a negative serum pregnancy test at Screening and a negative urine or serum pregnancy test within 24 hours prior to each vaccination
6. WOCBP must have used an acceptable method of contraception for 28 days prior to the first vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for 28 days after the last vaccination. A woman is considered of childbearing potential unless post-menopausal (defined as ≥ 12 months without a menstrual period) or surgically sterilized. (Acceptable contraception methods are restricted to abstinence, barrier contraceptives, intrauterine contraceptive devices or licensed hormonal products)
7. HIV antibody negative, hepatitis B surface antigen negative and negative antibody test to hepatitis C virus
8. White blood cells ≥ 2,500/mm^3 and < 11,000/mm^3
9. Hemoglobin within normal limits
10. Platelets ≥ lower normal limits
11. Adequate renal function defined as a calculated CrCl > 60 ml/min as estimated by the Cockcroft-Gault equation:

- For men: (140 – age in years) x (body weight in kg) ÷ (serum creatinine in mg/dl x 72) = CrCl (ml/min)
- For women: multiply the result by 0.85 = CrCl (ml/min)

12. Adequate hepatic function in the absence of other evidence of significant liver disease defined as:

- Total bilirubin ≤ 1.5 x ULN
- ALT, AST ≤ 1.5 x ULN
- Alk Phos ≤ 1.5 x ULN

13. Troponin I < 2 x ULN
14. Electrocardiogram (ECG) without clinically significant findings, e.g. without atrioventricular or intraventricular conditions or blocks such as incomplete/complete left or

complete right bundle branch block, second or third degree atrioventricular block, two premature ventricular contractions in a row, ST elevation consistent with ischemia, atrial or ventricular arrhythmia

- QTc prolongations > 500 ms which do not require clinical intervention should be discussed with the Medical Monitor before vaccination
- Following conditions can be included, if they do not require clinical intervention:
  - First degree atrioventricular block, PR interval prolongation, premature atrial contractions, occasional premature ventricular contractions, sinus bradycardia, right or left axis deviation, non-specific ST and T wave changes.

Further guidance is provided in Appendix VI.

5.3 Exclusion Criteria

1. Pregnant or breast-feeding women
2. Typical vaccinia scar
3. Known or suspected history of smallpox vaccination defined as visible vaccination scar or documentation of smallpox vaccination or as reported by the subject
4. History of vaccination with any poxvirus-based vaccine
5. History of any serious medical condition, which in the opinion of the investigator would compromise the safety of the subject
6. History of or active immunodeficiency or immunosuppression caused by acquired or congenital diseases or caused by ongoing treatments such as chronic (> 14 days) high-dose corticosteroids (> 5 mg prednisone [or equivalent] per day applied systemically, i.e. parenterally or orally), chronic or planned treatment with steroid eye drops or ointment at time of screening or radiation, or immunosuppressive drugs; low-dose corticosteroid topical products and nasal sprays used sporadically, i.e. pro re nata are permissible
7. Having had radiation or X-ray treatment (not routine X-rays) within the last 3 months
8. Post organ and bone-marrow transplant subjects whether or not receiving chronic immunosuppressive therapy
9. Recent surgery (including dental or eye) within 4 weeks prior to trial vaccination
10. History of or active autoimmune disease. Persons with vitiligo or thyroid disease taking thyroid hormone replacement are not excluded
11. Uncontrolled serious infection, i.e. not responding to antimicrobial therapy
12. History of malignancy, other than squamous cell or basal cell skin cancer, unless there has been surgical excision considered to have achieved cure. Subjects with history of skin cancer must not be vaccinated at the previous site of cancer

13. History of keloid formation
14. History or clinical manifestation of severe hematological, renal, hepatic, pulmonary, central nervous, cardiovascular or gastrointestinal disorders
15. History of coronary heart disease, myocardial infarction, angina, congestive heart failure, cardiomyopathy, stroke or transient ischemic attack, uncontrolled high blood pressure, significant arrhythmia with or without corrective/ablative surgery, or any other heart condition under the care of a doctor
16. Chest pain (that is diagnosed as cardiac related) or trouble breathing on exertion
17. Ten percent or greater risk of developing a myocardial infarction or coronary death within the next 10 years, e.g. using the National Heart, Lung and Blood Institute's Risk Assessment Tool: http://cvdrisk.nhlbi.nih.gov/calculator.asp
NOTE: This criterion applies only to subjects 20 years of age and older
18. History of an immediate family member (father, mother, brother, or sister) who has had onset of ischemic heart disease before the age of 50 years
19. Clinically significant psychological disorder not adequately controlled by medical treatment
20. Active or history of chronic alcohol abuse and/or intravenous and/or nasal drug abuse (within the past 6 months)
21. History of anaphylaxis or any severe allergic reaction or serious adverse reaction to a vaccine
22. Eczema of any degree or history of eczema
23. People with active AD (characterized by pruritus, eczematous lesions, xerosis (dry skin), and lichenification (thickening of the skin and an increase in skin markings) or with a history of AD
24. People with chronic exfoliative skin disorders/conditions
25. People with active current Varicella zoster, Herpes zoster, impetigo, uncontrolled acne, Darier's disease, recent tattoos or skin piercing (until it is healed, but not within 4 weeks prior to trial vaccination), or any acute skin disorders of large magnitude, e.g., laceration requiring sutures
26. People with a tattoo that covers the vaccination injection area (preventing assessment of the area and interfering with a vaccination take assessment photograph)
27. Having received any vaccinations or planned vaccinations with a live vaccine (except trial vaccine) within 28 days prior to or after trial vaccination
28. Having received any vaccinations or planned vaccinations with a killed vaccine within 14 days prior to or after trial vaccination

29. Administration or planned administration of immunoglobulins and/or any blood products during a period starting from three months prior to administration of the vaccine and ending at trial conclusion
30. Use of any investigational or non-registered drug or vaccine other than the trial vaccines within 28 days preceding the first dose of the trial vaccine or planned administration of such a drug /vaccine during the trial period
31. Blood donation for the duration of the trial
32. Acute disease (illness with or without a fever)
33. Temperature ≥ 100.4°F (38.0°C)
34. Known household contacts with, or occupational exposure to (other than minimal contact) any of the following:

- Pregnant women
- Children <12 months of age
- People with eczema or a history of eczema
- People with active AD or history of AD
- People with chronic exfoliative skin disorders/conditions
- People with active Varicella zoster, Herpes zoster, impetigo, uncontrolled acne, Darier's disease or any acute skin disorders of large magnitude, e.g., laceration requiring sutures, burn greater than 2×2 cm
- People with active or recent immunodeficiency disease or use of immunosuppressive medications, for example: have or take medication for HIV, AIDS, leukemia, lymphoma, or chronic liver problem, have or take medication for Crohn's disease, lupus, arthritis, or other immune disease; have had radiation or X-ray treatment (not routine X-rays) within the last 3 months; have ever had a bone-marrow or organ transplant (or take medication for that); or have another problem that requires steroids, prednisone or a cancer drug for treatment
- People having had eye surgery within the last 4 weeks

35. Known allergy to MVA-BN® vaccine or any of its constituents, e.g. tris(hydroxymethyl)-amino methane, including known allergy to egg or aminoglycoside (gentamycin)
36. Known allergies to ACAM2000® and its diluents including polymyxin B sulfate, neomycin sulfate, and phenol
37. Known allergies to VIG including thimerosal or previous allergic reaction to immunoglobulins
38. Known allergies to cidofovir, sulfa drugs, Tecovirimat (ST246) or probenecid
39. Trial personnel

6 Investigational Product (MVA-BN®) and Comparator (ACAM2000®)

6.1 MVA-BN®

MVA-BN® is a highly attenuated live vaccinia virus. It will be provided as liquid-frozen aliquots in 2 ml glass vials. One dose of 0.5 ml vaccine has a nominal virus titer of $1x10^8$ $TCID_{50}$ MVA BN®. MVA-BN® will be given s.c.

For further details please refer to current version of the Investigator's Brochure.

6.1.1 Production, Packaging and Labeling

MVA-BN®:
The MVA-BN® bulk drug substance is produced at Bavarian Nordic A/S and the MVA-BN® final drug product is formulated, filled and labeled at the contract manufacturer (b) (1) (A) [redacted].

Addresses:

Bavarian Nordic A/S

(b) (1) (A) [redacted]

(b) (1) (A) [redacted]

(b) (1) (A) [redacted]

The packages and vials will be labelled with the US IND label.

6.1.2 Shipment, Storage and Handling

MVA-BN® will be shipped temperature controlled from the warehouse to the clinical trial site. The package is handed over to the personnel in charge of vaccine preparation, e.g. the pharmacist. After receipt of vaccine this personnel is responsible for proper storage.

Liquid-frozen MVA-BN® must be stored at -4°F ± 9°F (-20°C ± 5°C) avoiding direct light. A vial should not be re-frozen once it has been thawed. Details on shipment, storage and handling are provided in BN's SOP (b) (1) (A) entitled "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN® (IMVAMUNE®) and Recombinant MVA-based Vaccines in Clinical Trials".

6.1.3 Preparation, Administration and Dosage

The preparation of the vaccine will be performed by authorized personnel only.

Details on vaccine preparation, administration and dosage of MVA-BN® is provided in BN's SOP (b) (1) (A), entitled "Storage, Handling and Vaccination Procedures of Liquid Frozen MVA-BN® (IMVAMUNE®) and recombinant MVA-based vaccines in Clinical Trials".

6.1.4 Accountability and Disposal

After receipt of MVA-BN®, the clinical trial site personnel have the responsibility for distribution, proper storage and vaccine accountability. Logs of receipt, temperature, maintenance, and disposal must be maintained by the responsible personnel in the trial regulatory file.

Used and unused vials should be stored in a safe place and remain the property of BN. The personnel of the respective clinical trial site are responsible for ensuring adequate accountability of all used and unused MVA-BN®. This includes acknowledgement of receipt of each shipment of MVA-BN® (quantity and condition) and MVA-BN® accountability using an MVA-BN® inventory log. The MVA-BN® inventory log will document quantity of MVA-BN® received, quantity of MVA-BN® used for vaccination (including lot number, date dispensed, subject identification number and initials of the person dispensing MVA-BN®) and quantity of MVA-BN® returned to BN or destroyed.

Additionally, the quantity of MVA-BN® returned to BN or destroyed has to be documented on an MVA-BN® return/destruction form. In case destruction at the clinical trial site is agreed, material should be autoclaved or incinerated and discarded at the clinical trial site according to local regulations.

Furthermore, used syringes should be autoclaved or incinerated and discarded at the clinical trial site according to local regulations.

6.2 ACAM2000®

For details regarding shipment/storage/handling and preparation/administration/dosage of ACAM2000® please refer to the ACAM2000® prescribing information (Appendix IVc; Section 17.7). The clinical trial site will follow local procedures in line with DoD guidance.

6.2.1 Accountability and Disposal

The military trial site personnel have the ultimate responsibility for distribution, proper storage, vaccine administration and vaccine accountability of ACAM2000®. ACAM2000® vaccine given under the auspices of the Defense Health Agency (DHA) and clinical trial site will follow local procedures in guidance with DoD guidelines. Logs of receipt, temperature, maintenance, and disposal are the responsibility of the site personnel following local procedures in line with DoD guidance.

6.2.2 Treatment of Adverse Events after ACAM2000® Vaccination

A smallpox factsheet containing information for clinicians and public health professionals entitled: "Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidovovir" can be found on the CDC website:

http://www.bt.cdc.gov/agent/smallpox/vaccination/mgmt-adv-reactions.asp and is contained in Appendix V; Section 17.15: Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir of this CTP.

The US Health Affairs policy memorandum (Appendix IV; Section 17.4) offers useful advice regarding the management of AEs after vaccination. These clinical guidelines are available at the DHA Web site at www.vaccines.mil.

As stated in the US Health Affairs Memorandum issued by the US Assistant Secretary of Defense in April 2008, VIG is indicated for the treatment or modification of certain conditions induced by the smallpox vaccine. Consultation with a board certified infectious disease or allergy-immunology specialist is required prior to administration. The VHC Network will provide and coordinate professional consultation services to optimize clinical use of VIG, and then maintain a registry of patients treated with VIG. Long-distance consultations will be arranged via the VHC Network's Vaccine Clinical Call Center ((b) (1) (A)). An infectious disease or allergy immunologist, in consultation with the VHC, and CDC physician, authorizes release of VIG. VIG is requested directly from the CDC by calling the CDC Director's Emergency Operation Center at ((b) (1) (A)) and request to speak with the Division of Bioterrorism Preparedness and Response on-call person. The CDC is the release authority for VIG.

7 Assessment of Immunogenicity and Efficacy

7.1 Humoral Immune Response

Analysis of humoral immune response is planned to occur at Visit 1 (baseline measurement) through Visit 4 for both groups and additionally for the Group 1 subjects at Visit 6, Visit 7 and at Visit 10 and for Group 2 subjects at Visit 5 and 6. Baseline (i.e. Visit 1 [Week 0]), Visit 4 (Week 4) and Visit 7 (week 8) blood samples will be drawn prior to any scheduled vaccination.

The immune response measured at the Peak Visits by validated vaccinia-specific PRNT and vaccinia-specific ELISA will be used as the relevant immunologic response for the assessment of non-inferiority.

Antibody responses to MVA-BN® and ACAM2000® will be measured using a vaccinia-specific PRNT and a vaccinia-specific ELISA which were established and validated at BN. Endpoint GMT titers will be done on all subjects, independent from their baseline immune status. The tests will be performed at BN, Martinsried, Germany. All immunological clinical analysis personnel will be blinded to subject randomization details.

The methods for collection, storage and handling of lab specimens for the immune analysis are specified in a separate manual which will be provided to the investigators before enrollment. Additionally, training will be provided on the procedures during the investigator meeting and/or at the initiation visit. The protocols for the analytical tests performed are detailed in the BN SOPs listed below in the assay sections. Copies of the SOPs (from BN and the CRO), effective at the time of trial conduct will be filed in the Trial Master File.

7.1.1 PRNT

The PRNT GMT is calculated by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. Antibody titers below the ACV will be given an arbitrary value of one for the purpose of calculation.

The seroconversion rate is defined as the percentage of initially seronegative subjects with appearance of antibody titers ≥ the ACV in a vaccinia-specific PRNT using Vaccinia Virus Western Reserve as challenge virus.

Details on the PRNT assay procedure can be found in SOP (b) (1) (A): "Human Plaque Reduction Neutralization Test Using Vaccinia Virus Western Reserve".

7.1.2 ELISA

The ELISA GMT is calculated by taking the antilogarithm of the mean of the $\log_{10}$ titer transformations. Antibody titers below the ACV will be given an arbitrary value of one for the purpose of calculation.

The seroconversion rate is defined as the percentage of initially seronegative subjects with appearance of antibody titers ≥ ACV in a vaccinia-specific ELISA using MVA as antigen.

Details on the ELISA assay procedure can be found in SOP (b) (1) (A): "Automated ELISA for Detection of Vaccinia Specific Antibodies in Human Sera".

7.2 Future Use of Lab Specimen

Serum specimens remaining after completion of all immunogenicity analysis for the trial are planned to be stored for future analysis supporting the licensure path of MVA-BN®. Future analyses would facilitate bridging trial data to animal immunogenicity data and/or to immune response data collected from subjects vaccinated with conventional smallpox vaccines.

Subjects will be asked for consenting to future storage / use of samples and will be informed about data protection measures. Specimens will be stored in BN's secured laboratory area or at an external storage facility in a coded, anonymized manner to ensure data protection. Genetic testing will not be performed.

7.3 Measurement of the Take

A digital photograph will be taken of the vaccination site at the visits 6-8 days and 13-15 days after scarification with ACAM2000®.

The system for capturing the digital photographs and measuring the area of the lesion is described in detail in the ITRC Charter.

The ITRC will confirm the correct measurement of the lesion area by reviewing blinded subject profiles (as described in the ITRC Charter). Statistical calculations for attenuation of take will be based on the ITRC confirmed lesion areas.

The healing will be confirmed by the investigator at the appropriate scheduled visit.

7.4 Assessment of ACAM2000® Vaccination Site

The vaccination site will be examined by the Investigator or designee on Day 0 (prior to vaccination), and Days 7, 14 and 28 post vaccination with ACAM2000®. The day 6-8 examination (Visit 8 for Group 1 and Visit 2 for Group 2) is critical to the determination of a successful vaccination, and the day 13-15 examination (Visit 9 for Group 1 and Visit 3 for Group 2) is critical to the determination of the co-primary endpoint and subjects should be strongly encouraged to return for these clinical visits on schedule. The examiner shall wear protective gloves during each examination.

During the examination, the vaccination site will be examined and scored for the following parameters:

- healing time (i.e. number of days until scab separates from the skin)
- major lesion diameter (mm)
- major erythema diameter (mm)
- major induration diameter (mm).

If the shape of the lesion, erythema and induration observed is not round but rather asymmetrical then the maximum cross-sectional measurement would be recorded.

The type of lesion will also be noted (specifying papule, vesicle, pustule, ulcer, crust or scab).

In the unlikely circumstance that there is more than one lesion, this fact will be noted in the CRF but the satellite lesions would not be measured.

Individual take rates will be classified as either full, partial or absent take. The categorization will be in line with the World Health Organization (WHO) criteria for a “Major Reaction” as listed in

the US Health Affairs Memorandum issued by the US Assistant Secretary of Defense in April 2008 (Appendix IVf; Section 17.10), namely:

A vesicular (blistery) or pustular (pus-filled) lesion or area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

After primary (first) vaccination, the vaccination site usually progresses as follows (and will be referred to as "full take" in the POX-MVA-006 CTP):

- The inoculation site becomes reddened and pruritic 3 to 4 days after vaccination.
- A vesicle surrounded by a red areola then forms, which becomes umbilicated (collapsed center) and then pustular by days 7 to 11 after vaccination.
- The pustule begins to dry; the redness subsides; and the lesion becomes crusted between the second and third week, the scab falls off, leaving a permanent scar that at first is pink in color but eventually becomes flesh colored.

7.5 Independent Take Review Committee

BN has established the blinded ITRC consisting of 3 physicians experienced in scarification of replicating smallpox vaccines. The ITRC will assess the responses of subjects vaccinated with ACAM2000®. This committee will act independent of the DSMB. The purpose of having an ITRC to review subject profiles is to provide an independent determination of take responses and to assure a consistent evaluation of subject responses. A Charter describes the details of the committee's requirements, organization and obligations.

The ITRC's determinations will be considered the source data for the analysis of the individual takes observed in the MVA-BN®-experienced ACAM2000® boosted subjects (Group 1) and the MVA-BN®-naïve ACAM2000® vaccinated subjects (Group 2).

More information on the ITRC's assessment criteria can be found in the ITRC Charter.

8 Safety and Reactogenicity

Taking into account the medical history of the subject, safety will be monitored by performing physical examinations including vital signs, routine laboratory measurements as well as by evaluating local and general solicited AEs and unsolicited AEs.

Using replication-competent 1st and 2nd generation vaccinia-based smallpox vaccines during smallpox vaccination programs in the USA during the last years, cases of acute myocarditis and pericarditis were observed (Cassimatis, 2004). Therefore special cardiac monitoring assessments will be performed.

8.1 Definitions

8.1.1 Medical History

Symptoms present before or at the screening visit will be documented in the medical history.

8.1.2 Baseline Signs and Symptoms

Any new signs, symptoms or changes in health starting after ICD signed and before the first vaccination will be recorded in the "baseline signs and symptoms" section of the CRF and in the subject`s research record. Symptoms starting prior to ICD being signed will be documented in medical history.

8.1.3 Adverse Events

New signs, symptoms or changes in health starting after the first vaccination are documented in the AE section. AEs are recorded based on unsolicited and solicited questioning (Section 8.1.3.1 and 8.1.3.2).

8.1.3.1 Unsolicited Adverse Events

Unsolicited AEs are defined as any untoward (undesirable) occurrence of a medical event in a clinical trial subject temporally associated with the administration of an Investigational Medicinal Product (IMP) or a medical product (MP) which does not necessarily have a causal relationship with this IMP/MP. Up to Visit 10 all AEs (e.g. feeling of ill-health, subjective symptoms and objective signs, intercurrent diseases, accidents, etc.) observed by the investigator and/or reported by the subject must be recorded in the CRF regardless of the assessment of causality in relationship with the IMP/MP.

Abnormal laboratory values assessed as being clinically significant by the investigator are to be documented as AEs. In addition, abnormal laboratory values fulfilling the Grade 3 or Grade 4 criterion according to the toxicity scale (Appendix I; Section 17.1) are to be documented as AE in the CRF, regardless of whether they are considered clinically relevant or not. Toxicity grade and seriousness of an AE will be assessed separately, i.e. a Grade 3 or Grade 4 AE will not automatically be regarded as serious.

At every trial visit up to Visit 10 in Group 1 and up to Visit 4 in Group 2, the investigator will ask the subject if they have experienced any AEs since their last visit. All intercurrent diseases reported by the subject need to be recorded by the investigator in the appropriate page of the CRF.

8.1.3.2 Solicited Adverse Events

Within this CTP solicited AEs are defined as all symptoms specifically listed in the memory aid provided to the subjects following each vaccination. The subjects are requested to monitor and record local symptoms (i.e. pain, redness (erythema), swelling, induration, itching (pruritus) and

vaccination site appearance (normal/healed, red spot, bump, reddish blister, whitish blister, scab, ulcer/crater, warmth, swollen >3in, red streaks, drainage) as well as general symptoms (i.e. body temperature, headache, muscle pain (myalgia), chills, nausea, fatigue, malaise, swollen lymphnodes) in the memory aid daily for the day of vaccination and the following 14 days (days 0-14, 15 day period). Any symptoms persisting beyond Day 14 post vaccination are recorded in a memory aid extension. The definition of AEs originates from the MVA-BN® Investigator's Brochure and the ACAM2000® Prescribing Information (Appendix IVc; Section 17.7).

8.1.3.3 Adverse Event of Special Interest

An AESI is defined in this trial as:

- Any cardiac sign or symptom developed since the first vaccination
- ECG abnormalities determined to be clinically significant
- Cardiac enzyme troponin I ≥ 2 x ULN (≥Grade 2; see toxicity scale, Appendix I; Section 17.1)

8.1.3.4 Serious Adverse Events

A SAE is any untoward medical occurrence or reaction that at any dose:

- Results in death
- Is life-threatening
  The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death, if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- or is an otherwise important medical event, e.g.
  - leads to suspicion of transmission of an infectious agent
  - suggests lack of efficacy of the product
  - documents an overdose of the product

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are 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.

8.2 Assessment

8.2.1 Relevant Medical History

Relevant medical history will be documented at the Screening Visit and will focus particularly on any important diseases and in case of infections or tumors, the pathogen involved or the pathological diagnosis, if available. Special attention should be given to history of prior allergic reactions, especially to vaccines.

In addition, smallpox vaccination history will be assessed (check for a smallpox vaccine scar and any documentation (written/oral) of previous smallpox vaccination, if available).

8.2.2 Prior and Concomitant Medications

All concomitant (ongoing) medications except homeopathic substances and dietary supplements must be recorded in the CRF and in the subject`s medical record including information about the indication, dosage regimen, and the onset and end of treatment.

The following medications, taken within three months prior to screening, will also be recorded in the CRF: Vaccines, corticosteroids (via any route of administration), other immune-modulating drugs, immunoglobulins and/or any blood products, investigational drugs and depot preparations which are still active at the date of screening.

8.2.3 Physical Examination

Complete physical examination

A complete physical examination will be performed at the Screening Visit. The examination includes a review of major organ systems as well as height and weight. The examination should be directed at finding evidence of any infections, tumors and lymphadenopathy. In addition, auscultation of the heart and lungs to check specifically for signs of any heart condition will be performed.

Targeted physical examination

A targeted physical examination, guided by any signs or symptoms previously identified or any new symptoms that the subject has experienced since the last visit, is conducted at visits according to the Trial Procedure Schedule during the active trial phase. In addition, auscultation of the heart and lungs will be performed.

A grading scale for lymphadenopathy would apply as follows:

Grade 0 (normal finding): no palpable lymph nodes

Grade 1 (mild): lymph nodes up to a diameter of 1 cm, ipsilateral or bilaterally enlarged lymph nodes, signs of tenderness

Grade 2 (moderate): lymph node diameter greater than 1 cm, ipsilateral or bilaterally enlarged lymph nodes, pain, skin redness, warmth, limiting instrumental activities of daily living (ADL) (instrumental ADL refer to performing work related duties, routine physical training activities, etc.)

Grade 3 (severe): lymph node(s) diameter exceeds 2 cm, severe pain, general symptoms like fever and sweating limiting self-care activities of daily living (self-care ADL refer to performing personal needs, and not bedridden).

8.2.4 Vital Signs

Vital signs will be measured at visits according to the Trial Procedure Schedule. Blood pressure, respiration rate and pulse rate will be taken after the subject has been sitting for at least two minutes. Body temperature will be measured orally.

8.2.5 Unsolicited Adverse Events

During every trial visit following screening, the investigator has to report any unsolicited AE experienced by the subject.

All intercurrent diseases reported when the investigator actively inquiries from the subject will be documented in the source data and all required details (e.g. start and stop date, severity) will be assessed. Unsolicited AEs will be reported in the AE section of the CRF.

AEs will be assessed and documented at all visits of the active trial phase and if ongoing after the active trial phase followed until resolution or until the remote FU visit at the latest.

SAEs and AESIs will be assessed and documented at all trial visits, including the remote FU Visit. Ongoing AESIs and SAEs after first vaccination will be followed up until resolution or achievement of stable clinical conditions.

Assessment of Intensity

For all unsolicited AEs not represented in the Toxicity Scale for Laboratory Values (Appendix I; Section 17.1), grading of the maximum intensity will be based on the following descriptions:

Grade 1 An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with activities of daily living.

Grade 2 An AE which is sufficiently discomforting to interfere with activities of daily living.

Grade 3 An AE which prevents activities of daily living. (Such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.)

Assessment of Causality

The relationship between the occurrence of an AE and the IMP and the Comparator will be assessed using the categories presented below. For expedited reporting and all other purposes, the categories “none” and “unlikely” will represent no evidence or argument to suggest a causal relationship, while “possible”, “probable” and “definite” will be seen to convey that there is evidence or argument to suggest a causal relationship. Following worst case scenario all AEs without a causality assessment from the investigator will be classified as “possible”:

None	• The time interval between the administration of the IMP or Comparator and the occurrence or worsening of the AE rules out a relationship, and/or • another cause is established and there is no evidence of a (concomitant) causal connection with or worsening caused by the IMP or Comparator.
Unlikely	• The time interval between administration of the IMP or Comparator and the occurrence or worsening of the AE makes a causal relationship unlikely, and/or • the known effects of the IMP, Comparator or substance class provide no indication of a (concomitant) causal connection with or worsening caused by the IMP or Comparator and there is another cause which serves as an adequate explanation, and/or • although the known effects of the IMP, Comparator or substance class make it possible to derive a plausible causal chain with regard to a (concomitant) causal connection or worsening; however, another cause is considerably more likely, and/or • another cause of the AE has been identified and a (concomitant) causal connection with or worsening caused by the IMP or Comparator is unlikely.
Possible	• A plausible causal chain with regard to a (concomitant) causal connection with / worsening of the AE can be derived from the pharmacological properties of the IMP, Comparator or substance class. However, other approximately equally likely causes are known, or • although the pharmacological properties of the IMP, Comparator or substance class provide no indication of a (concomitant) causal connection with / worsening of the AE, there is no other known cause which provides an adequate explanation.
Probable	• The pharmacological properties of the IMP, Comparator or substance class, and/or • the course of the AE after discontinuation of the trial drug and possible subsequent re-exposure, and/or • specific findings (e.g. positive allergy test or antibodies against the IMP / Comparator / metabolites) suggest a (concomitant) causal connection with / worsening of the AE resulting from the IMP or Comparator; however another cause cannot completely be ruled out.
Definite	• The pharmacological properties of the IMP, Comparator or substance class and/or • the course of the AE after discontinuation of the IMP or Comparator and possible subsequent re-exposure, and/or • specific findings (e.g. positive allergy test or antibodies against the trial drug / metabolites) definitely indicate that there is a (concomitant) causal connection with / worsening of the AE resulting from the IMP or Comparator and there are no indications of other causes.

8.2.6 Solicited Adverse Events

After each vaccination subjects receive a memory aid to record solicited local and general AEs most likely to occur on the day of vaccination and the following 14 days (days 0-14; 15 day period).

All solicited symptoms observed after vaccination with details concerning the intensity and the course of the reaction should be documented there. The investigator or designee will collect this information during the following scheduled visits and transfer it to the CRF. Local and general reactions still ongoing after 14 days post vaccination will be measured or examined each day until resolution or Visit 10 (Group 1) or Visit 4 (Group 2) respectively.

In case of severe and unexpected local and/or general reactions, the subject should be instructed to contact the trial physician outside of scheduled trial visits.

8.2.6.1 Solicited Local Adverse Events

The solicited local symptoms pain, redness (erythema), swelling, induration, itching (pruritus) and vaccination site appearance (normal/healed, red spot, bump, reddish blister, whitish blister, scab, ulcer/crater, warmth, swollen >3in, red streaks, drainage) are to be documented in the memory aid by the subject.

To standardize procedures, uniform rulers will be handed out to all subjects for measurements of erythema, swelling and induration diameters, as will digital thermometers for oral measurements of body temperature.

Assessment of Intensity

Injection site erythema	size measured in diameter
Injection site swelling	size measured in diameter
Injection site induration	size measured in diameter

The maximum severity will be scored as follows:

0	=	0
1	=	< 30 mm
2	=	≥ 30 – <100 mm
3	=	≥ 100 mm

Injection site pruritus:

0	=	No symptoms
1	=	Mild: routine daily activities not impaired
2	=	Moderate: routine daily activities impaired
3	=	Severe: prevents routine daily activities

Injection site pain:

0 = No pain
1 = Pain when touched
2 = Pain when moving the limb
3 = Spontaneously painful

For red spot, bump, reddish blister, whitish blister, scabs, ulcers/craters, warmth, swollen > 3 in., red streaks or drainage the presence or absence of the symptom is captured in the memory aid. The injection site pruritus and injection site pain is rated by the subject in the memory aid.

Assessment of Causality

Solicited local AEs are defined as being related to the vaccine.

8.2.6.2 Solicited General Adverse Events

The solicited general symptoms body temperature, headache, myalgia, chills, nausea, fatigue, malaise, swollen lymph nodes, and are to be documented in the memory aid by the subject.

Assessment of Intensity

Subjects are asked to document the solicited general AEs in the memory aid as described in Table 3 below. In the subject's memory aid, the grading of maximum symptom intensity is described in basic, easily understood language based on the following descriptions:

Table 3 Grading of General Symptoms from the Subject's Memory Aid

MedDRA coded Preferred Term General AEs	Grade	Maximum Severity
Body temperature*	0	< 99.5°F (< 37.5°C)
	1	≥ 99.5 – <100.4°F (≥ 37.5 – < 38.0°C)
	2	≥ 100.4 – <102.2 F (≥ 38.0 – < 39.0°C)
	3	≥ 102.2 – <104°F (≥ 39.0 – < 40.0°C)
	4	≥ 104°F (≥ 40.0°C)
Headache, Myalgia, Chills, Nausea, Fatigue, Malaise,	0	No symptoms
	1	Mild: routine daily activities not impaired
	2	Moderate: routine daily activities impaired
	3	Severe: prevents routine daily activities
Swollen lymph nodes	Yes/No	

*Pyrexia is defined as oral temperature ≥ 100.4°F (≥ 38.0°C).

Assessment of Causality

Causal relationship between solicited general AEs and the vaccine will be assessed by the investigator using the same categories as for unsolicited AEs (see Section 8.2.5).

8.2.7 Cardiac Assessment

To evaluate the cardiac profile of MVA-BN®, targeted physical exams including auscultation of the heart and lung will be performed (Section 8.2.3). Any kind of cardiac signs (i.e. discovered by the physician during examination of the subject) or symptom(s) (i.e. experienced and reported by the subject) detected during the trial such as but not limited to chest pain, dyspnea, arrhythmia or edema are recorded.

ECG
A standard 12-lead ECG will be taken at the Screening Visit, at Visit 3 for both groups, and at Visit 9 for Group 1 only. At Visit 6 (for Group 1 only) an ECG is only done if clinically indicated. ECGs will be evaluated by a centralized procedure. The workflow and communication flow will be provided in a separate manual.

Cardiac Risk Factors
The individual cardiac risk factor is calculated before the first vaccination (for subjects 20 years of age and older), using the National Heart, Lung and Blood Institute's risk assessment tool (http://cvdrisk.nhlbi.nih.gov/calculator.asp). Subjects with a 10 percent or greater risk of developing a myocardial infarction or coronary death within the next 10 years are excluded from trial participation.

In addition, the family cardiac risk factor is evaluated at the Screening Visit. Subjects with an immediate family member (father, mother, brother, or sister), who has had onset of ischemic heart disease before 50 years of age are also excluded from trial participation.

Troponin I
Troponin I will be measured at the Screening Visit and at Visit 3, and at Visit 9 for Group 1 only. At any other visits troponin I will only be measured if clinically indicated.

Cardiac events fulfill the definition of an AESI as described in Section 8.3.2. The investigator will be asked to assess the clinical significance of the case.

Case definitions as published by the CDC (MMWR, May 30, 2003) are provided in Appendix III; Section 17.3 in order to:

- help investigators to recognize possible events of acute myocarditis and/or pericarditis and
- distinguish from unspecific and isolated ECG abnormalities without or with unclear clinical significance.

Questions:
The following specific cardiac questions will be routinely asked to the subject at the trial visits on the day of each vaccination; and the trial visits 2 weeks following each vaccination (Visits 3, 6

and 9 for Group 1; Visit 3 for Group 2) and 4 weeks following each vaccination (Visits 4, 7 and 10 for Group 1; Visit 4 for Group 2).

- Since your last visit, have you developed any chest pain, pressure, or discomfort that is beyond what is usual for you?
- Since your last visit, have you developed any shortness of breath at rest or exertion that is beyond what is usual for you?
- Since your last visit, have you noticed any swelling of your ankles, feet, or legs that is beyond what is usual for you?

If the answer to one of the question is "yes", further evaluations as outlined in Figure 1 are initiated.

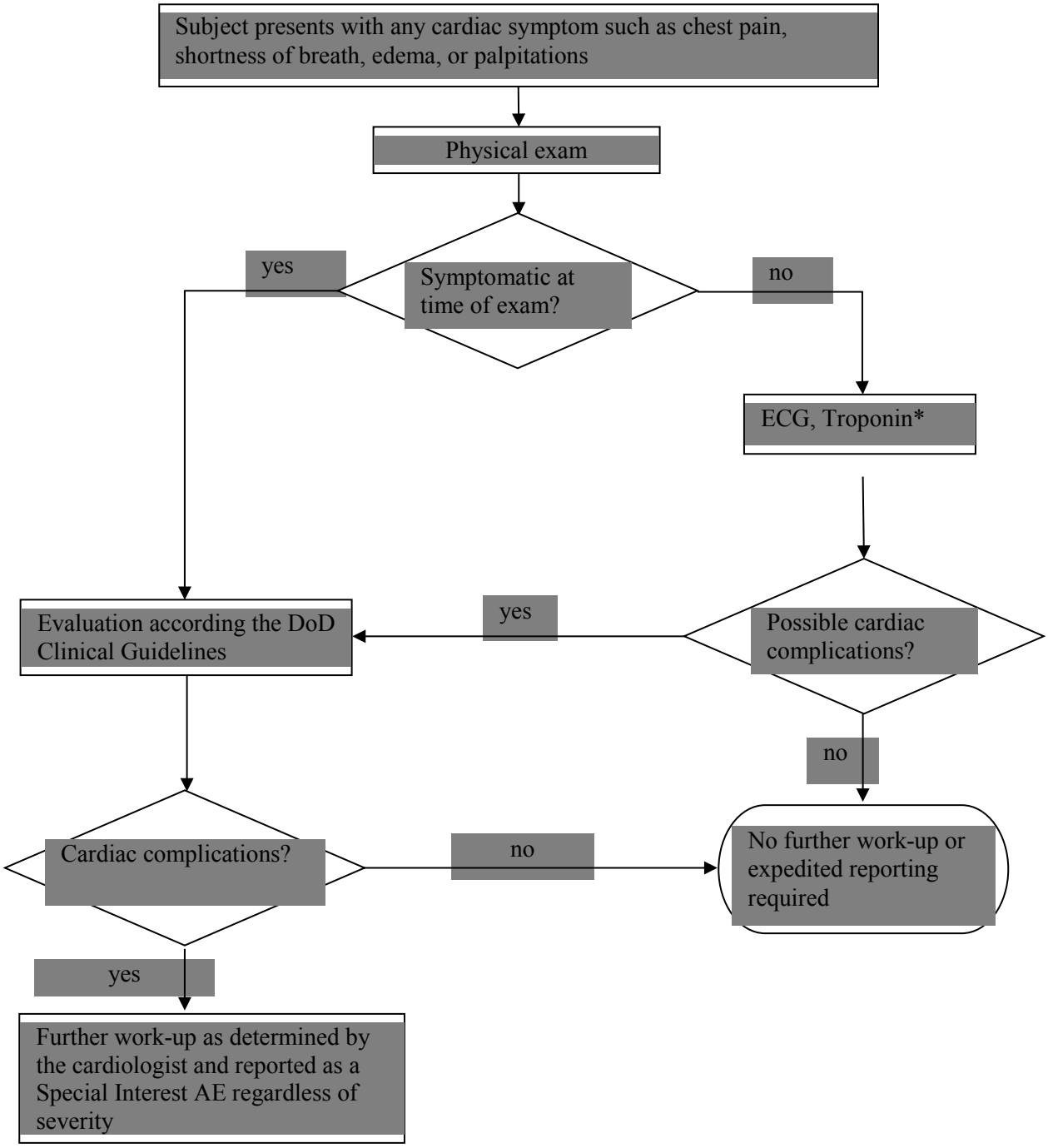
Subjects who develop any kind of cardiac signs or symptoms during the trial such as, but not limited to chest pain, dyspnea, arrhythmia or edema are referred to a local cardiologist for cardiac evaluation as described in the DoD Clinical Guidelines for Post-Smallpox Vaccine Associated Myopericarditis (Appendix II; Section 17.2). All treatment emergent AESIs will be followed up until complete resolution or until the sequelae are stable and considered to be permanent.

In any case of cardiac signs or symptoms, or increased laboratory results for Troponin I, the subject will be asked to attend for an unscheduled visit at the site, in order to perform or repeat Troponin I testing, to perform a physical examination for cardiac symptoms and to record an unscheduled ECG.

Further details regarding the follow-up of AESIs are described in the 'Investigator's Manual – Follow-up of Adverse Events of Special Interest'.

Figure 1 outlines the algorithm for assessment of cardiac events.

Figure 1: Algorithm for Assessment of Cardiac Events



*At any protocol-scheduled ECG and/or troponin I abnormality, the algorithm will begin at this point.

8.2.8 Safety Laboratory Measurements

The intensity of laboratory / systemic quantitatively measured toxicities will be graded according to the toxicity scale in Appendix I; Section 17.1. These grading scales include the laboratory values determined with the routine safety parameters. In case of other laboratory values not included in the routine safety laboratory and not listed in Appendix I; Section 17.1, the National Cancer Institute Common Toxicity Criteria Table, Version 4.03, published June 14, 2010 will be used for grading of laboratory toxicities.

Safety laboratory (hematology and serum chemistry) is determined at the Screening Visit and Visit 3 for all subjects and at Visit 6 and Visit 9 for Group 1 only. If clinically indicated Safety laboratory tests can be performed at any other visit(s). The safety laboratory measurements are performed at the site specific local laboratory. Laboratory normal ranges are provided by the local laboratory and filed in the Regulatory File. Safety laboratory parameters to be evaluated are:

Hematology:
Complete blood count (CBC) with total and differential white blood cell count (WBC)

Serum chemistry:
Total bilirubin, Alk Phos, AST, ALT, serum creatinine, sodium, potassium, calcium, troponin I (troponin I mandatory at the Screening Visit, Visit 3, Visit 9 and in addition at any other visits only if clinically indicated)

Pregnancy test:
A β-human choriogonadotropin (HCG) pregnancy test will be conducted for all WOCBP at screening, within 24 hours prior to each vaccination and at the individual last active trial phase visit . At Screening Visit, a serum β-HCG pregnancy test will be performed; all other pregnancy tests will be conducted as either urine or serum β-HCG tests.

The following parameters will only be evaluated during the screening period for assessment of inclusion / exclusion criteria:
HIV
Hepatitis B surface antigen
Antibodies against hepatitis C virus
Cholesterol (total Cholesterol, HDL, LDL)

8.2.9 Pregnancy

As per inclusion criteria, women of childbearing potential must have a negative serum pregnancy test at Screening Visit and a negative serum or urine pregnancy test within 24 hours prior to each vaccination. In addition, they must have used an acceptable method of contraception for 28 days prior to the first vaccination, must agree to use an acceptable method of contraception during the trial, and must avoid becoming pregnant for 28 days after the last vaccination. Nevertheless, IMP

exposed pregnancies cannot be excluded with certainty. Subjects who become pregnant prior to the first vaccination will be excluded from the trial and are regarded as screening failure. Subjects who become pregnant during the active trial period (up to and including one month [minimum 28 days] after receiving a dose of vaccine) must not receive additional doses of vaccine but may continue other trial procedures at the discretion of the investigator (Withdrawal from Further Trial Vaccination see Section 4.2.5). All IMP exposed pregnancies (i.e. up to 28 days after IMP administration) should be followed up until term or termination.

Subjects should be instructed to notify the investigator or designee if it is determined – also after completion of the trial - that they became pregnant either during the trial or within one month (minimum 28 days) after receiving the last vaccine dose.

8.3 Reporting

8.3.1 Reporting of Serious Adverse Events

All SAEs occurring throughout the entire course of the trial have to be reported to the CRO Drug Safety (DS) Department. The clinical trial site has to send by e-mail or fax the completed SAE form to the CRO DS Department within 24 hours of becoming aware of the SAE.

SAE reports should be faxed to the following number:

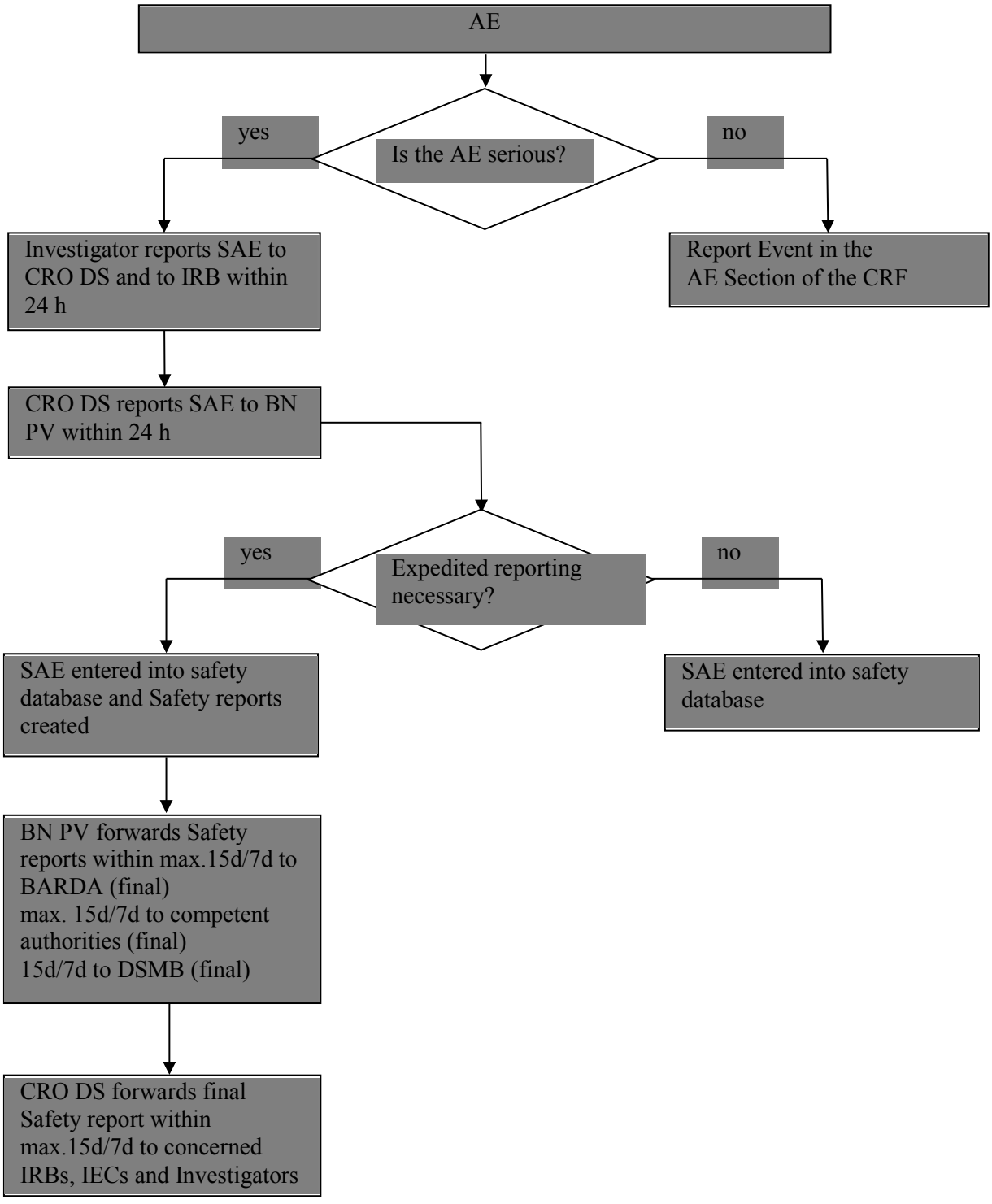
(b) (1) (A) [redacted]

The investigator should not delay reporting because of missing information. Nonetheless, the report should be as complete as possible. This initial notification should include, as a minimum, sufficient information to permit identification of the following:

- the reporter (investigator's name and contact information)
- the subject
- involved trial medication
- AE(s)
- Seriousness criterion and/or criterion for AE
- date of onset

The CRO DS Department alerts BN Pharmacovigilance (PV) Department of all SAEs and provides the available information within 24 hours. BN is responsible for expedited as well as periodic reporting to the involved regulatory authorities (e.g. FDA, Paul-Ehrlich-Institut) according to applicable laws and guidelines. Regulatory authorities will be notified as soon as possible but no later than 7 days after first knowledge of fatal or life-threatening unexpected SAE with an at least possible relationship to the IMP (serious adverse drug reaction [SADR]) and no later than 15 days after knowledge of any other unexpected SADR. In addition BN will report the SAEs to the responsible Biomedical Advanced Research and Development Authority (BARDA) representative when applicable and forward them to the DSMB. All unanticipated problems involving risk to subjects or others and SAEs related to trial participation will be promptly reported to the HQ USAMRMC IRB by phone ((b) (1) (A)), by e-mail ((b) (1) (A)), or by facsimile ((b) (1) (A)), or sent to the U.S. Army Medical Research and Materiel Command, ATTN: (b) (1) (A) . A complete written report will follow the initial notification. All other adverse events will be reported at Continuing Review. Figure 2 outlines the reporting process and timelines for SAEs.

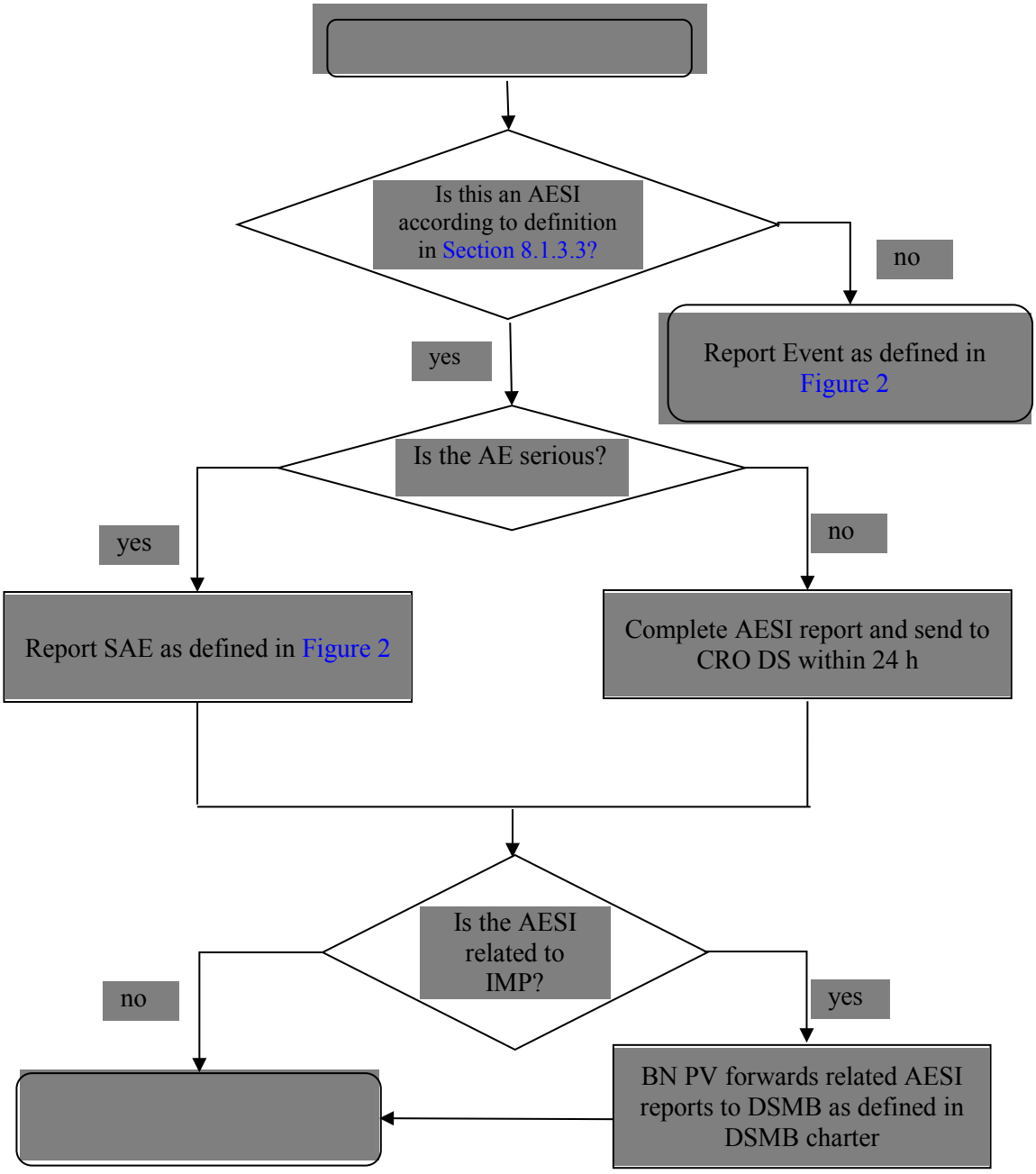
Figure 2 Algorithm for Reporting of SAEs



8.3.2 Reporting of Adverse Event of Special Interests

AESIs occurring throughout the entire course of the trial will be reported as outlined in Figure 3.

Figure 3 Algorithm for Reporting of AESIs



8.3.3 Reporting of Pregnancy

If a subject becomes pregnant during the active trial period (up to and including one month [minimum 28 days] after receiving a dose of vaccine) this pregnancy must be reported to BN on a Pregnancy Report Form within 24 hours of the investigator's becoming aware of the event. If ACAM2000® is administered during pregnancy or if the vaccinee lives in the same household with or has close contact with a pregnant woman the vaccinee should be apprised of the potential hazard to the fetus. These cases will be reported to the OHU&E and/or HQ USAMRMC IRB as appropriate.

A reportable pregnancy should be followed to term, any premature terminations reported, and the health status of the mother and child including date of delivery and the child's gender and weight should be reported to BN as soon as possible after delivery.

Any event during pregnancy fulfilling the criteria for an SAE will be reported as SAE to BN PV. However, hospitalization for delivery is a prospectively planned hospitalization and is not considered a SAE per se.

8.3.4 Health Recordkeeping Requirements for Investigational New Drug Products

In accordance with Army Regulation (AR) 40-562, all IND vaccines that are administered must be recorded in the individual's permanent health record or DoD approved electronic Immunization Tracking System. For vaccines, the documentation is the same as that required for other vaccines with an annotation "IND" with the vaccine name. This recordkeeping requirement is in addition to any recordkeeping requirements of the FDA-approved IND protocol.

9 Statistical Considerations

9.1 Randomization Procedure

Randomized treatment assignments for the subjects will be done after confirmation of subject's eligibility. The randomization will be performed in a 1:1 ratio using a validated Interactive Web Randomization (IWR) portal provided by a third party organization (Endpoint). Endpoint will store the randomization list in a secure environment. A fixed block size will be used for the randomization, but the block size will not be generally known by the clinical trial team.

9.2 Co-Primary Trial Hypotheses

9.2.1 Immunogenicity Hypothesis

The immunogenicity co-primary endpoint is to assess non-inferiority of MVA-BN® compared to ACAM2000® in terms of antibody response at the Peak Visit, i.e. 28 days after an ACAM2000®

vaccination and 42 days after the first MVA-BN® vaccination measured by validated vaccinia-specific PRNT.

Suppose m1 is the PRNT $\log_{10}$ titer mean in Group 1 (MVA-BN® followed by ACAM2000®) and m2 is the PRNT $\log_{10}$ titer mean in Group 2 (ACAM2000® only). The test of non-inferiority will be applied for the following hypothesis:

H0: $m1 - m2 \leq -\Delta$ versus H1: $m1 - m2 > -\Delta$ where

Δ is the non-inferiority margin. For the PRNT the non-inferiority margin will be 0.301 on the $\log_{10}$ scale (which is equivalent to a doubling on the original titer scale for the GMT). This is the same Δ as was used for the assessment of non-inferiority of ACAM2000® to Dryvax® (ACAM2000 VRBPAC Briefing Document, April 2007).

The above hypotheses will be tested for the PRNT using a t-test on the difference of the two means based on the assumption that the $\log_{10}$ titer values have a normal distribution (which has been the case in all previous MVA-BN® studies). Specifically, a one-sided 97.5% confidence interval for the difference of the $\log_{10}$ titer means (based on the assumption of a common standard deviation [SD]) will be calculated. If the lower limit of this confidence interval is greater than $-\Delta$, then the null hypothesis will be rejected for the respective assay and non-inferiority of MVA-BN® to ACAM2000® will have been demonstrated.

9.2.2 Efficacy Hypothesis

The efficacy co-primary hypothesis of the trial is to assess if the median of the MLA following ACAM2000® vaccination is significantly reduced for subjects in Group 1 who received prior MVA-BN® vaccinations compared to those in Group 2 who received no prior MVA-BN® vaccinations. Specifically the ratio of each median plus one will be tested:

$H_0: \ 1 - \frac{M_1}{M_2} \leq \lambda$ versus $H_1: \ 1 - \frac{M_1}{M_2} > \lambda$

i.e. the null hypothesis (H_0) is that 1 minus the ratio in median MLA in Group 1 (M_1) over the median MLA in Group 2 (M_2) is less than or equal to a predefined constant λ, which is tested against the one-sided alternative hypothesis (H_1) that the ratio > λ. This test will be performed by using the 95% asymptotic Hodges-Lehmann confidence interval (Lehmann, 1975) on the log10 MLA values and the confidence limits will be anti-logged back on to the original scale (see Statistical Analysis Plan for further details). Specifically, only the anti-log of the upper 95% Hodges-Lehmann confidence interval of the log10 MLA values between groups is used, with a one-sided significance level of 2.5%, and this needs to be below 1-λ for the null hypothesis to be rejected, and thus the co-primary endpoint will be met. However, for completeness the upper and lower confidence limits along with the point estimate of the Hodges-Lehmann shift estimator (which can be slightly different from the ratio of medians) will be reported. Note that a positive

offset of 1 will be added to any zero MLA values in order to avoid problems with taking logarithms of zero.

The clinical justification of the choice of λ=40% is that this is the reduction that has been seen in vaccinia-experienced subjects compared to vaccinia-naïve subjects who were (re-)vaccinated with a first generation smallpox vaccine (Talbot, 2006) and is discussed further in the attached Statistical Analysis Plan.

If one or both of the day 6-8 or day 13-15 photographs are missing then the photograph will be recorded as missing and the assessment of attenuation will not be made.

9.3 Endpoints

9.3.1 Co-Primary Endpoints

- PRNT GMT at the Peak Visits
- MLA in mm^2 after scarification with ACAM2000®

9.3.2 Secondary Endpoints

Immunogenicity

GMT at the Peak Visits and individual peak measured by vaccinia-specific ELISA.

GMTs at the individual peak measured by vaccinia-specific PRNT.

GMTs at all antibody blood sample time points measured by vaccinia-specific PRNT and vaccinia-specific ELISA.

PRNT seroconversion rates at Peak Visits defined as the percentage of initially seronegative subjects with appearance of antibody titers equal or greater than the ACV in a vaccinia-specific PRNT.

ELISA seroconversion rates at Peak Visits defined as the percentage of initially seronegative subjects with appearance of antibody titers equal or greater than the ACV in a vaccinia-specific ELISA.

Efficacy

Investigator assessed Maximum Lesion Diameter (MLD) in mm after scarification with ACAM2000®

Investigator assessed Lesion diameter in mm at Day 6-8 after scarification with ACAM2000®

Investigator assessed Lesion diameter in mm at Day 13-15 after scarification with ACAM2000®

The individual take will be classified as either full or partial or absent take by a blinded ITRC.

Lesion area in mm² at day 6-8 after scarification with ACAM2000®

Lesion area in mm² at day 13-15 after scarification with ACAM2000®

(The correct measurement of the lesion area will be confirmed by a blinded ITRC).

Safety and Reactogenicity

Occurrence, relationship to vaccine and intensity of any SAE.

Occurrence of any cardiac sign or symptom indicating a case of myo-/pericarditis, i.e. AESIs

Occurrence of any Grade 3 or 4 AEs possibly, probably or definitely related to vaccine within 28 days after each vaccination.

Occurrence, relationship to vaccine and intensity of any non-serious AEs within 28 days after each vaccination.

Occurrence of solicited general AEs (body temperature, headache, myalgia, chills, nausea, fatigue, malaise, swollen lymph nodes) within 15 days after each vaccination (days 0-14): Intensity, duration and relationship to vaccination.

Occurrence of solicited local AEs (pain, redness (erythema), swelling, induration, itching (pruritus), and vaccination site appearance (normal/healed, red spot, bump, reddish blister, whitish blister, scab, ulcer/crater, warmth, swollen >3in, red streaks, drainage) within 15 days after each vaccination (days 0-14): Intensity and duration.

Daily measurement of lesion size, erythema and induration based on physical appearance of vaccination site as documented in the memory aid.

- major lesion diameter (mm) each day
- major erythema diameter (mm) each day
- major induration diameter (mm) each day

If the shape of the lesion, erythema (excludes lymphangitis) and induration observed is not round but rather asymmetrical then the largest (or major) cross-sectional measurement would be recorded.

9.4 Sample Size Calculation

The immunogenicity co-primary objective of the trial is to demonstrate that the main immunogenicity endpoint can be met, i.e. to demonstrate the non-inferiority of MVA-BN® to ACAM2000® in terms of neutralizing antibody response at the Peak Visit. Hence the following sample size calculation was performed for the main immunogenicity endpoint.

Assuming a standard significance level of 5%, a power of ≥ 90% and the same expected PRNT GMTs in the MVA-BN® group and the ACAM2000® group, then the only remaining parameter is the SD of the $\log_{10}$ mean of the titers. As a basis for calculation, the overall calculated value of this SD at Visit 4 in 3 phase II MVA-BN® trials (POX-MVA-005, POX-MVA-008, POX-MVA-011) is 0.807. However, this value of 0.807 is an estimate and an approximate 95% confidence interval can be placed around it, namely (0.756, 0.866). Adopting the worst case scenario of the upper limit of the confidence interval, i.e. SD = 0.866, this yields a required sample size for this trial of 175 in the PPS in both groups.

In order to account for an approximate 20% rate for exclusion from the PPS, a total of 220 subjects will be recruited into each of the groups.

The efficacy co-primary endpoint is to determine if there is a relative reduction in MLA between the two groups. Using the Hodges-Lehmann method, the confidence interval of the median of the differences of the log10 MLA values of the two groups was calculated.

To calculate the likely power for this analysis data from the NIH sponsored POX-MVA-002 trial was used as a basis for calculations, which was performed using Bootstrap methodology. In the POX-MVA-002 trial some subjects were randomly assigned either MVA-BN®/MVA-BN®/Dryvax® (M/M/D) or Placebo/Placebo/Dryvax® (P/P/D). After the Dryvax® vaccination, the major diameter of the lesion was measured at various visits, including a Day 6-8 visit and a Day 13-15 visit. From these the maximum lesion area was also estimated by assuming the lesions were elliptical with a major axis given by the reported diameter, which was twice as large as the minor axis of the ellipse. It should be noted that assuming the lesions to be perfectly circular generates the largest possible difference in areas for two different diameters, and therefore is the best possible scenario for the power calculation. The assumption of the lesion having an elliptical form is considered a more realistic assumption.

Using this data a simple case resampling non-parametric bootstrap simulation was performed to estimate the likely ratio of the medians of the maximum lesion area that could be detected using the above test with 90% power. The proposed sample size of n=175 subjects in the PPS of each group gave a power at least 90% to show a significant reduction in the median of Group 1 compared to the median of Group 2 of at least λ=40% (further details of the calculations are given in the attached Statistical Analysis Plan).

Hence the overall power for meeting both co-primary endpoints is at least 80% (as 90% × 90% > 80%).

9.5 Trial Cohorts/Datasets to be Evaluated

For the statistical analysis the included subjects will be divided up into the following datasets:

Full Analysis Set (FAS): This is the subset of subjects who received at least one dose of vaccine and for whom safety data are available.

The analysis of safety will be performed on this analysis set.

Per Protocol Set (PPS): This is the subset of subjects who adhere to all protocol requirements applicable to that particular trial group for the active trial phase without a major protocol violation. The decision whether a protocol deviation is major or not, for the classification of subjects to subsets, will be made case-by-case in a data review meeting prior to database closure.

The primary endpoint dataset will be the PPS. All confirmatory testing is based on this subgroup. For further descriptive purposes, the same statistical procedures will be applied to the FAS.

Initially Seronegative Subset (ISS): A subject of the PPS will be part of the initially seronegative subgroup, if the subject is seronegative for both ELISA and PRNT at baseline. The immunogenicity analysis will be repeated on this subgroup as a robustness analysis to confirm that there is no effect on the result of subjects who may have been initially seropositive influencing the analysis.

9.6 Biometrical Evaluation

As soon as the last subject has completed the remote FU and after any necessary settlement of queries etc. in the CRFs, data will be locked. A full analysis of the data available will be performed.

All data obtained in this trial and documented in the CRFs will be listed. For parameters of interest, summary tables with descriptive group statistics for continuous variables will be prepared. For ordinal/dichotomous variables summary tables showing the absolute and relative count in each category will be prepared.

Full details of the analyses will be defined in a Statistical Analysis Plan which will be finalized prior to database lock. The CRO will be responsible for data management and statistical evaluation. Data will be analyzed using SAS®. The procedure for accounting for missing, unused and spurious data will be given in the Statistical Analysis Plan.

Antibody titers and resulting seroconversion rates will be assessed by vaccinia-specific PRNT and vaccinia-specific ELISA methods as described in Section 7. The primary immunogenicity

endpoint are the GMTs for PRNT at the Peak Visit (the most important secondary immunogenicity endpoint are the GMTs for the ELISA at Peak Visit). The primary immunogenicity hypothesis is to show that the humoral immune response of the trial Group 1 is not statistically inferior compared to the trial Group 2 for the PRNT endpoint.

In a first step, the co-primary null hypotheses, as stated in Section 9.2, will be tested. All statistical tests for secondary endpoints and comparisons are regarded as descriptive. No adjustment for multiple testing will therefore be done.

Clinical laboratory test results will be marked whether the result is below, within or above the respective reference range. The number of values outside of the reference range will be counted.

The ECGs will be evaluated by a centralized procedure as described in the ECG Assessment Plan. Detailed descriptive analysis of the reasons/category of ECG abnormalities will be performed.

The occurrence of solicited local and general AEs within 2 week after each vaccination will be summarized on a per subject and per vaccination basis.

Unsolicited AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding terminology. The intensity of unsolicited AEs will be graded according to Section 8.2.5.

AESIs will be separately listed and tabulated.

SAEs will be listed separately. Each SAE will be described individually in detail.

10 Ethical Aspects

10.1 Ethical and Legal Regulations

The PIs are to ensure that this clinical trial is conducted in complete accordance with the provisions of the 2013 version of the Declaration of Helsinki, the Belmont Report, the national laws and other guidelines for the conduct of clinical trials like ICH GCP to guarantee the greatest possible subject protection.

10.2 Good Clinical Practice

The procedures set forth in this protocol are designed to ensure that all protocol personnel abide by the national laws in which the trial is conducted, Code of Federal Regulations (CFR) governing IRBs and informed consent (32 CFR 219 and Army Regulation (AR) 70-25), USAMRIID 70-25, and ICH Guidelines for GCP and protection of human subjects. Clinical research protocols using FDA-regulated investigational products will be conducted in accordance with Title 21 CFR, Title 32 CFR, and Defense and Army regulations including DODI 3216.01 ,

DODI 3216.02, DODI 6200.02 , AR 40-38 (for clinical investigations), and AR 70-25 (for RDT&E research) to afford research participants protection of their rights and welfare.

Proper training of the investigational staff, a careful Informed Consent process, and the oversight of an IRB experienced in the review of clinical research involving military staff will be used to assure that their trial participation is ethical.

The PI confirms this by signing this protocol.

10.3 Approval by an IEC/IRB

Prior to initiation of the trial, the PI or designee will submit the trial protocol, sample ICD, recruiting message/poster and/or e-mail, and other requested documents to the Institutional Review Board (IRB) for review and approval. It is the responsibility of the Investigator or the research site coordinator to promptly report changes or unanticipated problems during the conduct of the trial and submit annual and final study reports to the IRB as required.

All changes to the protocol must be submitted for review and approval by the HQ USMRMC IRB before initiating the changes. The ICD must be revised to concur with any modifications, as appropriate, and also must be reviewed and approved with the modifications. A subject already enrolled in the trial will be informed about the revision and asked to sign the revised ICD if the modification directly affects the subject. A copy of the revised, signed, and dated ICD will be given to the subject. All original versions of the ICD will be retained as part of the subject's trial record and retained at USAMRIID.

The protocol must be reviewed by the competent IEC/IRB according to the national laws of the respective clinical trial site before the first subject is included in this trial.

To especially cover the ethical aspects of subjects in a military setting, a respective IRB approved by the DoD will review all relevant trial documents.

If one of the investigators is a member of one of these committees, he/she may not vote on any aspect of the review of this protocol.

The Sponsor will assure that the IEC / IRB is informed of any amendment to the protocol and any unanticipated problems involving risks to human subjects included in the trial. Such information will be provided to the IEC / IRB at intervals appropriate to the degree of subject risk involved, but not less than once a year. Copies of all correspondence between the investigator and the IEC / IRB must be forwarded immediately to the Sponsor. In case of withdrawal of IEC / IRB approval of the trial, the Sponsor has to be contacted immediately by facsimile, e-mail or telephone.

10.4 Confidentiality and Data Protection

The PI of the respective clinical trial site is obliged to ensure anonymity of the subject. He/she has to make sure that all documents including CRFs provided (e.g. in the course of a marketing authorization procedure) to third parties (in this case: to the manufacturer of MVA-BN® or to an authority) contain no subject names.

Only a subject and center number may identify subjects. Their name or medical record number may not be used. The PI keeps separate confidential subject logs for trial enrollment which allows subject numbers to be matched with names and addresses of subjects at any time. Documents not meant to be passed on to third parties have to be stored confidentially by the PI. According to USAMRIID policy, each individual enrolled in the trial will be assigned a subject's identification number following the format identified in the USAMRIID SOP (b) (1) (A): Clinical Trials Enrollment: Assignment of Subject Study Identification Numbers and Documentation of Subject Study Participation. Upon receipt of an individual's consent, the volunteer will be considered officially enrolled as a trial participant. Subject information will be entered onto the current version of the USAMRIID Study Enrollment/Withdrawal Log (USAMRIID SOP (b) (1) (A)).

In addition, Subject Identification Numbers (SIN) will be used in the event it becomes necessary to identify data specific to a single subject. All data and medical information obtained about subjects during the course of this research will be considered privileged and confidential. Subjects will not be identified by name in any published report, presentation of results, or protected health information (PHI) provided to collaborating institutions (Privacy Act of 1974, 5 U.S.C., Section 552A and AR 340-21). Completed trial records to include signed ICD, logs, CRFs will be stored in a secure fashion by the PI (or a designee) at USAMRIID. Representatives of the USAMRIID OHU&E and the HQ USAMRMC IRB may review research records as a part of their responsibility to protect human volunteers in research.

Clinical members of the team will be able to identify subjects because of the written consent process to be followed. The Health Insurance Portability and Accountability Act (HIPAA) requires that researchers obtain volunteers' permission (Authorization) to use health information about them that is either created by or used in connection with the research proposed in this protocol. For this trial, PHI will include a volunteer's medical/immunization records, and clinical data obtained during the course of this trial. There is no expiration date for this Authorization.

Data that are considered PHI under HIPAA legislation as described earlier are coded, linked to subjects only via a SIN, and acceptable under HIPAA as a limited data set. Identified data (signed consent documents and enrollment logs linking subject names and SINs) collected during the course of the trial will be given to the PI (or designee) and maintained in a secure fashion in accordance with standard procedures at USAMRIID.

Activities pertaining to this trial will be performed in compliance with HIPAA legislation. Government and contractor staff will be trained in the provisions of the HIPAA prior to contact with trial subjects. Certifications for staff already trained will be submitted to USAMRIID for approval. The PI will be responsible for retaining sufficient information about each subject, i.e., name, address, telephone number, social security number, and identity in the trial so that the USAMRIID OHU&E AND HQ USAMRMC IRB may have review this information should the need arise. There is the possibility that findings from analysis of the blood provided for this trial may be used in other research studies and could potentially have some commercial application.

Any information collected in the course of the trial may be made available only to persons directly involved in this trial (PI and his staff members, monitors, statisticians) or to authorized persons by the Sponsor or the PI or authorities. The Sponsor of the trial will only receive pseudonymized data for analysis.

11 Informed Consent

Written informed consent, in compliance with 21 CFR 50, 32 CFR 219, AR 70-25 and ICH guidelines will be obtained before any trial-related procedures are initiated. The PI or designee will present the protocol in lay terms to the subject singly or in groups. Unit officers and senior NCOs in the chain of command will not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects (DODI 3216.02). However, it is not the intent to recruit from assembled units. Questions regarding the nature of the protocol, the means by which the trial is to be conducted, and the risks to the participants will be solicited on an individual basis. Any question that cannot be answered by the investigator or designee will be referred to the PI. No subject will be expected to grant consent until questions have been answered to his/her satisfaction. By signing the appropriate place(s) on the IRB approved ICD, subjects are giving permission for the following:

- Blood samples to be collected as specified in this protocol
- Trial personnel to access PHI per HIPAA Authorization
- Authorize the monitor, quality assurance personnel (of the CRO and Sponsor) and regulatory authorities to inspect source documents for quality assurance purposes. (Such verifications will always be conducted at the clinical trial site and under the ethical supervision of the PI. All aspects of the confidentiality of the subject's data will be guaranteed.)
- Unused serum to be stored for possible future testing.

Informed consent principle mandates that subjects be informed of the primary potential risks and benefits of participating in the trial. This information will allow the subject to make a personal risk-versus-benefit decision and understand the following general principles:

- The individual is free to ask any questions that will allow him/her to understand the nature of the protocol
- Participation is entirely voluntary
- Refusal to participate involves no penalty
- Withdrawal from participation at any time is allowed without penalty or loss of benefits to which the subject is otherwise entitled.

The ICD must be signed and dated and retained by the PI as part of the trial records. Should the protocol be modified, the ICD must be revised to reflect the changes to the protocol. If the subject is directly affected by the change, the volunteer will receive a copy of the revised ICD for review. If the subject decides to continue participation then the subject must sign and date the ICD. Each subject will receive a copy of the signed and dated ICD.

The informed consent regulations of Title 21, Part 50 (Protection of Human Subjects) of the CFR require a statement in the informed consent document regarding the availability of clinical trial information on ClinicalTrials.gov. In accordance with Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) a description of this clinical trial will be made available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. The Web site will not include information that can identify the subject. At most, the Web site will include a summary of the results.

A signed copy of the informed consent must be given to each subject and the signed original must remain at the clinical trial site and be available for verification by the monitor or competent regulatory authorities at any time.

12 Case Report Forms and Retention of Records

12.1 Case Report Forms

In this trial, an electronic CRF will be used.

All CRFs are to be filled out completely by the trial personnel, then reviewed and signed by the PI or designee to confirm their correctness.

It is the PI’s responsibility to ensure that all subject data entered including discontinuations or changes in trial or other medications in the CRF are accurate and supported by the subject's medical records unless the CRF has been declared as source documentation by BN. The CRFs for any subject leaving the trial should be completed at the time of the final visit or shortly thereafter.

12.2 Retention of Records

Essential documents as listed in ICH GCP need to be archived according to ICH GCP and national law, whatever is longer.

To meet regulatory requirements, the original source data and a copy of the CRF data will be stored at USAMRIID. In case an electronic CRF will be used in the trial, data will be stored and archived according to the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Modeling (ODM) (see www.cdisc.org for details). Since CDISC ODM is also the source for the Electronic Data Capture-web-based system, no transcription of data is necessary. If needed, paper copies (file printouts) can be created from the ODM file.

It is the policy of the USAMRMC that data sheets are to be completed for all subjects participating in research (Form 60-R, Volunteer Registry Data Sheet). The data sheets will be entered into this Command's Volunteer Registry Database. The information to be entered into this confidential data base includes the subject's name, address, and Social Security Number; study title; and dates of participation. The intent of this data base is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that USAMRMC can exercise its obligation to ensure research subjects are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years. The Volunteer Registry Database is a separate entity and is not linked to the study database. Copies of forms completed for the database (60-Rs) are kept in the regulatory file for the protocol.

12.3 Monitoring of the Trial

A Clinical Research Associate (CRA) will be contracted by BN to perform monitoring services according to ICH GCP.

Monitoring will be conducted according to the monitoring plan which must be approved by BN and the CRO. The monitoring plan will specify in detail the items for source data verification and other tasks to be performed by the CRA during the clinical trial site visit.

The CRA is responsible for obtaining an overview of the course of the trial in co-operation with the investigators, checking if the clinical trial protocol is being observed, and helping the investigators to solve any problems which may arise. All documents in the context with this clinical trial will be handled confidentially at all times.

The PI has agreed to give the CRA access to relevant hospital or clinical records to confirm their consistency with the CRF entries and to obtain an adequate overview of the course of the trial. The CRA verifies that the entries in the CRF are complete, accurate, correct and supported by source documents. In addition the CRA will verify that all required data documented in the

source were transferred accurately in the CRF. This will be done under preservation of data protection.

The source data verification must be performed by direct insight in the subject's medical record. If a subject refuses to consent to this procedure, he/she may not be enrolled in the trial. The clinical trial site will provide direct access to all trial related data for the purpose of monitoring and auditing by local and regulatory authorities. The PI (or a representative) has further agreed to support the monitor in solving any problems he/she discovers during his/her visits.

13 USAMRIID Relevant Administrative Procedures

13.1 Protocol Modifications

All changes to the protocol must be submitted for review and approval by the HQ USMRMC IRB before initiating the changes. The ICD must be revised to concur with any modifications, as appropriate, and also must be reviewed and approved with the modifications. A subject already enrolled in the trial will be informed about the revision and asked to review and (if in agreement) sign the revised ICD if the modification directly affects the subject. A copy of the revised, signed, and dated ICD will be given to the subject. All original versions of the ICD will be retained as part of the subject's trial record and retained at USAMRIID or other secured storage facility for 75 years, per USAMRIID regulations.

13.2 Exceptions

An exception is any action that differs from the current version of the protocol and is not part of the ordinary operations or standards regarding trial procedures. Prior to implementation, such exceptions will require approval by the IRB to include the HQ USAMRMC IRB .

13.3 Protocol Deviation Procedures

The PI or designee will be responsible for identifying and recording all deviations which are defined as isolated occurrences involving a procedure that did not follow the protocol or a protocol-specific procedure. All deviations from the protocol and actions taken will be recorded on the appropriate CRF and placed in the trial specific regulatory file. Any deviation from the protocol that affects subjects' safety or rights and/or the integrity of the study must be promptly reported to the HQ USAMRMC IRB (e-mail: (b) (1) (A) [redacted] and include them in the annual and final trial reports..

13.4 Compensation

Subjects will receive $50 compensation for each trial blood draw. Subjects will be paid for trial blood draw within an appropriate time frame. Compensation for this protocol will comply with

24 USC 30 and DoDI 3206.02. In addition, subjects will be compensated for travel expenses required to get to and from the clinical trial site.

13.5 Medical Care for Research-Related Injuries

All subjects taking part in research conducted by the Army are authorized to receive medical care in Army MTFs for research-related injuries, in accordance with AR 70-25 and 40-38. The AR 40-400, paragraph 3-56, affirms that medical care is available at Army MTFs for research-related injuries of subjects participating in research under Army regulation 70-25 or 40-38, and that medical care charges will be waived.

If a subject is injured because of participation in this research and is a DoD healthcare beneficiary (e.g., active duty military, military spouse or dependents) the subject is entitled to medical care for that injury within the DoD healthcare system, as long as the subject remains a DoD healthcare beneficiary and medical care will be free.

Transportation to and from Army hospital(s) or clinic(s) will not be provided. The PI is the primary contact for the subject who believes they have sustained a research related injury.

13.6 Problems or Questions

Problems or questions about this trial should be addressed to the Principal Investigator, (b) (1) (A) [redacted]. Questions concerning an individual's rights as a trial volunteer should be addressed to Office of Human Use and Ethics, (b) (1) (A) [redacted].

14 Audits (b) (1) d Inspections

Audits and inspections may be carried out by the quality assurance department, local authorities, or authorities to whom information on this trial has been submitted. All documents pertinent to the trial must be made available for such audits / inspection after an adequate announcement. Informed consent of subjects participating in this trial has to include the consent in this access to source documents.

15 Responsibilities of the Principal Investigator

The PI agrees to carry out the trial in accordance with the guidelines and procedures outlined in this clinical trial protocol. The PI especially consents to strictly adhere to the ethical principles mentioned in Section 10.1 of this protocol.

Changes to the protocol require written "Amendments to the protocol" and written approval by the Principal Investigator. Changes are allowed only if the trial value is not reduced and if they are ethically justifiable. The amendment must be passed on to all participating investigators with the obligation to adhere to its provisions. If warranted, the subject information has to be changed accordingly.

It is within the responsibility of the investigator that the CRF has to be completed in a timely manner after each subject visit and signed after the subject has finished the trial for each subject participating in the trial.

At the conclusion of the trial, the investigator will return all partly used, unused and empty vaccine containers to the Sponsor or the vaccine containers will be destroyed at the clinical trial site according to local legal requirements.

The investigator may ask to terminate the trial due to administrative or other reasons. If this should be the case, appropriate measures which safeguard the interests of the participating subjects must be taken after verification and consultation with the PI.

Each investigator will maintain appropriate medical and research records for this trial, in compliance with ICH GCP (E6), Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. He/she will permit authorized representatives of the Sponsor and regulatory agencies to review (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety and progress.

The PI agrees to follow the detailed publication policy included in the clinical trial agreement.

By signing this protocol, the PI confirms that he/she has read the entire clinical trial protocol, agrees to its procedures, and will comply strictly with the formulated guidelines.

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17 Appendices

17.1 Appendix I: Toxicity Scale for Laboratory Values

Grade 1 or Grade 2 toxicity is only graded according to Table 4 and Table 5, if the value is outside of the institutional normal range applicable for this trial.

Estimating severity grade

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

Grade 1	An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with activities of daily living.
Grade 2	An AE which is sufficiently discomforting to interfere with activities.
Grade 3	An AE which prevents activities of daily living. Such an AE would, for example, prevent attendance at work and would necessitate the administration of corrective therapy.
Grade 4	Life-threatening or disabling

Serious or life-threatening AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: Seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression.

Table 4 Toxicity Scale for Serum Chemistry

Lab Value	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Sodium – Hyponatremia mmol/L	< Lower Limit of Normal (LLN) - 132	130 - 131	125 - 129	< 125
Sodium – Hypernatremia mmol/L	> ULN – 149	150 - 154	155 - 159	≥ 160
Potassium – Hyperkalemia mmol/L	> ULN – 5.9	6.0 - 6.5	6.6 - 7.0	> 7.0
Potassium – Hypokalemia mmol/L	< LLN – 3.1	2.5 - 3.0	2.0 - 2.4	< 2.0
Calcium – Hypercalcaemia mmol/L	> ULN – 2.89	2.90 - 3.09	3.10 - 3.30	> 3.30
Calcium- Hypocalcaemia mmol/L	< LLN – 2.00	1.76 - 2.00	1.50 -1.75	< 1.50
Serum creatinine mg/dl	> ULN– -< 1.5 x ULN	≥ 1.5 - < 3 x ULN	≥ 3- 6 x ULN	> 6 x ULN
Alkaline Phosphatase increase by factor	> 1.25 – < 2.0 x ULN	≥ 2.0 - < 3.0 x ULN	≥ 3.0 x ULN	
Liver Function Tests increase by factor	> 1.0 – < 2.5 x ULN	≥ 2.5 - < 4 x ULN	≥ 4 x ULN	
Total Bilirubin increase by factor	> ULN – 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Cardiac troponin I increase by factor	>ULN – <2.0 x ULN	≥ 2.0 - < 5.0 x ULN	≥ 5.0 x ULN	
Total Cholesterol mg/dl	> ULN – 300	> 300 - 400	> 400	

Table 5 Toxicity Scale for Hematology

Lab Value	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) g/dl	< LLN - ≥ 10.5	< 10.5 - ≥ 10.0	< 10.0	
Hemoglobin (Male) g/dl	< LLN - ≥ 12.5	< 12.5 - ≥ 11.0	< 11.0	
WBC Increase cell/mm^3	> ULN - < 15,000	≥ 15,000 - < 20,000	≥ 20,000	
WBC Decrease cell/mm^3	< LLN - ≥ 2,500	< 2,500 - ≥ 1,500	< 1,500	
Lymphocytes Decrease cell/mm^3	< LLN - ≥ 750	< 750 - ≥ 500	< 500	
Neutrophils Decrease cell/mm^3	< LLN - ≥ 1,500	< 1,500 - ≥ 1,000	< 1,000	
Platelets Decreased cell/mm^3	< LLN - ≥ 75,000	< 75,000 - ≥ 50,000	< 50,000	

17.2 Appendix II: DoD Clinical Guidelines for Post-Smallpox Vaccine Associated Myopericarditis, Vaccine Healthcare Centers Network

DoD Clinical Guidelines for Post-Smallpox Vaccine Associated Myopericarditis
Vaccine Healthcare Centers Network (VHCN)

Vaccine(s) administered in past 30 days

Clinical symptoms: Chest pain, shortness of breath, palpitations, syncope, dry cough, or any suspected cardiopulmonary symptom(s)

Initial Evaluation

History: Characterize symptoms[1]
Past medical history[2]
- Include detailed vaccination hx

Risk factors for cardiac symptoms[3]

Physical Examination[4]
Laboratory[5] (Troponin I/T, BNP, ESR, usCRP, CK-MB, **Viral surveillance**)
Diagnostics[6] (Electrocardiogram, Echocardiogram, CXR (PA/Lat), Pulmonary function testing, Imaging studies (Cardiac MRI with Gadolinium)

A. Symptoms only

A. Cardiology Consultation
- Document normal ECG, troponin, CK, CRP, other studies as indicated during acute symptoms[5,6]
- Consider non-cardiac etiology[7]

Therapeutic options[8]: NSAIDs +/- colchicine, other Rx
Management & Recovery[9]
- Activity based on exercise tolerance and clinical assessment
- 4 week clinical F/U visit, ECG, echocardiogram, and exercise stress test to clear for return to full duty
- For ongoing or persistent symptoms, refer to cardiology (stress test not recommended)

B. Symptoms + objective abnormality[11]

B. Cardiology Consultation
- Differential includes myo-pericarditis and acute coronary syndrome[5,6,7,11]

Special labs and diagnostics[5,6] as indicated

B1. Symptoms with objective ECG abnormality but without positive cardiac enzymes or LV dysfunction[11]

Therapeutic options[8]: NSAIDs +/- colchicine, other Rx
Management & Recovery[9]
- No strenuous activity for 6 weeks
- 6 week clinical F/U visit, ECG, echocardiogram, exercise stress test to clear for return to full duty; repeat abnormal studies
- For ongoing or persistent symptoms, refer to cardiology (stress test not recommended)

B2. Symptoms with positive cardiac enzymes, depressed LV function, and/or imaging c/w myocarditis[11]

Therapeutic options[8]: NSAIDs, other Rx
Management & Recovery[9]
- No strenuous activity for 6 weeks
- 6 week clinical F/U visit, ECG, echocardiogram, exercise stress test as clinically indicated; repeat abnormal studies (including cardiac enzymes)
- Activity as tolerated & deployment restriction for a minimum of 6 months
- Cardiology F/U at 6 months

B3. Includes B2 and any of the following: LVEF < 45%, sustained dysrhythmias, and/or hemodynamic instability[11]

- **Early Transfer** to Tertiary Care Center - consider myocardial Biopsy

Therapeutic options: see **Footnote 8**
Management & Recovery[9]
- No strenuous activity for 6 weeks
- Close clinical F/U as directed by cardiologists (echocardiogram, ECG, exercise stress test)
- Activity as tolerated & deployment restriction for a minimum of 6 months
- Cardiology F/U at 6 months for repeat evaluation (reassess deployability)

Refer **all** cases to VHC Network for clinical case review, entry into DoD Smallpox Vaccine Myopericarditis Registry, filing of VAERS report and natural history surveillance.[10] With referral include: Patient and provider contact information, Echocardiograms, ECG, cardiac isoenzyme results, & copies of pertinent records.

Consultation: Call the DoD Vaccine Clinical Call Center at (b) (1) (A) to request VHC and/or military cardiology clinical consultation.

FOOTNOTES: The following guidance is for reference. Not every suggestion will be applicable to every patient. Recommendations are to be applied as diagnostic and therapeutic needs or questions arise and should be in conjunction with VHC staff consultation.

Footnote 1	**Characterize symptoms, including chest pain type**	Specify symptom location, character, onset, duration, intensity/severity, frequency, accompanying/associated symptoms, and alleviating/aggravating factors. All associated clinical symptoms should be detailed. Categorize patient's chest pain type if present (choose one): 1. Pericarditis chest pain: Chest pain that is typical and made worse by supine position, improved with leaning forward, pleuritic, constant a. Detailed history is critical to case definition of suspect pericarditis – see case definitions, page 5 2. Myocarditis chest pain: angina-like, diffuse; not necessarily positional or pleuritic 3. Atypical chest pain: Pain, pressure, or discomfort in the chest, neck, or arms not clearly exceptional or not otherwise consistent with pain or discomfort of myocardial ischemic origin. **Reference:** Box 10, Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. (2006, February 3) *MMWR:Morbidity and Mortality Weekly Report, 55*(RR01);1-16. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm
Footnote 2	**Assess past medical history**	Detailed review of all systems, with attention to the following disorders: ▪ Lung disease ▪ Gastrointestinal disease ▪ Vascular disease (e.g., stroke, transient ischemic attack, peripheral arterial disease) ▪ Musculoskeletal disorders (e.g., impingement syndrome, thoracic outlet syndrome) ▪ Vaccination history and adverse events (with specific lot number, if available) **Reference:** PMH study guide http://medinfo.ufl.edu/year1/bcs96/clist/history.html
Footnote 3	**Risk Factors for Cardiac Symptoms**	▪ Personal History of angina, myocardial infarction (MI), congestive heart failure (CHF), percutaneous coronary intervention (e.g., balloon angioplasty, stent, atherectomy), coronary artery bypass graft (CABG), catheterization with stenosis ≥ 50%. ▪ Age, sex, race/ethnicity (ethnicity: Hispanic or Latino, Not Hispanic or Latino; Race: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White)) ▪ Diabetes, hypertension, smoking, dyslipidemia, family history of CAD (especially prior to age 55), obesity, physical inactivity, stress, and excessive alcohol consumption. **Reference:** http://www.americanheart.org/presenter.jhtml?identifier=4726
Footnote 4	**Physical Examination**	Perform a focused PE to include: gender and race/ethnicity, vital signs, ht, wt, detailed exam to include vaccination site, cardiac (jugular venous pressure if able), pulmonary, peripheral edema and lymphadenopathy. Reference: http://meded.ucsd.edu/clinicalmed/introduction.htm
Footnote 5	**Laboratory studies**	Report normal range as defined by individual hospital laboratory standards. Record units and normal range for laboratory.
Laboratory studies: All patients		
	Complete blood count	CBC at presentation, to include differential, with emphasis on eosinophil and lymphocyte count should be noted.
	Cardiac enzymes	All Creatinine Kinase (CK), CK-MB, and troponin (I/T) values should be noted. For troponin data, document 99th percentile cut-off for testing system used as well as name of testing system if available.
	Inflammatory markers	All erythrocyte sed rate and C-reactive protein (CRP) (ultrasensitive, if available) values should be noted.
Laboratory studies as clinically indicated:		
	Immune complex screening	All Complement related assay studies (including C3, C4, CH50, C1q & C3D-binding assays) with values should be noted.
	Brain natriuretic peptide	Consider BNP if dyspnea is present.
	Viral surveillance	**Smallpox vaccine related myopericarditis is a diagnosis of exclusion.** No smallpox vaccine related cases have exhibited viral etiology to date**.** When considering other etiologies, viral surveillance is indicated.
	Serologies and PCR	Consider ID consultation; PCR for vaccinia if available (consult CDC/VHC). All **coxsackie A/B (enteroviruses), adenovirus, CMV, Parvovirus B19, influenza A/B, HHV-6, HSV-1, HIV, RSV**, dengue, echovirus, encephalomyelitis, Epstein-

		Barr, Lyme, rhabdovirus, varicella, variola, yellow fever, hepatitis A/B/C IgM, and core IgG values and titers during the evaluation should be noted; obtain specimens for convalescent titers at 4 week interval.
	Other Cultures	Consider ID consultation; all viral cultures (nasal wash, urine, feces) for adenovirus, influenza viruses, parvovirus B19 or enteroviruses should be noted.
	Autoimmunity screening	Note all ANA, Anti-DS DNA, ENA, and similar values during the evaluation. Consider additional special studies such as myocardial auto-antibodies. ***Consult VHC Network for current information.***
Footnote 6	**Diagnostics**	
Diagnostics: All patients		
	Electrocardiogram (ECG)	Note date, time, rate, rhythm, the presence of ectopy and abnormalities in waves, intervals and segments. Provide copies of relevant ECGs to patient and incorporate in record. **Typical ECG manifestations:** **Pericarditis:** Acute 1. Diffuse ST segment elevation, particularly leads I,II, III, aVF, aVL, and V5-V6 2. Diffuse PR segment depression 3. PR segment elevation in lead aVR Evolving 1. T-wave changes: notched, biphasic. Or low-voltage inversions. **Myocarditis:** 1. Diffuse T-wave inversions without ST segment abnormality 2. Incomplete atrioventricular conduction blocks (usually transient) 3. Intraventricular conduction blocks (usually transient) *When myocarditis and pericarditis occur together, ST segment abnormalities also may be evident. **Reference:** Demangone, D. (2006) ECG manifestations: Noncoronary heart disease. *Emergency Medicine Clinics of North America.* (24) pp.113-131.
	Chest X-ray	PA and Lateral
Other diagnostics as clinically indicated:		
	Echocardiogram	If only a range is estimated for ejection fraction (EF), note the midpoint of the range. For pericardial effusions, record estimate of size and/or clinical significance (small effusions may not be diagnostic).
	Pulmonary functions	With DLCO if indicated; diffusion capacity corrected for hemoglobin is a sensitive measure of pulmonary interstitial disease and increased risk for hypoxia with activity.
	Stress test	Indicate whether an exercise tolerance, stress-echocardiogram, or nuclear/pharmacological stress test was performed during the hospital stay and the result of the testing, if performed. Clinical correlation is recommended in the cases of a negative stress test result.
	Cardiac catheterization	If vessel occlusion identified, note the anatomical region affected and the degree of stenosis present.
	Holter & Event Monitor	Consider for dysrhythmia evaluation
	Imaging	Consider cardiac MRI with gadolinium (with T2W imaging and early/delayed enhancement) for cases with depressed EF and/or elevated Troponin as soon as feasible after onset of symptoms. **Reference:** Friedrich et al. Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper. *JACC,* 2009; 53(17):1475-87.
	Myocardial Biopsy	Consider myocardial biopsy if heart failure is severe or worsening.
Footnote 7	**Differential Diagnosis**	Consider viral myocarditis, acute coronary syndrome (myocardial infarction), aortic dissection, pneumothorax, pulmonary embolism, musculoskeletal pain, esophageal disorder (gastroesophageal reflux, esophageal spasm), systemic autoimmune disease.
Footnote 8	**Therapeutic options**	***Consult VHC Network for current information.***
	Symptoms only (A) OR symptoms with objective findings, but with negative cardiac enzymes and no LV dysfunction (B1)	Non-steroidal anti-inflammatory therapy with or without colchicine (colchicine in addition to Conventional Therapy for acute pericarditis: Results of the colchicine for acute pericarditis (COPE) trial. Imazio M, et al. *Circulation* 2005; 112:2012-16.)

	Symptoms w/ positive cardiac enzymes or depressed LV function or imaging c/w myocarditis (B2)	Non-steroidal anti-inflammatory therapy. Other treatments to be considered in consultation with Cardiology and the VHCN to include corticosteroid treatment (after biopsy if possible). Consider biopsy for viral PCR, culture and assessment of inflammation (presence of eosinophils). Consider corticosteroids with evidence of eosinophilic inflammation and clinical deterioration.
	Progressive symptoms (LVEF < 45%, sustained dysrhythmias, hemodynamic instability) (B3)	▪ Conventional heart failure treatments (e.g., ACE inhibitors, nitrates, diuretics, select beta-blockers such as carvedilol or metoprolol succinate) ▪ Strongly consider early referral for myocardial biopsy to guide optimal treatment. ▪ Consider corticosteroids (preferably after biopsy) if no evidence of active infection and/or with evidence of eosinophils in inflammatory infiltrate. ▪ Consider Vaccinia Immune Globulin (VIG)/IVIG only with expert consultant case review via VHC Network.
Footnote 9	**Management and Recovery**	Whenever possible, standardized follow up should be coordinated with the Vaccine Healthcare Centers Network. **Reference** (Deployment Restriction): Maron et al. Task Force 4: HCM and other cardiomyopathies, mitral valve prolapse, myocarditis, and Marfan syndrome. *JACC*;45 (8):1340–5. http://content.onlinejacc.org/cgi/content/full/45/8/1340.
	Symptoms only (A) OR Symptoms with objective findings, but without positive cardiac enzymes or LV dysfunction (B1)	▪ Light physical activity at own pace for 4 weeks (A) ▪ No strenuous activity for 6 weeks (B1) ▪ Follow up in 4 weeks (A) to 6 weeks (B1) **Asymptomatic at follow-up** ▪ Repeat any previously abnormal studies ▪ Clinical evaluation to include stress test to assess exercise tolerance prior to clearance for return to duty ▪ Long-term follow-up will be completed by VHC Network **Symptomatic and/or persistent/abnormal findings at follow-up** ▪ Repeat any previously abnormal studies ▪ Clinical evaluation to include stress test (unless contraindicated) ▪ Repeat MRI if had previous enhancements or if symptomatic. Repeat at 12-18 months ▪ Consult cardiology for further recommendations ▪ Long-term follow-up will be completed by VHC Network

	Symptoms with positive cardiac enzymes or mild depressed LV function or imaging c/w myocarditis (B2) OR Progressive symptoms (LVEF < 45%, sustained dysrhythmias, hemodynamic instability) (B3)	▪ No strenuous activity for 6 weeks; deployment restriction for 6 months
		▪ Clinical evaluation at 6 weeks and 6-12 months
		Asymptomatic at follow-up
		▪ Repeat any previously abnormal studies at 6 weeks and 6-12 months
		▪ Stress test at 6 weeks to assess exercise tolerance for rehabilitation; repeat at 6-12 months to assess exercise tolerance prior to clearance for deployment
		▪ Long-term follow-up will be completed by VHC Network
		Symptomatic and/or persistent/abnormal findings at follow-up
		▪ Clinical evaluation to include enzymes, ultra sensitive CRP, ECG, ECHO, stress test (unless contraindicated)
		▪ Repeat MRI if had previous enhancements or if symptomatic. Repeat at 6 months to assess for clearance for deployment.
		▪ Clinical evaluation at 6 months to include repeat ECHO, stress test, and MRI
		  ▪ If normal and asymptomatic, clear for deployment
		  ▪ If normal and symptomatic, consult cardiology
		  ▪ If abnormal MRI with continued symptoms, not cleared for deployment
		▪ Continue cardiology follow-up at 6 -12 month intervals until asymptomatic
		▪ Long-term follow-up will be completed by VHC Network

Footnote 10	**Disability Assessment**	The majority of patients have recovered within 1 year. The natural history of this condition remains unknown. Careful functional assessment post-acute phase has not yielded definitive objective parameters. The long-term natural history of this condition (e.g., late onset arrhythmias, cardiomyopathy, recurrent myocarditis) has not been well defined. Development of new cardiac complications within 5 years following an episode of hypersensitivity myocarditis associated with immunization should be reported to the VHC Network clinical case management registry.

Footnote 11	**Case Definitions for Myocarditis and Pericarditis** *MMWR:Morbidity and Mortality Weekly Report* 2003;52:492-6, http://www.cdc.gov/mmwr/PDF/wk/mm5221.pdf *MMWR:Morbidity and Mortality Weekly Report,* 2006;55(RR01);1-16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm		
	Objective abnormalities		
Myo-carditis	**Suspect** (1) Symptoms (dyspnea, palpitations, or chest pain) (2) ECG abnormalities beyond normal variants, not documented previously (ST/T abnormality, paroxysmal supraventricular tachycardia, ventricular tachycardia, atrioventricular block, frequent atrial or ventricular ectopy) OR Focal or diffuse depressed LV function of uncertain age by an imaging study (3) Absence of evidence of any other likely cause	**Probable** (1) Meets symptom criteria for suspected myocarditis (2) In addition, meets one of the following: Elevated levels of cardiac enzymes (Creatine Kinase-MB fraction, Troponin T or Troponin I), OR new onset of depressed LV function by imaging, OR abnormal imaging consistent with myocarditis (MRI with gadolinium, gallium-67 scanning, anti-myosin antibody scanning)	**Confirmed** Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy.
Peri-carditis	**Suspect** (1) Typical chest pain (made worse by supine position, improved with leaning forward, pleuritic, constant) (2) No evidence for alternative cause of such pain	**Probable** (1) Meets criteria for suspected pericarditis (2) Has one or more of the following: Pericardial rub on auscultation OR ECG with diffuse ST-segment elevations or PR depressions not previously documented OR echocardiogram revealing an abnormal pericardial effusion	**Confirmed** Histopathologic evidence of pericardial inflammation in pericardial tissue from surgery or autopsy

17.3 Appendix III: Case Definitions Acute Myocarditis / Pericarditis

17.3.1 Case Definition for Acute Myocarditis

A possible case of acute myocarditis is defined by the following criteria and the absence of evidence of any other likely cause of symptoms:

Presence of dyspnea, palpitations, or chest pain of probable cardiac origin in a subject with either one of the following:

- ECG abnormalities beyond normal variants, not documented previously, including
- ST-segment or T-wave abnormalities,
- Paroxysmal or sustained atrial or ventricular arrhythmias,
- AV nodal conduction delays or intraventricular conduction defects, or
- Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy, or
- Evidence of focal or diffuse depressed left ventricular (LV) function of indeterminate age identified by an imaging trial (e.g., echocardiography or radionuclide ventriculography).

A probable case of acute myocarditis, in addition to the above symptoms and in the absence of evidence of any other likely cause of symptoms, has one of the following:

- Elevated cardiac enzymes, specifically, abnormal levels of cardiac troponin I, troponin T, or creatine kinase myocardial band (a troponin test is preferred);
- Evidence of focal or diffuse depressed LV function identified by an imaging trial (e.g., echocardiography or radionuclide ventriculography) that is documented to be of new onset or of increased degree of severity (in the absence of a previous trial, findings of depressed LV function are considered of new onset if, on FU studies, these findings resolve, improve, or worsen); or
- Abnormal result of cardiac radionuclide imaging (e.g., cardiac magnetic resonance imaging with gadolinium or gallium-67 imaging) indicating myocardial inflammation.

A case of acute myocarditis is confirmed if histopathologic evidence of myocardial inflammation is found at endomyocardial biopsy or autopsy.

17.3.2 Case Definition for Acute Pericarditis

A possible case of acute pericarditis is defined by the presence of

- Typical chest pain (i.e., pain made worse by lying down and relieved by sitting up and/or leaning forward) and no evidence of any other likely cause of such chest pain.

A probable case of acute pericarditis is a possible case of pericarditis, or a case in a person with pleuritic or other chest pain not characteristic of any other disease, that, in addition, has one or more of the following:

- Pericardial rub, an auscultatory sign with one to three components per beat,
- ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions that are not previously documented, or
- Echocardiogram indicating the presence of an abnormal collection of pericardial fluid (e.g., anterior and posterior pericardial effusion or a large posterior pericardial effusion alone).

A case of acute pericarditis is confirmed if histopathologic evidence of pericardial inflammation is evident from pericardial tissue obtained at surgery or autopsy.

17.4 Appendix IV: US Health Affairs Memorandum Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program

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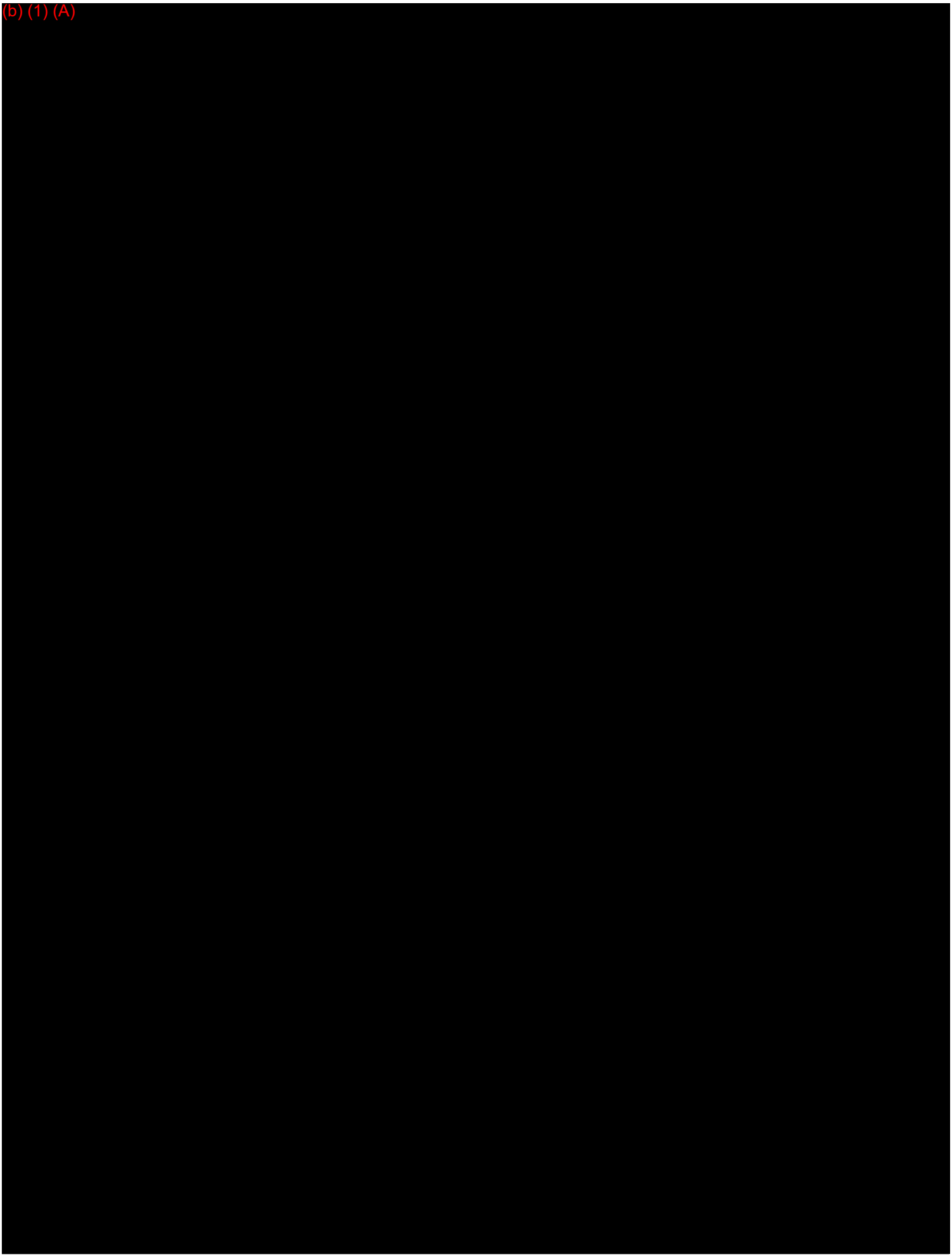

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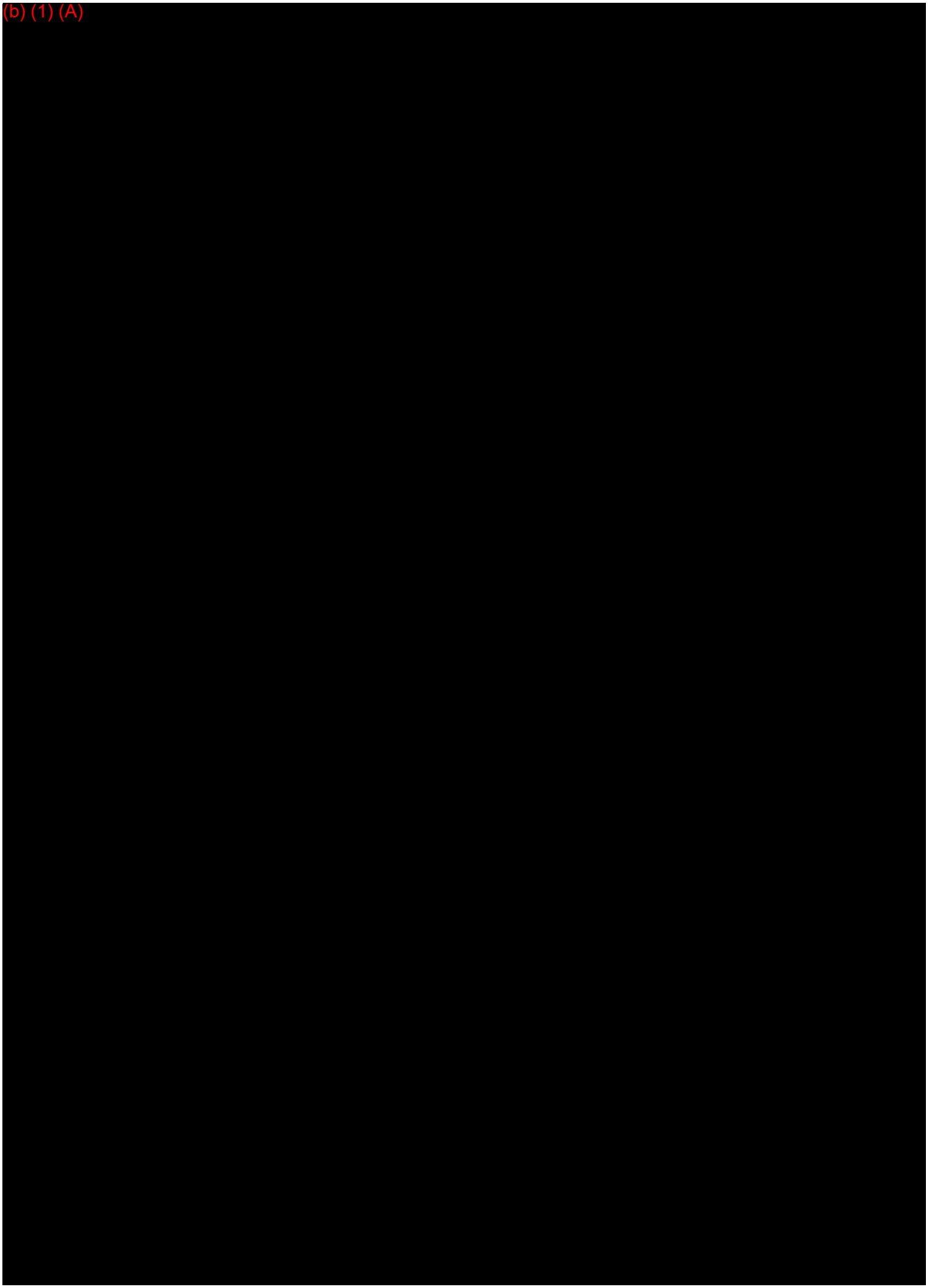
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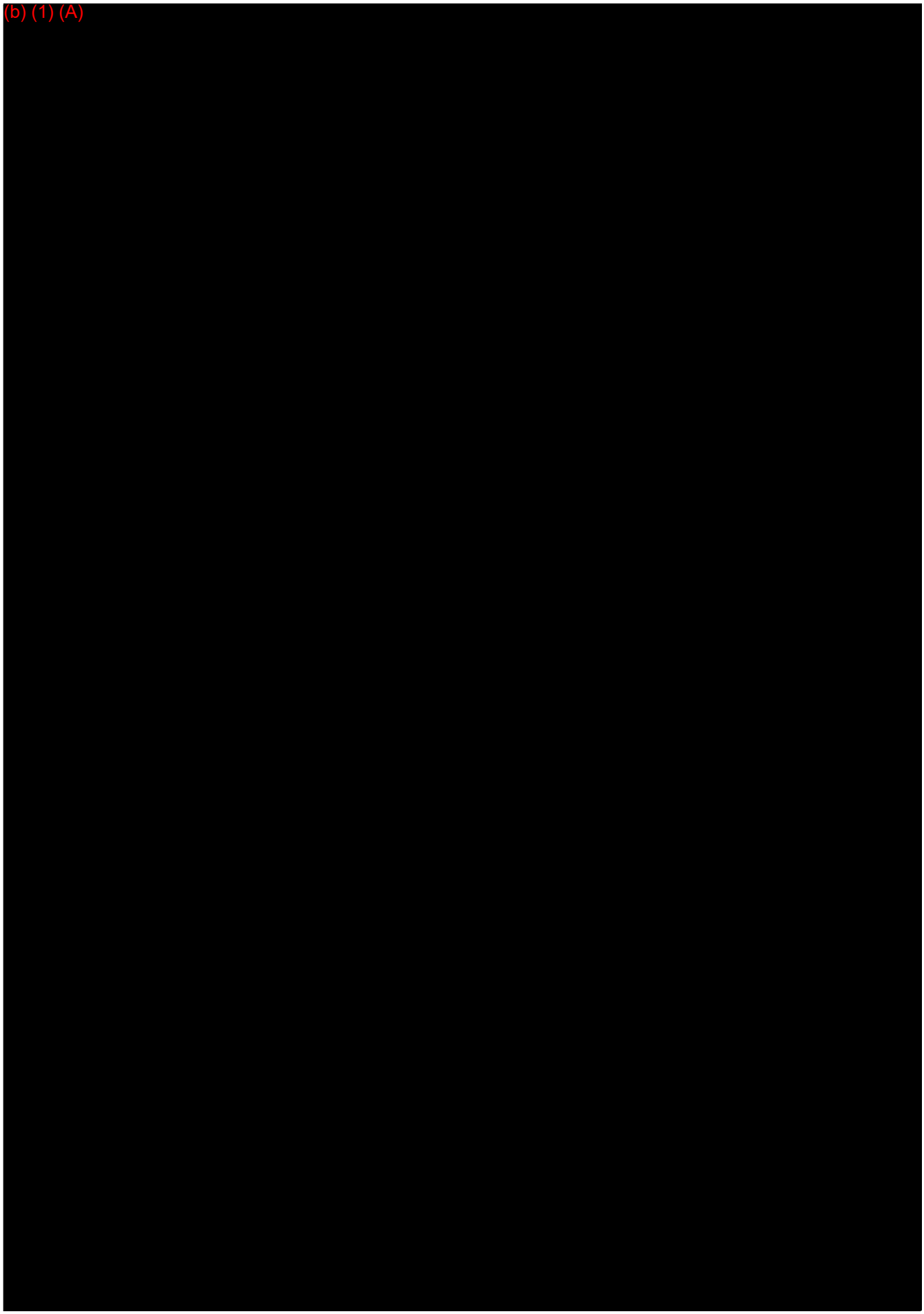

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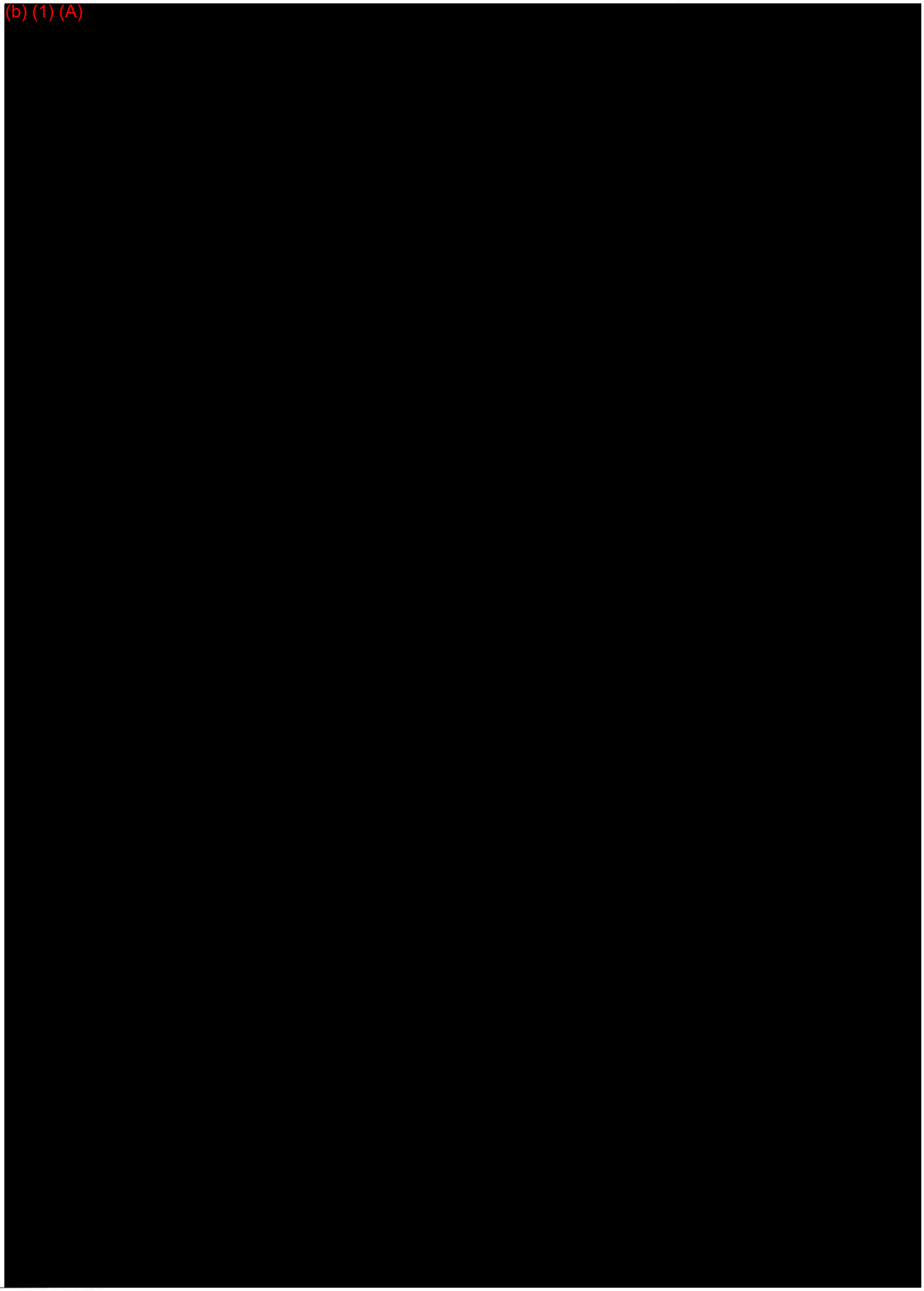
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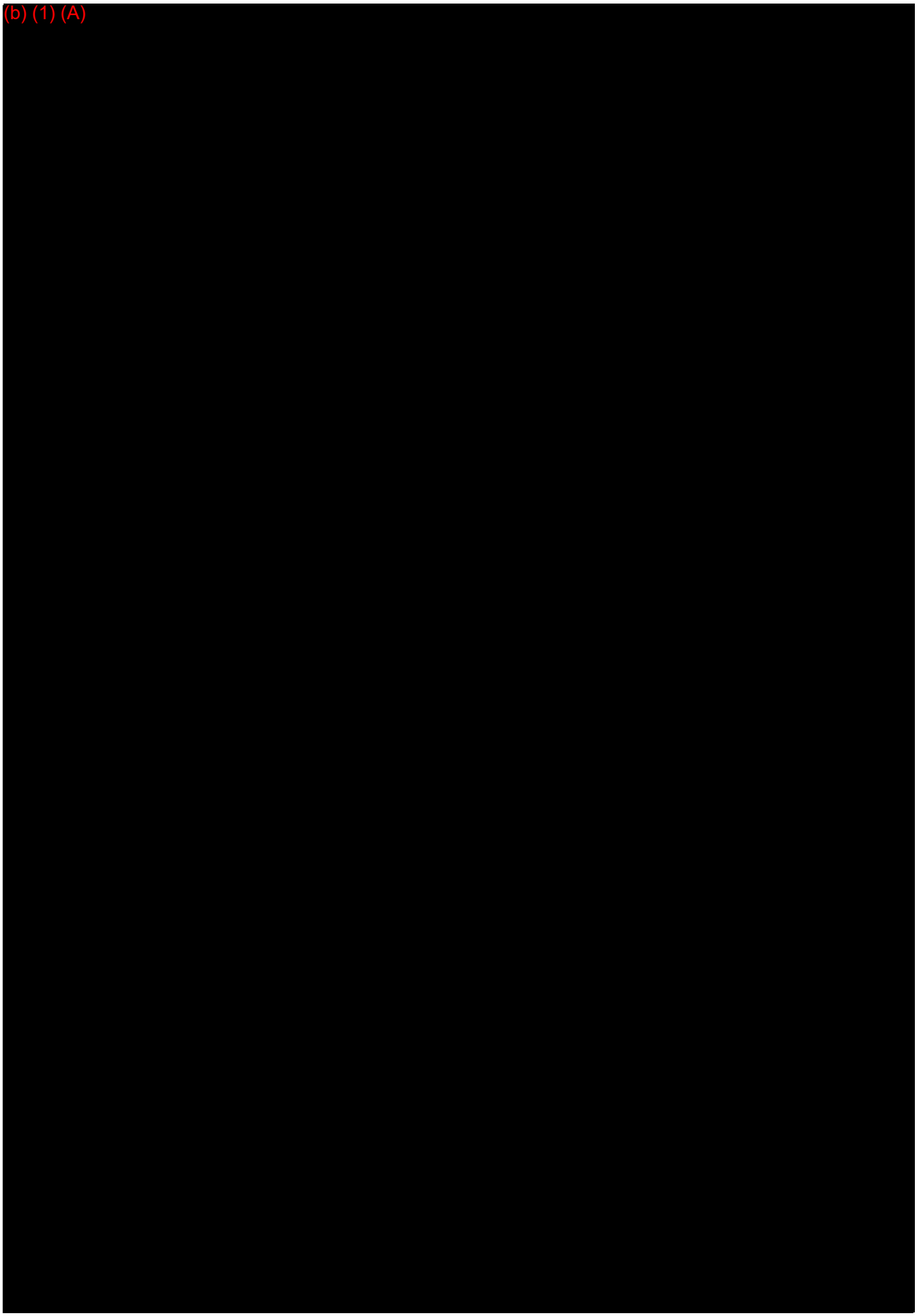
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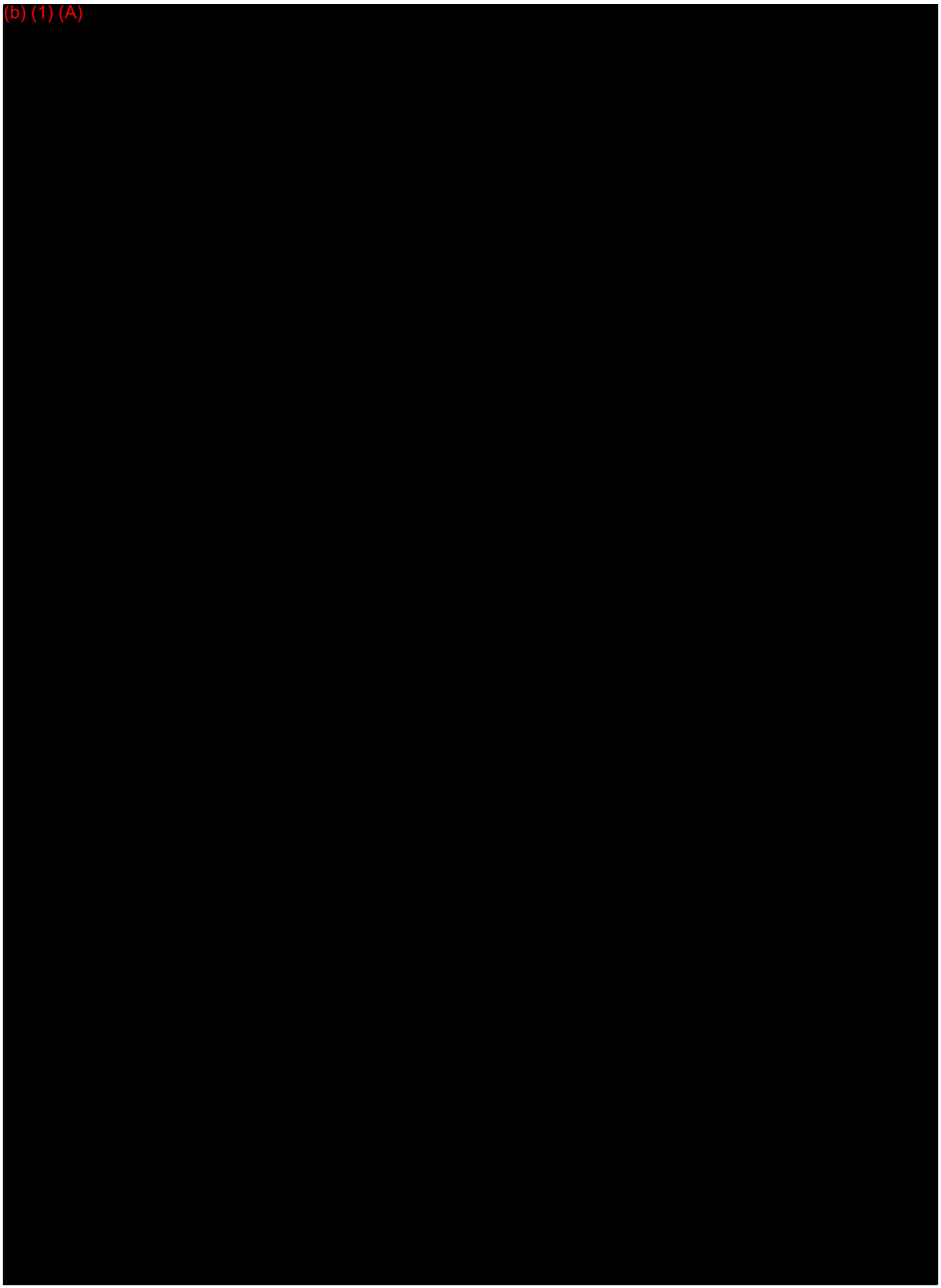

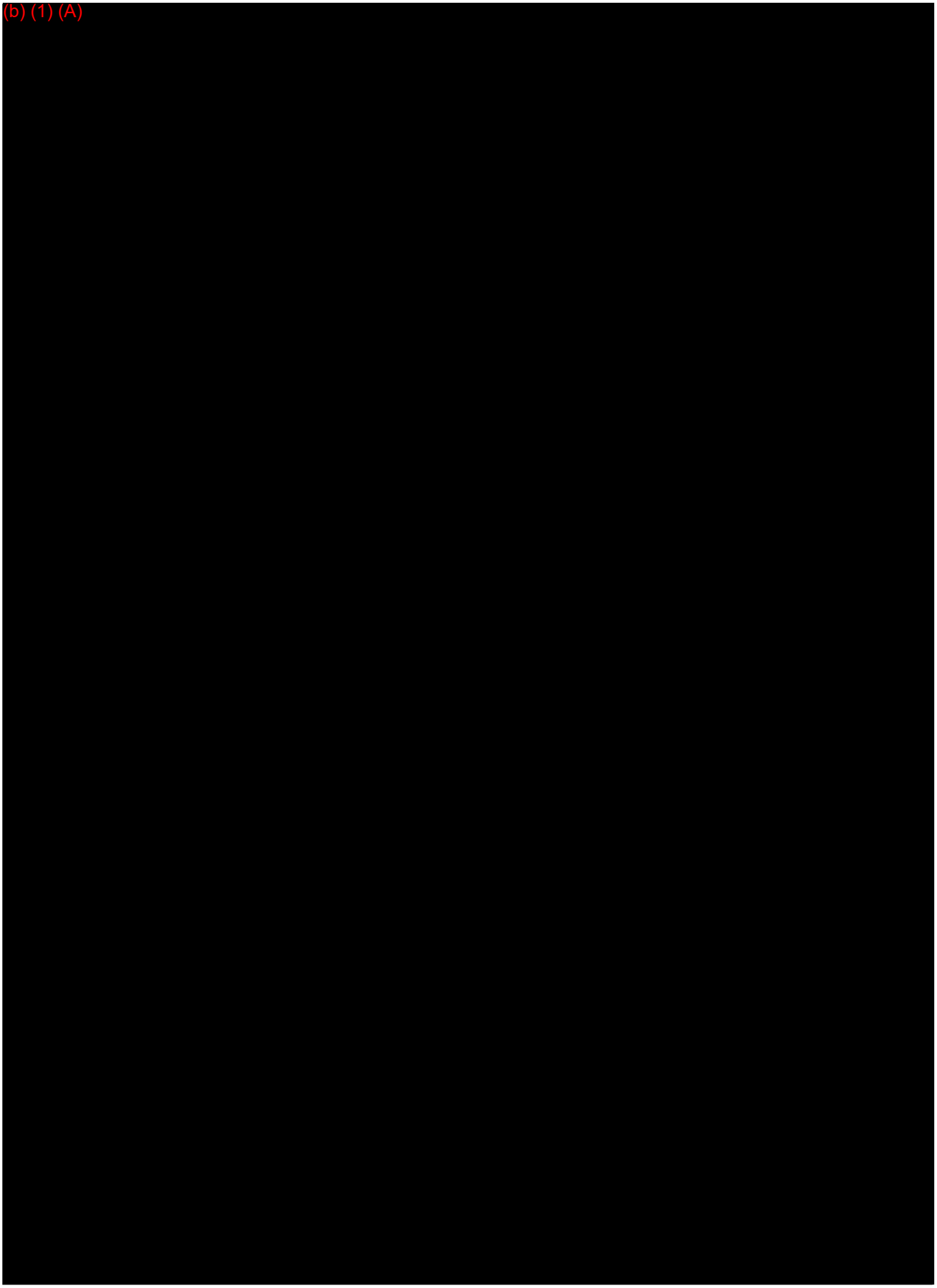
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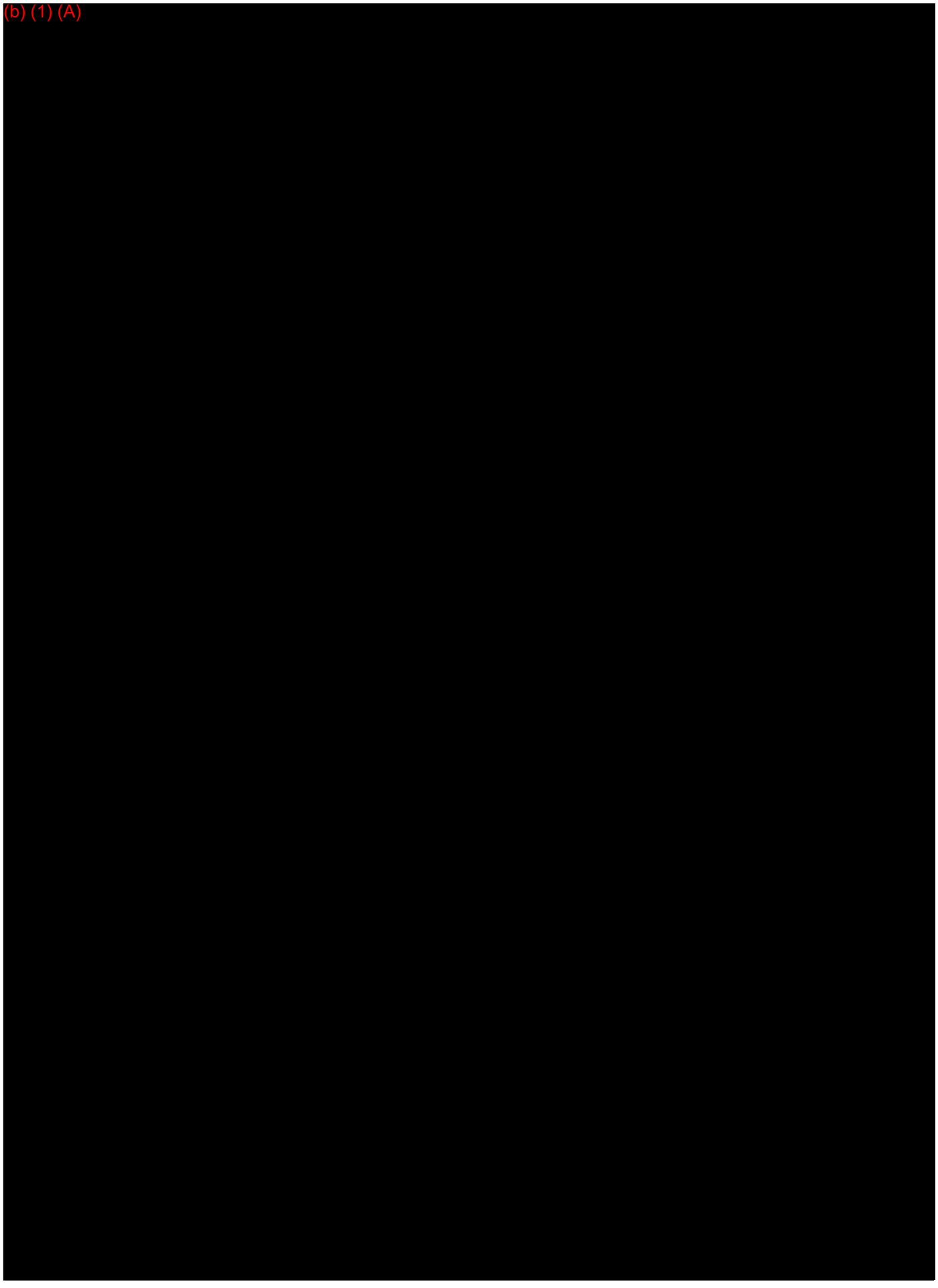

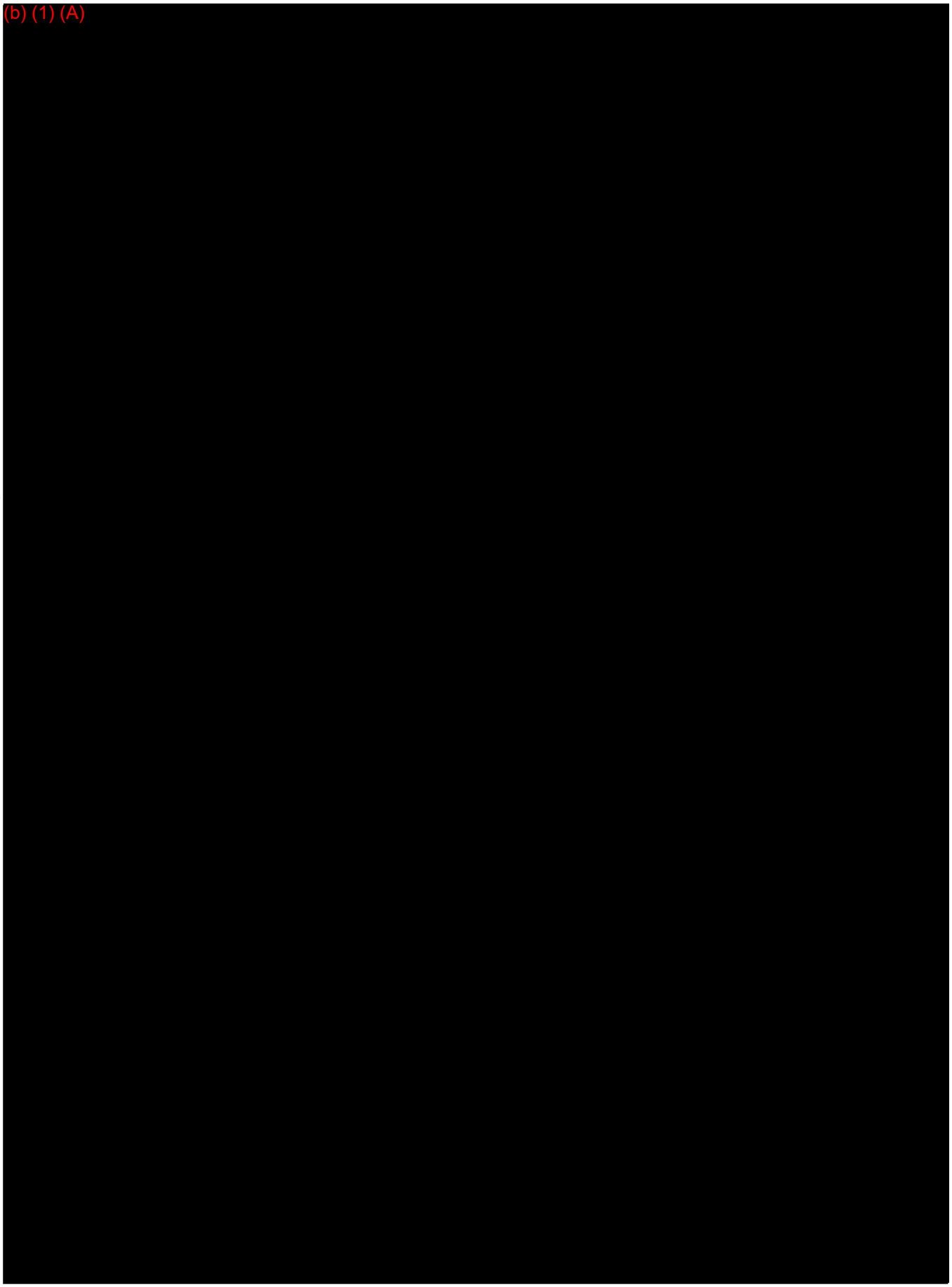
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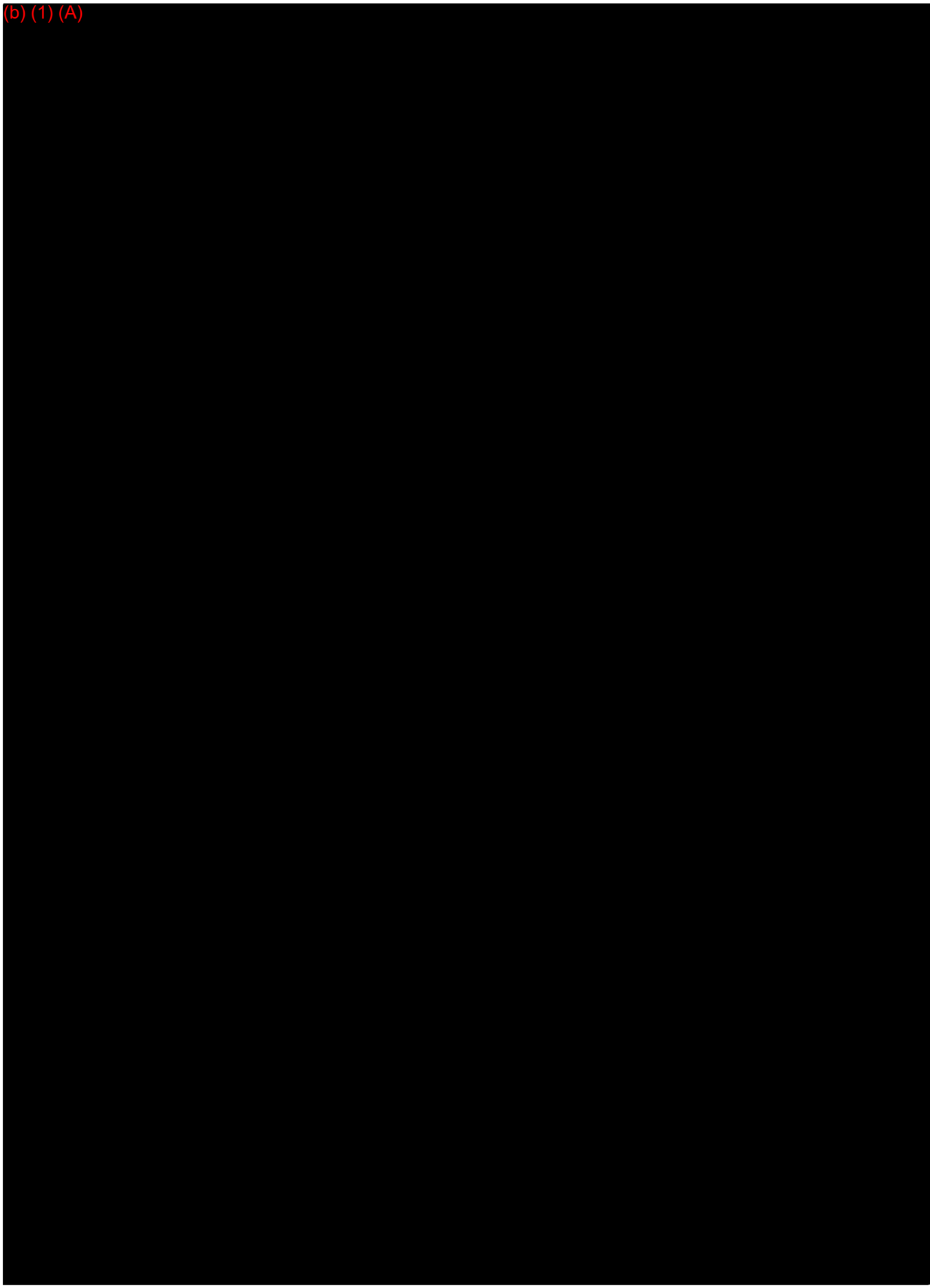
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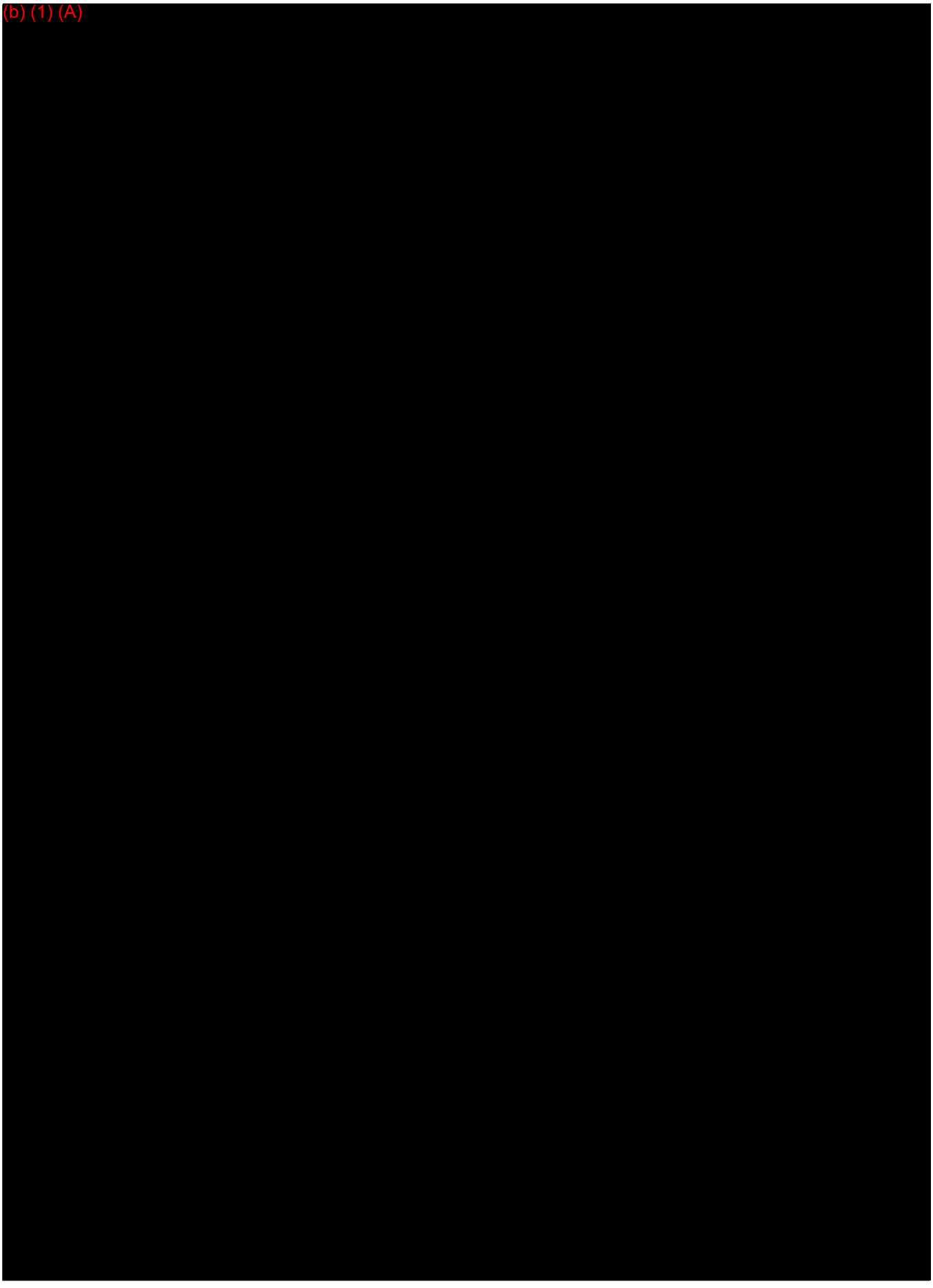

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17.5 Appendix IVa: Attachment 1 to US Health Affairs Memorandum 'Medication Guide ACAM2000®'

Note: The US Health Affairs Memorandum; Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program attaches the version from 14 August 2007 for the Medication Guide ACAM2000™. This CTP replaces the Medication Guide ACAM2000™ Version 14 August 2007 with the latest version from June 2012.

Medication Guide

Smallpox (Vaccinia) Vaccine, Live

ACAM2000®

Please read this Medication Guide before you receive a vaccination with ACAM2000. This Guide does not take the place of talking to your healthcare provider about ACAM2000 and the smallpox disease.

What is the most important information I should know about the ACAM2000 smallpox vaccine?

- **If you are at a high risk for being exposed to smallpox, you should be vaccinated even if you have health problems, unless you have certain problems with your immune system.** People who have health problems may have a higher chance of getting serious side effects from vaccination but are also those who have a higher chance of dying from the smallpox disease.
- **ACAM2000 may cause serious heart problems called myocarditis and pericarditis, or** swelling of the heart tissues. In studies, about 1 in every 175 persons who got the vaccine for the first time may have experienced myocarditis and/or pericarditis. On rare occasions these conditions can result in an irregular heart beat and death. Your chances of getting heart problems from the vaccine are lower if you have already had this vaccine before. You can have myocarditis and/or pericarditis even if you have no symptoms. **Call your healthcare provider or get emergency help right away if you have:**
    - **chest pain or pressure**
    - **fast or irregular heartbeat**
    - **breathing problems**

  See "**What are the possible side effects of ACAM2000?**"
- **Because the vaccine has a live virus, it can spread to other parts of your body or to other people if you touch the vaccination site and then touch other parts of your body or other people.** The vaccine virus can spread until the vaccination scab falls off (2 to 4 weeks after vaccination). **If the virus is spread to a person who should not get the vaccine, the side effects can be very serious and life-threatening.**

  See "**How do I care for the smallpox vaccination site?**"

What is the ACAM2000 smallpox vaccine?

ACAM2000 is a prescription vaccine used to protect people against smallpox disease. It is for use in people who have a high chance of getting the disease.

ACAM2000 contains live vaccinia virus (a "pox"-type virus) to protect against smallpox disease.

Who should not get the ACAM2000 smallpox vaccine?

- **In an emergency, you should be vaccinated if you are at high risk for getting smallpox disease even if you have health problems (except if you have certain problems with your immune system as discussed below).**
- Your healthcare provider may not give you ACAM2000 if you have problems with your immune system. You may have immune system problems if you:
    - have leukemia
    - have lymphoma
    - have had a bone marrow or organ transplant
    - have cancer that has spread
    - have HIV, AIDS
    - have cellular or humoral immune deficiency
    - are being treated with radiation
    - are being treated with steroids, prednisone, or cancer drugs

How do I receive ACAM2000?

ACAM2000 smallpox vaccine is not a shot like other vaccines. Your healthcare provider will make 15 pokes in the skin of your upper arm with a needle containing ACAM2000. The pokes are not deep, but will cause a drop of blood to form. This is called the vaccination site.

It is important to care for the vaccination site properly so that the virus doesn't spread to other parts of your body or to other people. You can infect another part of your body or other people until the scab falls off.

How do I care for the ACAM2000 vaccination site?

It is important to <u>ALWAYS</u>:

1. **Wear bandages to cover the entire vaccination site.**
2. **Wear sleeves to cover the site.**
3. **Wash your hands, wash your hands, wash your hands.**

- **When changing bandages or caring for your vaccination site, wear gloves. Use an absorbent bandage to completely cover your vaccination site.**
    - Change your bandage when it begins to soak through (at least every 1 to 3 days).
    - Throw away gloves and used bandages in sealed or double plastic bags. A small amount of bleach can be added to the bag to kill the virus.
- **Wear clothes with sleeves to cover the site and prevent scratching the vaccination site**. It is especially important to wear a bandage and sleeves to bed to avoid scratching.
- **Wash your hands frequently** with alcohol-based cleansers or soap and water.

    - Be sure to wash your hands each time you change your bandage or if you touch the vaccination site.
- Do not use creams or ointments on the vaccination site because they will delay healing and can spread the virus.
- Do not scratch or pick at the vaccination site.
- You can take a bath or shower, but don't touch or scrub the vaccination site.
    - It is best to cover the vaccination site with a waterproof bandage.
    - If the vaccination site gets wet, dry the site with toilet paper and flush it. (Do not use a cloth towel because it can spread the virus.)
    - Cover the vaccination site with a loose gauze bandage after bathing to allow it to dry out.
- Do not use a bandage that blocks air from the vaccination site. This could cause the skin at the vaccination site to soften and wear away.
- If you exercise enough to cause sweat to drip, use a waterproof bandage on the vaccination site when exercising.
- Wash clothing, towels, bedding or other items that may have come in contact with the vaccination site separately from other wash. Use hot water with detergent and bleach.
- When the scab falls off, throw it away in a sealed plastic bag with a small amount of bleach. Wash your hands afterwards.

What should I expect at the vaccination site and in the weeks following vaccination?

- If vaccination is successful, a red and itchy bump forms at the vaccination site in 2 to 5 days. Over the next few days, the bump becomes a blister and fills with pus. During the second week, the blister dries up and a scab forms. The scab falls off after 2 to 4 weeks, leaving a scar. People vaccinated for the first time may have a larger reaction than those being revaccinated. See expected responses below:

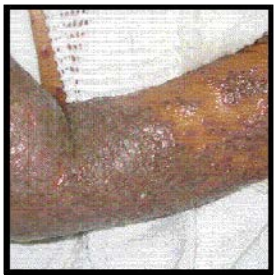
Smallpox Vaccination Site:
expected response after vaccination

Note: After 6 to 8 days, check to be sure that your vaccination site looks like one of the pictures above. If it does not look like this, see your healthcare provider because you may need to be revaccinated.

- If you need medical care in the month after your vaccination, tell your healthcare provider you just got a smallpox vaccination.
- Certain people, such as laboratory workers who work with smallpox, are at risk of being exposed to smallpox over a long period of time. These people may need a booster vaccination every 3 years to maintain protection against smallpox.

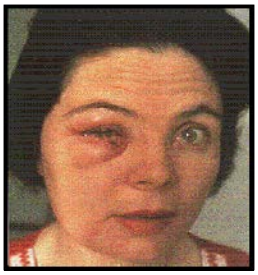
What should I avoid after getting vaccinated with the ACAM2000 smallpox vaccine?

- **For 4 weeks after vaccination AND until the vaccination site has healed, you should avoid:**
    - **getting pregnant.** Smallpox vaccine may rarely cause infection in an unborn baby if the mother is vaccinated during pregnancy. This infection usually results in stillbirth or death.
    - **handling babies or breastfeeding.**
    - **swimming or hot tub use.**
    - **donating blood.**
    - **Tuberculin (TB) testing.** Smallpox vaccine may cause the TB test to give the wrong result.
- Avoid rubbing, scratching or touching the vaccination site.
- Until the vaccination scab falls off, do **NOT**:
    - have contact with people who cannot get the vaccine to prevent accidental spread of the vaccine virus. This includes physical contact and household contact. If there is someone in your household who should not get the vaccine, such as a pregnant woman, an infant, or someone who has an illness, you should not stay in the house until the vaccination scab falls off.
    - share a bed, clothes, towels, linen, or toiletries with unvaccinated people.



Don't scratch that itch.

Vaccine virus can accidentally spread to a family member, close contact, or another part of your body.



- We don't know if the vaccine virus can be spread to cats, dogs, or other household pets, or whether pets can spread the virus to other people in the household. Try to keep the vaccine virus from reaching your pet. See "**How do I care for the smallpox vaccination site?"**

What are the possible side effects of ACAM2000?

ACAM2000 may cause serious heart problems, including myocarditis and pericarditis. This can happen within 3 to 4 weeks after you get the vaccine. Call your healthcare provider or get emergency help right away if you have:

- **chest pain or pressure**
- **fast or irregular heartbeat**
- **breathing problems**

Most people who get myocarditis and/or pericarditis seem to get better after a few weeks. But heart problems may last longer in some people, and in rare cases, could lead to death.

Other serious side effects include:

- swelling of the brain or spinal cord
- problems with the vaccination site blister, such as it becoming infected
- spreading of the vaccine virus to other parts of your body or to another person
- severe allergic reaction after vaccination
- accidental infection of the eye (which may cause swelling of the cornea causing watery painful eyes and blurred vision, scarring of the cornea, and blindness)

Common side effects include:

- itching
- swollen lymph nodes
- sore arm
- fever
- headache
- body ache
- mild rash
- fatigue

The risks for serious vaccine side effects are greater for people who:

- have skin problems called eczema or atopic dermatitis
- have skin problems, such as burns, impetigo, contact dermatitis, chickenpox, shingles, psoriasis, or uncontrolled acne
- have had heart problems
- have serious heart or blood vessel problems including angina, previous heart attack, artery disease, congestive heart failure, stroke, or other cardiac problems
- smoke or have high blood pressure, high cholesterol, diabetes, high blood sugar, or a family history of heart problems
- are breastfeeding
- are pregnant, could be pregnant, or plan to become pregnant
- are less than 1 year old
- are taking steroid eye drops or ointment

- have had problems after previous doses or are allergic to ACAM2000 or any part of ACAM2000 such as antibiotics neomycin or polymyxin B

Tell your healthcare provider if you have any of the above conditions.

The virus from your vaccination can spread to other people and cause serious side effects. It is important to tell your healthcare provider if you:

- live or work with a person who has skin problems (like eczema, dermatitis, burns, psoriasis, bad acne) or is suffering from impetigo, chickenpox or shingles
- live or have close contact with a baby, or a person who is pregnant or breastfeeding
- live or have close contact with a person who has an immune deficiency or cardiac disease

See **"How do I care for the ACAM2000 vaccination site?"**

Tell your healthcare provider about any side effect that bothers you or that does not go away.

To report SUSPECTED SIDE EFFECTS (ADVERSE REACTIONS), contact sanofi pasteur Inc. at (b) (1) (A)) or VAERS at (b) (1) (A) and https://vaers.hhs.gov

General information about the safe and effective use of ACAM2000

This Medication Guide provides a summary of the most important information about ACAM2000. Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. If you would like more information or have any questions, talk to your healthcare provider. You can ask your healthcare provider for information about ACAM2000 that is written for healthcare professionals. You can also visit http:www.sanofipasteur.us/acam2000. The vaccine should not be used for a condition other than that for which it is prescribed.

What are the ingredients in ACAM2000?

ACAM2000: live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health Strain) and grown in African Green Monkey kidney (Vero) cells

Inactive ingredients: 6-8 mM HEPES (pH 6.5-7.5), 2% human serum albumin USP, 0.5 – 0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of the antibiotics neomycin and polymyxin B

Diluent for ACAM2000: 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP

This Medication Guide has been approved by the U.S. Food and Drug Administration.

17.6 Appendix IVb: Attachment 2 to US Health Affairs Memorandum 'Smallpox Trifold Brochure'

Note: The US Health Affairs Memorandum; Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program attaches the version from 1 August 2007 for the Tri fold Brochure Smallpox Vaccine and the Smallpox Vaccination Program. This CTP replaces the Tri fold Brochure Smallpox Vaccine and the Smallpox Vaccination Program Version 1 August 2007 with the latest version from 14 August 2014.

What is the smallpox vaccine?

Smallpox vaccine contains a weakened live virus called "vaccinia." Vaccinia is a virus related to smallpox but does NOT cause the disease. After one dose of vaccine, about 95% of people develop protection within 5 to 10 days. Currently, in a pre-event setting, a booster dose is recommended every 10 years to maintain immunity.

The smallpox vaccine that is licensed in the U.S. is called ACAM2000. The vaccine is delivered in the upper arm by pricking the top layer of skin 15 times. The pricking is not deep and should not cause any active bleeding at the site.

Who should not get smallpox vaccine?

Prior to receiving the smallpox vaccine, individuals are required to complete the Smallpox Vaccination Screening Form. Individuals that should not receive the smallpox vaccine include those:

- With a weak immune system due to disease, medication, or radiation therapy
- With any previous history of eczema, atopic dermatitis or persistent skin rashes
- With a current active case of the following skin conditions: (Once the skin condition is healed you may be vaccinated)
  - burns
  - impetigo
  - contact dermatitis
  - chickenpox
  - shingles
  - psoriasis
  - uncontrolled acne
  - an active case of herpes or any other open skin condition
- Who are pregnant or could be pregnant
- Who live with or have intimate contact with a person who has any of the above conditions
- With serious heart or blood vessel conditions (such as angina, heart attack, coronary artery disease, congestive heart failure, stroke, other cardiac problems)
- With at least 3 cardiac risk factors to include:
  - smoking
  - high blood pressure
  - high cholesterol
  - diabetes
  - family history of heart disease

Continued on following page ▶

USAPHC
U.S. ARMY PUBLIC HEALTH COMMAND
http://phc.amedd.army.mil

Report any illness or adverse event that may occur after vaccination to your healthcare provider or the Vaccine Adverse Events Reporting System (VAERS). You can submit a VAERS report online at http://vaers.hhs.gov/ or call 1-800-822-7967.

More information from Military Vaccine Agency-Vaccine Healthcare Centers Network (MILVAX-VHCN)

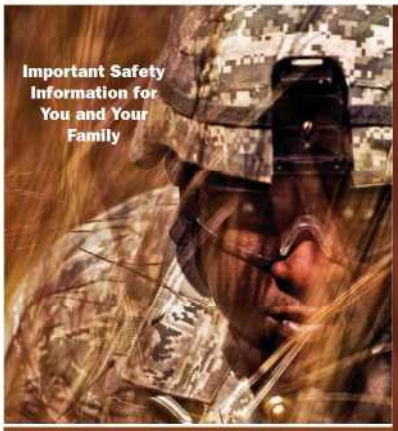
- **For routine 24/7 clinical consultation or exemption assistance:**
  Phone: 1.866.210.6469
  E-Mail: https://askvhc.amedd.army.mil/Questions/NewQuestionUnRegistered.aspx
- **For information about vaccines or policies:**
  Phone: 877.GETVACC (877.438.8222) DSN 761.4245
  E-Mail: DoDvaccines@mail.mil
  Website: www.vaccines.mil
- **Civilian Healthcare Providers:**
  If military member presents to you for a condition that may be an adverse event caused by a military vaccination, please provide the appropriate care.
  For authorization and payment contact;
  The Military Treatment Facility (MTF) where the member is enrolled, OR contact the **Military Medical Support Office (MMSO)** 888.647.6676 if not enrolled to an MTF.

MILVAX VHC
http://www.vaccines.mil

Use of trademarked names does not imply endorsement by the U.S. Army but is intended only to assist in identification of a specific product.

Approved for public release, distribution unlimited.

TA-186-0714



Important Safety Information for You and Your Family

What You Need to Know About Smallpox Vaccine

What is smallpox?

Smallpox is a contagious and infectious disease caused by the variola virus. Smallpox can be deadly; resulting in death for about 3 out of 10 unvaccinated individuals. Survivors are often left with scars on their bodies and their eyes, resulting in blindness.

How does the smallpox virus spread and what are the symptoms?

The virus is usually spread by prolonged face-to-face contact with an infected person, by direct contact with infected body fluids or contaminated objects like clothing, towels, or bedding. Symptoms of smallpox begin with a high fever, head and body aches, and fatigue. A pustular rash typically develops 12 to 14 days after exposure lasting for about 3 weeks. A person infected with the smallpox virus is contagious from the time fever starts, but is most highly contagious when a rash begins. The infected person can spread the disease until the last scab falls off. There is no specific treatment to cure a smallpox infection, and the only way to prevent the disease is through vaccination.

Why is the Department of Defense vaccinating personnel?

Due to vaccination of the masses, smallpox was declared eradicated in 1980, and routine smallpox vaccination stopped. Although no cases of smallpox have been reported since the eradication, the potential exists for the virus to be used as a biological weapon by enemies of the U.S. The DoD began the current smallpox vaccination program in 2002 to protect personnel traveling to high threat areas.

Who is required to receive the vaccine?

Smallpox vaccination is mandatory for uniformed personnel deploying or assigned to the Korean Peninsula for 15 or more consecutive days. Vaccinations are also mandatory for some emergency-essential personnel and contractors, certain uniformed personnel assigned to special units, and comparable U.S. government civilian employees.

For more details on the specific criteria for each of these groups, please see applicable DoD and Service policies.

Who should not get smallpox vaccine? (continued from previous page)

- Using eye drops or ointment
- Who are breastfeeding
- With recent tattoos (30 days or less), tattoos must be healed before receiving the vaccine and no new tattoos should be gotten until the vaccination site is healed
- Who have had problems after previous doses or are allergic to the vaccine or any of its component

What should I expect the vaccination site to look like after receiving the vaccine?

If vaccination is successful, after 2 to 4 days a red and itchy bump will form at the vaccination site. Over the next few days, the bump becomes a blister and fills with pus. During the second week, the blister dries up and a scab forms. The scab falls off after 2 to 4 weeks, leaving a scar. The vaccine virus is present on the skin at the vaccination site for 30 days after vaccination and until the site is healed.

Smallpox Vaccination Site

Day 4	Day 7	Day 14

To verify proper vaccination, it is important for a healthcare provider to evaluate your vaccination site 6 to 8 days after receiving the vaccine. People vaccinated for the first time may have a larger reaction than those being revaccinated. Your site may not look exactly like the picture, because everyone responds differently to the vaccine. However, if your vaccination site does NOT look similar to one of the pictures above, on or between days 6 to 8 after vaccination, see your healthcare provider; you may need to be revaccinated. If you have any questions or concerns about the smallpox vaccination site, contact your healthcare provider.

How will I feel after vaccination?

Most individuals experience mild reactions that usually peak 3 to 12 days after vaccinations and rarely last more than 30 days. The most common reactions include:

- Itching at and around the vaccination site
- Swollen and/or sore lymph nodes in the armpit and neck
- Arm may become sore and red around vaccination site
- Fever, headache, and body ache
- Fatigue

On rare occasions individuals may experience more serious side effects that require immediate medical attention. If you experience any of the below symptoms it is important that you seek immediate medical care at the nearest medical facility.

- Rash or sores elsewhere on the body days to several weeks after vaccination
- Allergic reaction (hives, wheezing, or light headed) after vaccination
- A serious skin rash in people with eczema or atopic dermatitis
- Ongoing infection of skin with tissue destruction or site is unable to heal
- Confusion, paralysis, numbness, change in vision, or weakness of arm, leg, or face.
- Chest pain, rapid heartbeat, exercise intolerance, shortness of breath or any other heart symptoms within 30 days of vaccination. These symptoms may indicate an inflammation in and around the heart. Seek immediate medical care if you experience any of these symptoms.

Remember to inform your doctor that you recently received a smallpox vaccination. Contact the 24-hour DoD Vaccine Healthcare Centers Network at 1.866.210.6469 for immediate clinical consultation and register with the ACAM2000™ Myopericarditis Registry at 619.553.9255/DSN 553.9255 or NHRC.VaccineRegistry@med.navy.mil

Adverse events after vaccination should be reported to the Vaccine Adverse Events Reporting System (VAERS). Submit VAERS online at http://vaers.hhs.gov or call 1.800.822.7967.

How should I care for the vaccination site?

Remember the three "W's":

1. Wear a non-stick bandage that covers the vaccination site
2. Wear long sleeves to cover the bandage
3. Wash your hands!!

To reduce complications and spreading of the disease elsewhere on your body or to someone else:

- Keep site completely covered with a dry non-stick bandage (i.e., Band-Aid®, telfa™ pad). DO NOT use gauze
- Avoid directly touching the vaccination site
- Do NOT let others touch your vaccination site or materials that may have touched your blister; like clothing and bandages
- Keep site as dry as possible and when showering keep site covered
- Avoid swimming, wrestling, or other contact sports until site is healed
- Wash your hands frequently with soap and water or a alcohol- based hand sanitizer

Make sure you cover the site with a bandage and wear long sleeves to prevent scratching; especially in bed. Change your bandages frequently so surface remains dry. If you exercise enough to cause sweat to drip, use a waterproof or reinforced bandage. When not around others, you can leave the site uncovered; air drying will speed healing. Minimize close contact with infants until the site is healed; at least 30 days after vaccination.

Normal bathing can continue, but don't touch or scrub the vaccination site. Be careful when toweling off so as not to spread the virus to other parts of your body. Dry the site last by blotting with tissue, toilet paper, or paper towel. Discard used bandages and tissue paper in sealed or double plastic bags. You may add bleach, alcohol, or soap to the bag to kill the virus. Reapply a clean, dry bandage after showering and do not use creams or ointments; they will delay healing and can spread the virus.

Do not share clothes, towels, linen, or toiletries with others. To avoid the handling of these items by others, vaccine recipients should wash their own laundry in hot water with detergent.

Can the vaccine virus be sexually transmitted?

No, the virus is not passed through kissing or sex, and is not airborne. Although rare, transfer of the vaccine virus to a spouse and intimate partner has occurred. You can be intimate with your partner; however, be sure to follow all precautions as stated above, such as wearing a bandage and long sleeves; if the vaccination site is not properly covered, you may spread the virus to your partner. Be sure to thoroughly wash your hands before and after sexual contact.

What if I become pregnant within 4 weeks of my vaccination?

Women should avoid getting pregnant for 4 weeks after receiving the smallpox vaccination

A very rare complication of women vaccinated during pregnancy is called fetal vaccinia. There have been only three cases in the 20th century and no reported cases since the U.S. started the smallpox program in 2003. If you received the smallpox vaccine within 42 days from conception it is recommended you enroll in the National Smallpox Vaccine in Pregnancy Registry by calling 619.553.9255/DSN 553.9255 or email at NHRC.birthregistry@med.navy.mil. The registry will collect important health information and can answer the many questions from participants and their healthcare providers.

There is no specific treatment for smallpox disease, and the only prevention is vaccination.

17.7 Appendix IVc: Attachment 3 to US Health Affairs Memorandum 'ACAM2000® Prescribing Information'

Note: The US Health Affairs Memorandum; Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program attaches the version from 8/2007 for the ACAM2000™ Prescribing Information. This CTP replaces the ACAM2000™ Prescribing Information Version 8/2007 with the latest ACAM2000® Prescribing Information Version 12/2015.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all information needed to use ACAM2000 safely and effectively. See full prescribing information for ACAM2000.

ACAM2000, (Smallpox (Vaccinia) Vaccine, Live,)

Lyophilized preparation for percutaneous scarification

Initial U.S. Approval: 2007

WARNING:

See full prescribing information for complete boxed warning

- **Myocarditis and pericarditis (suspect cases observed at a rate of 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3)), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), 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 certain individuals and may result in severe disability, permanent neurological sequelae and/or death [see Warnings and Precautions (5)].**

----------INDICATIONS AND USAGE----------

ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

----------DOSAGE AND ADMINISTRATION----------

- ACAM2000 must be administered only by vaccine providers with training to safely and effectively administer the vaccine by the percutaneous route (scarification). The manufacturer is responsible for ensuring that such training is available to all vaccine providers, as required by the manufacturer's Risk Management Plan. (2.3)
- A droplet of ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a bifurcated needle. ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. (2.3)
- The droplet (0.0025 mL) of reconstituted vaccine is picked up with a bifurcated needle by dipping needle into ACAM2000 vial. (2.3)
- See full prescribing information for instructions for vaccine preparation (2.2), administration including provision of the Medication Guide to vaccinees and instruction to vaccinees about vaccination site care, (2.3) and interpretation of response to vaccination. (2.4)
- Re-vaccination may be recommended (e.g. every 3 years). (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Lyophilized powder reconstituted with packaged diluent. After reconstitution, each vial has approximately 100 doses of 0.0025 mL of live vaccinia virus containing 2.5 – 12.5 x 10^5 plaque forming units. (3)

----------CONTRAINDICATIONS----------

- Individuals with severe immunodeficiency who are not expected to benefit from the vaccine. These individuals may include persons who are undergoing bone marrow transplantation or persons with primary or acquired immunodeficiency states who require isolation (4).

-- ----------WARNINGS AND PRECAUTIONS----------

- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic dilated cardiomyopathy. (5.1, 5.2)
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, fetal vaccinia and fetal death. (5.1)
- Ocular vaccinia and blindness. (5.3)
- These risks, including risks of severe disability and/or death, are increased in vaccinees with:
  - Cardiac disease (5.2).
  - Eye disease treated with topical steroids. (5.3)
  - Congenital or acquired immune deficiency disorders. (5.4)
  - History or presence of eczema and other skin conditions. (5.5)
  - Infants < 12 months of age. (5.6)
  - Pregnancy (5.7)
- 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 stated for vaccinees. (5.10)

----------ADVERSE REACTIONS----------

Common adverse events include inoculation site signs and symptoms, lymphadenitis, and constitutional symptoms, such as malaise, fatigue, fever, myalgia, and headache (6.1). These adverse events are less frequent in revaccinated persons than persons receiving the vaccine for the first time.

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.

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi Pasteur. at 1-800-822-2463 (1-800-VACCINE) or VAERS at 800-822-7967 and https://vaers.hhs.gov.

----------USE IN SPECIFIC POPULATIONS----------

- ACAM2000 may rarely cause fetal infection, usually resulting in stillbirth or death. (8.1)
- ACAM2000 live vaccinia virus may be transmitted from a lactating mother to her infant causing complications in the infant from inadvertent inoculation. (8.3)
- ACAM2000 may be associated with an increased risk of serious complications in children, especially in infants younger than 12 months. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: [09/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING:

- Suspected cases of myocarditis and/or pericarditis have been observed in healthy adult primary vaccinees (at an approximate rate of 5.7 per 1000, 95% CI: 1.9-13.3) receiving ACAM2000 [see Warnings and Precautions (5.1)].
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), 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 [see Warnings and Precautions (5)].

  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.

1 INDICATIONS AND USAGE

ACAM2000® is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

2 DOSAGE AND ADMINISTRATION

ACAM2000 must be administered only by vaccine providers with training to safely and effectively administer the vaccine by the percutaneous route (scarification). ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route.

2.1 Instructions for Vaccine Preparation

2.1.1 Reconstitution

ACAM2000 is reconstituted by addition of 0.3 mL of diluent to the vial containing lyophilized vaccine. **Note: this 0.3 mL of diluent is not the entire content of the diluent vial.** ACAM2000 should only be reconstituted with 0.3 mL of the diluent provided. The vaccine vial should be removed from cold storage and brought to room temperature before reconstitution. The flip cap seals of the vaccine and diluent vials are removed, and each rubber stopper is wiped with an isopropyl alcohol swab and allowed to dry thoroughly. Using aseptic technique and a sterile 1 mL syringe fitted with a 25 gauge x 5/8" needle (provided), draw up 0.3 mL of diluent and transfer the entire content of the syringe to the vaccine vial. Gently swirl to mix but try not to get product on the rubber stopper. The reconstituted vaccine should be a clear to slightly hazy, colorless to straw-colored liquid free from extraneous matter. Reconstituted vaccine should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is observed, the vaccine should not be used and the vial should be disposed safely. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)]

2.1.2 Storage following Reconstitution

After reconstitution, ACAM2000 vaccine may be administered within 6 to 8 hours if kept at room temperature (20-25°C, 68-77°F). Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) up to 30 days, after which it should be discarded as a biohazardous material. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)] Exposure of reconstituted vaccine to room temperature during vaccination sessions should be minimized by placing it in refrigerator or on ice between patient administrations.

2.2 Preparation / Handling Precautions and Instructions for Disposal

Personnel preparing and administering the vaccine should wear surgical or protective gloves 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.

2.3 Vaccination Instructions

All vaccine providers must receive education on the proper administration as required by the U.S. Food and Drug Administration. All vaccine providers also receive a Medication Guide to distribute to each vaccinee prior to administering the vaccine. In the event of an actual smallpox emergency, declared by the Secretary of the U.S. Department of Health and Human Services, vaccine providers may follow educational instructions they receive from the manufacturer, such as how to educate vaccinees without a Medication Guide.

The site of vaccination is the upper arm over the insertion of the deltoid muscle.

No skin preparation should be performed unless the skin at the intended site of vaccination is obviously dirty, in which case an alcohol swab(s) may be used to clean the area. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the live vaccine virus by the alcohol.

Remove the vaccine vial cap. Remove bifurcated needle from individual wrapping. Submerge bifurcated end of needle in reconstituted vaccine solution. The needle will pick up a droplet of vaccine (0.0025 mL) within the fork of the bifurcation. Use aseptic technique, i.e., do not insert the upper part of the needle that has been in contact with fingers into the vaccine vial, and never re-dip the needle into the vaccine vial if the needle has touched skin.

Deposit the droplet of vaccine onto clean, dry skin of the arm prepared for vaccination. The needle is held between thumb and first finger perpendicular to the skin. The wrist of the hand holding the needle of the vaccinator rests against the patient's arm. Rapidly make 15 jabs of the needle perpendicular to the skin through the vaccine droplet to puncture the skin, within a diameter of about 5 mm. The jabs should be vigorous enough so that a drop of blood appears at the vaccination site.

Any excess droplets of vaccine and blood should be wiped off the skin using a dry gauze pad and discarded in a biohazard container. Discard the needle in a biohazard sharps container. Close the vaccine vial by reinserting the rubber cap and return to a refrigerator or place on ice unless it will be used immediately to vaccinate another subject. [See Storage Following Reconstitution (2.1.2)]

Cover the vaccination site loosely with a gauze bandage, using first aid adhesive tape to keep it in place. This bandage provides a barrier to protect against spread of the vaccinia virus. If the vaccinee is involved in direct patient care, the gauze should be covered with a semipermeable (semiocclusive) dressing as an additional barrier. A semipermeable dressing is one that allows for the passage of air but does not allow for the passage of fluids.

Wash hands with soap and warm water or with alcohol-based hand rubs such as gels or foams after direct contact with the vaccination site, the bandage or clothes, towels or sheets that might be contaminated with virus from the vaccination site. This is vital in order to remove any virus from your hands and prevent contact spread.

Put the contaminated bandages in a sealed plastic bag and throw them away in the trash.

Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.

Don't use a bandage that blocks air from the vaccination site. This may cause the skin at the vaccination site to soften and wear away. Use loose gauze secured with medical tape to cover the site.

Don't put salves or ointments on the vaccination site.

2.4 Instructions for Interpreting Vaccination Response

2.4.1 Primary Vaccinees

In an individual vaccinated for the first time (primary vaccination), the expected response to vaccination is the development of a major cutaneous reaction (characterized by a pustule) at the site of inoculation. The lesion evolves gradually, with appearance of a papule at the site of vaccination after 2-5 days. The papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination. The pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar. (See Figure 1) Formation of a major cutaneous reaction by day 6-8 is evidence of a successful 'take' and acquisition of protective immunity. An equivocal reaction is any reaction that is not a major reaction, and indicates a non-take (vaccination failure) due to impotent vaccine or inadequate vaccination technique.

2.4.2 Previously Vaccinated Individuals (Revaccination)

Successful vaccination in an individual previously exposed to vaccine is confirmed when a major cutaneous reaction [See Primary Vaccinees (2.4.1) and Figure 1] is observed 6 to 8 days post-vaccination. However any prior vaccination may modify (reduce) the cutaneous response upon revaccination (Figure 2) such that the absence of a cutaneous response does not necessarily indicate vaccination failure. Previously vaccinated individuals who do not have a cutaneous response on revaccination do not require revaccination to try to elicit a cutaneous response.

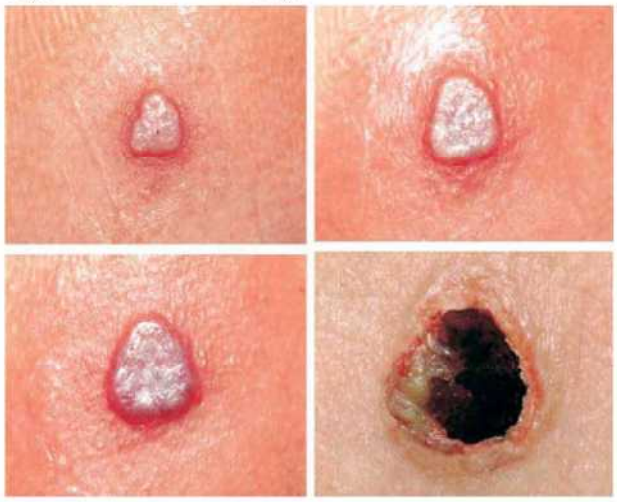
2.4.3 Vaccination Failures

Individuals who are not successfully vaccinated (i.e., vaccination failures) after primary vaccination may be revaccinated again in an attempt to achieve a satisfactory take. The vaccination procedures should be checked, and vaccination repeated with vaccine from another vial or vaccine lot, employing the same technique described in 2.3 [See Vaccination Instructions (2.3)].

If a repeat vaccination is conducted using vaccine from another vial or vaccine lot fails to produce a major reaction, healthcare providers should consult the Centers for Disease Control and Prevention (CDC) at (404) 639-3670 or their state or local health department before giving another vaccination.

Figure 1: Progression of major cutaneous reaction after primary vaccination[1]

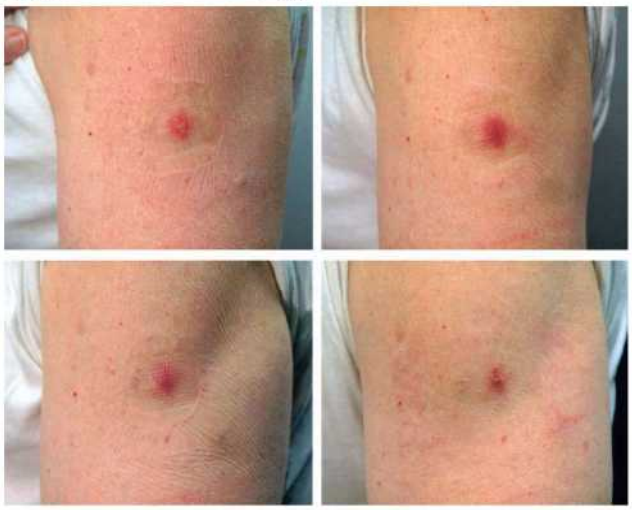
Day 5 **Day 8**



Day 10 **Day 14**

Figure 2: Progression of major cutaneous reaction after revaccination[1]

Day 3 **Day 7**



Day 10 **Day 14**

2.5 Booster Schedule

Persons at continued high risk of exposure to smallpox (e.g., research laboratory workers handling variola virus) should receive repeat ACAM2000 vaccination every three years.

2.6 Smallpox Vaccination Recommendations from US Government Agencies

Additional information may be obtained from U.S. Department of Defense (http://www.dtic.mil/whs/directives/corres/html/620503.htm) and U.S. Centers for Disease Control and Prevention (CDC) about smallpox vaccination (http://www.bt.cdc/gov/agent/smallpox/vaccination).

3 DOSAGE FORMS AND STRENGTHS

After reconstitution of the lyophilized preparation, each vial has approximately 100 doses of 0.0025 mL of vaccinia virus (live) containing 2.5-12.5x10^5 plaque forming units / dose.

4 CONTRAINDICATIONS

There are very few absolute contraindications to this vaccine for those who are at high risk for smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection. See *Warnings and Precautions* (5) for persons who are at higher risk of experiencing serious vaccination complications.

Severe Immune Deficiency

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems. Individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000. These individuals may include individuals who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation.

5 WARNINGS AND PRECAUTIONS

Persons at greatest risk of experiencing serious vaccination complications are often those at greatest risk for death from smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

5.1 Serious Complications and Death

Serious complications that may follow either primary live vaccinia smallpox vaccination or revaccination include: myocarditis and/or pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, blindness, and fetal death in pregnant women. These complications may rarely lead to severe disability, permanent neurological sequelea and death. Based on clinical trials, symptoms of suspected myocarditis or pericarditis (such as chest pain, raised troponin/cardiac enzymes, or ECG abnormalities) occur in 5.7 per 1000 primary vaccinations. This finding includes cases of acute symptomatic or asymptomatic

myocarditis or pericarditits or both. Historically, death following vaccination with live vaccinia virus is a rare event; approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations have occurred after vaccination with live vaccinia virus. Death is most often the result of sudden cardiac death, postvaccinial encephalitis, progressive vaccinia, or eczema vaccinatum. Death has also been reported in unvaccinated contacts accidentally infected by individuals who have been vaccinated.

5.1.1 Incidence of Serious Complications in 1968 US Surveillance Studies

Estimates of the risks of occurrence of serious complications after primary vaccination and revaccination, based on safety surveillance studies conducted when live vaccinia virus smallpox vaccine (i.e., New York City Board of Health strain, Dryvax®) was routinely recommended, are as follows:

Table 1A - Rates of reported complications[a] associated with primary vaccinia vaccinations (cases/million vaccinations)[b]

Age (yrs)	<1	1-4	5-19	≥20	Overall rates[h]
Inadvertent inoculation[c] §	507.0	577.3	371.2	606.1	**529.2**
Generalized vaccinia	394.4	233.4	139.7	212.1	**241.5**
Eczema vaccinatum	14.1	44.2	34.9	30.3	**38.5**
Progressive vaccinia[d]	--[g]	3.2	--[g]	--[g]	**1.5**
Post-vaccinial encephalitis	42.3	9.5	8.7	--[g]	**12.3**
Death[e]	5	0.5	0.5	unknown	--
Total[f]	**1549.3**	**1261.8**	**855.9**	**1515.2**	**1253.8**

[a] See article for descriptions of complications.
[b] Adapted from Lane JM, Ruber FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis. 1970; 122:303-309.
[c] Referenced as accidental implantation.
[d] Referenced as vaccinia necrosum.
[e] Death from all complications.
[f] Rates of overall complications by age group include complications not provided in this table, including severe local reactions, bacterial superinfection of the vaccination site, and erythema multiforme.
[g] No instances of this complication were identified during the 1968 10-state survey.
[h] Overall rates for each complication include persons of unknown age.

Table 1B - Rates of reported serious complications[a] associated with vaccinia revaccinations (cases/million vaccinations)[b]

Age (yrs)	<1	1-4	5-19	≥20	Overall rates[b]
Inadvertent inoculation[c]	[g]	109.1	47.7	25.0	**42.1**
Generalized vaccinia	[g]	[g]	9.9	9.1	**9.0**
Eczema vaccinatum	[g]	[g]	2.0	4.5	**3.0**
Progressive vaccinia[d]	[g]	[g]	[g]	6.8	**3.0**
Post-vaccinial encephalitis	[g]	[g]	[g]	4.5	**2.0**
Death[e]	--	--	--	--	--
Total[f]	[g]	**200.0**	**85.5**	**113.6**	**108.2**

See Table 1A for explanation of footnotes.

5.1.2 Incidence of Serious Complications and Emergence of Myocarditis and/or Pericarditis in 2002-2005

Data on the incidence of adverse events among U.S. military personnel and civilian first responders vaccinated with Dryvax®, a licensed live vaccinia virus smallpox vaccine, during vaccination programs initiated in December 2002 are shown below in Table 2. The incidence of preventable adverse events (eczema vaccinatum, contact transmission, and auto-inoculation) were notably lower in these programs when compared with data collected in the 1960s; presumably because of better vaccination screening procedures and routine use of protective bandages over the inoculation site. Myocarditis and pericarditis were not commonly reported following smallpox vaccination in the 1960s, but emerged as a more frequent event based on more active surveillance in the military and civilian programs.

Table 2 - Serious adverse events in 2002-2005 [5]

Adverse event	Department of Defense program (n=730,580[a]) as of Jan05		Department of Health and Human Services program (n=40,422) as of Jan04[b]	
	N	Incidence/ million	N	Incidence /million
Myo/pericarditis	86	117.71	21	519.52
Post-vaccinal encephalitis	1	1.37	1	24.74
Eczema vaccinatum	0	0.00	0	0.00
Generalized vaccinia	43	58.86	3	74.22
Progressive vaccinia	0	0.00	0	0.00
Fetal vaccinia	0	0.00	0	0.00
Contact transmission	52	71.18	0	0.00
Auto-inoculation (non-ocular)	62	84.86	20	494.78
Ocular vaccinia	16	21.90	3	74.22

[a] 71% primary vaccination; 89% male; median age 28.5 yr
[b] 36% primary vaccination; 36% male; median age 47.1 yr

5.1.3 Myocarditis and Pericarditis in the ACAM2000 Clinical Trial Experience

In clinical trials involving 2983 subjects who received ACAM2000 and 868 subjects who received Dryvax®, ten (10) cases of suspected myocarditis [0.2% (7 of 2983) ACAM2000 subjects and 0.3% (3 of 868) Dryvax® subjects] were identified. The mean time to onset of suspected myocarditis and/or pericarditis from vaccination was 11 days, with a range of 9 to 20 days. All subjects who experienced these cardiac events were naïve to vaccinia. Of the 10 subjects, 2 were hospitalized. None of the remaining 8 cases required hospitalization or treatment with medication. Of the 10 cases, 8 were sub-clinical and were detected only by ECG abnormalities with or without associated elevations of cardiac troponin I. All cases resolved by 9 months, with the exception of one female subject in the Dryvax® group, who had persistent borderline abnormal left ventricular ejection fraction on echocardiogram. The best estimate of risk for myocarditis and pericarditis is derived from the Phase 3 ACAM2000 clinical trials where there was active monitoring for potential of myocarditis and pericarditis. Among vaccinees naïve to vaccinia, 8 cases of suspected myocarditis and pericarditis were identified across both treatment groups, for a total incidence rate of 6.9 per 1000 vaccinees (8 of 1,162). The rate for the ACAM2000 treatment group were similar: 5.7 (95% CI: 1.9-13.3) per 1000 vaccinees (5 of 873 vaccinees) and for the Dryvax® group 10.4 (95% CI: 2.1-30.0) per 1000 vaccinees (3 of 289 vaccinees). No cases of myocarditis and/or pericarditis were identified in 1819 previously vaccinated subjects. The long-term outcome of myocarditis and pericarditis following ACAM2000 vaccination is currently unknown.

5.2 Cardiac Disease

Ischemic cardiac events, including fatalities, have been reported following smallpox vaccination; the relationship of these events, if any, to vaccination has not been established. In addition, cases of non-ischemic, dilated cardiomyopathy have been reported following smallpox vaccination; the relationship of these cases to smallpox vaccination is unknown.

There may be increased risks of adverse events with ACAM2000 in persons with known cardiac disease, including those diagnosed with previous

myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest pain or shortness of breath with activity, stroke or transient ischemic attack, or other heart conditions. In addition, subjects who have been diagnosed with 3 or more of the following risk factors for ischemic coronary disease: 1) high blood pressure; 2) elevated blood cholesterol; 3) diabetes mellitus or high blood sugar; 4) first degree relative (for example mother, father, brother, or sister) who had a heart condition before the age of 50; or 5) smoke cigarettes may have increased risks.

5.3 Ocular Complications and Blindness

Accidental infection of the eye (ocular vaccinia) may result in ocular complications including keratitis, corneal scarring and blindness. Patients who are using corticosteroid eye drops may be at increased risk of ocular complications with ACAM2000.

5.4 Presence of Congenital or Acquired Immune Deficiency Disorders

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems, including patients with leukemia, lymphoma, organ transplantation, generalized malignancy, HIV/AIDS, cellular or humoral immune deficiency, radiation therapy, or treatment with antimetabolites, alkylating agents, or high-dose corticosteroids (>10 mg prednisone/day or equivalent for ≥2 weeks). The vaccine is contraindicated in individuals with severe immunodeficiency [See Contraindications (4)]. Vaccinees with close contacts who have these conditions may be at increased risk because live vaccinia virus can be shed and be transmitted to close contacts.

5.5 History or Presence of Eczema and Other Skin Conditions

Persons with eczema of any description such as, atopic dermatitis, neurodermatitis, and other eczematous conditions, regardless of severity of the condition, or persons who have a history of these conditions at any time in the past, are at higher risk of developing eczema vaccinatum. Vaccinees with close contacts who have eczematous conditions, may be at increased risk because live vaccinia virus can shed and be transmitted to these close contacts. Vaccinees with other active acute, chronic or exfoliative skin disorders (including burns, impetigo, varicella zoster, acne vulgaris with open lesions, Darier's disease, psoriasis, seborrheic dermatitis, erythroderma, pustular dermatitis, etc.), or vaccinees with household contacts having such skin disorders might also be at higher risk for eczema vaccinatum.

5.6 Infants (< 12 months of Age) and Children

ACAM2000 has not been studied in infants or children. The risk of serious adverse events following vaccination with live vaccinia virus is higher in infants. Vaccinated persons who have close contact with infants, e.g., breastfeeding, must take precautions to avoid inadvertent transmission of ACAM2000 live vaccinia virus to infants.

5.7 Pregnancy

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal vaccinia and fetal death. If ACAM2000 is administered during pregnancy, the vaccinee should be apprised of the potential hazard to the fetus [See Use in Specific Populations (8.1)]. Vaccinees with close contacts who are pregnant may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

5.8 Allergy to ACAM2000 Smallpox Vaccine or its Components

ACAM2000 contains neomycin and polymyxin B. Persons allergic to these components may be at higher risk for adverse events after vaccination.

Both the vaccine and diluent vial stoppers do not contain latex material.

5.9 Management of Smallpox Vaccine Complications

The CDC can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia (smallpox) vaccination. Vaccinia Immune Globulin (VIG) is indicated for certain complications of vaccination live vaccinia virus smallpox vaccine. If VIG is needed or additional information is required, physicians should contact the CDC at (404) 639-3670, Monday through Friday 8 AM to 4:30 PM Eastern Standard Time; at other times call (404) 639-2888.

5.10 Prevention of Transmission of Live Vaccinia Virus

The most important measure to prevent inadvertent auto-inoculation and contact transmission from vaccinia vaccination is thorough hand washing after changing the bandage or after any other contact with the vaccination site.

Individuals susceptible to adverse effects of vaccinia virus, i.e., those with cardiac disease, eye disease, immunodeficiency states, including HIV infection, eczema, pregnant women and infants, should be identified and measures should be taken to avoid contact between those individuals and persons with active vaccination lesions.

Recently vaccinated healthcare workers should avoid contact with patients, particularly those with immunodeficiencies, until the scab has separated from the skin at the vaccination site. However, if continued contact with patients is unavoidable, vaccinated healthcare workers should ensure the vaccination site is well covered and follow good hand-washing technique. In this setting, a more occlusive dressing may be used. Semipermeable polyurethane dressings are effective barriers to shedding of vaccinia. However, exudate may accumulate beneath the dressing, and care must be taken to prevent viral spread when the dressing is changed. In addition, accumulation of fluid beneath the dressing may increase skin maceration at the vaccination site. Accumulation of exudate may be decreased by first covering the vaccination with dry gauze, then applying the dressing over the gauze. The dressing should be changed every 1-3 days [See Self Inoculation and Spread to Close Contacts (17.3) and Care of the Vaccination Site and Potentially Contaminated Materials (17.4)].

5.11 Blood and Organ Donation

Blood and organ donation should be avoided for at least 30 days following vaccination with ACAM2000.

5.12 Limitations of Vaccine Effectiveness

ACAM2000 smallpox vaccine may not protect all persons exposed to smallpox.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome) and eczema vaccinatum. Severe disability, permanent neurological sequelae, and/or death may occur. Death of unvaccinated individuals who have contact with vaccinated individuals. [See Warnings and Precautions (5.1)].
- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic, dilated cardiomyopathy [See Warnings and Precautions (5.1)].
- Ocular complications and blindness [See Warnings and Precautions (5.3)].

6.1 Overall Adverse Reaction Profile

Information regarding the safety of ACAM2000 has been derived from three sources: 1) ACAM2000 clinical trial experience (Phase 1, 2 and 3 clinical trials), 2) data compiled during the era of routine smallpox vaccination using other NYCBH vaccinia vaccines and 3) adverse event data obtained during military and civilian smallpox vaccination programs (2002-2005) that used Dryvax®, a licensed live vaccinia virus smallpox vaccine.

- General Disorders and Administrative Site Conditions: In the ACAM2000 clinical studies 97% and 92% of vaccinia-naïve and previously vaccinated subjects, respectively, experienced one or more adverse event. Common events included injection site reactions (erythema, pruritus, pain and swelling) and constitutional symptoms (fatigue, malaise, feeling hot, rigors and exercise tolerance decreased). Across all ACAM2000 studies 10% of vaccinia-naïve and 3% of previously vaccinated subjects experienced at least one severe adverse event (defined as interfering with normal daily activities).
- Nervous System Disorder: Overall, 50% and 34% of vaccinia-naïve subjects and previously vaccinated subjects, respectively, reported headaches in ACAM2000 studies. There have been reports of headache following smallpox vaccination which required hospitalization. Although <1% of the subjects in the ACAM2000 program experienced severe headaches, none required hospitalization.

  Neurological adverse events assessed among the 2002 - 2005 military (n=590,400) and DHHS (n=64,600) programs temporally associated with smallpox vaccination included headache (95 cases), non-serious limb paresthesias (17 cases) or pain (13 cases) and dizziness or vertigo (13 cases). Serious neurologic adverse events included 13 cases of suspected meningitis, 3 cases of suspected encephalitis or myelitis, 11 cases of Bell palsy, 9 seizures (including 1 death), and 3 cases of Guillain-Barre syndrome. Among these 39 events, 27 (69%) occurred in primary vaccinees and all but 2 occurred within 12 days of vaccination. There have also been cases of photophobia following smallpox vaccination, some of which required hospitalization.
- Musculoskeletal and Connective Tissue Disorders: Across all ACAM2000 studies, severe, vaccine-related myalgia was seen in 1% of

vaccinia-naïve subjects and <1% of previously vaccinated subjects. Other adverse events included back pain, arthralgia and pain in extremity and none occurred with a frequency of more than 2% in either the vaccinia-naïve or previously vaccinated populations.

- Blood and Lymphatic System Disorders: The only adverse event occurring at ≥5% in the ACAM2000 studies were lymph node pain and lymphadenopathy. The incidence of severe lymph node pain and lymphadenopathy was <1%.
- Gastrointestinal (GI) Disorders: Commonly reported GI disorders among ACAM2000-treated subjects included nausea and diarrhea (14%), constipation (6%), and vomiting (4%). Severe abdominal pain, nausea, vomiting, constipation diarrhea and toothache accounted for all the severe adverse events reported and occurred in <1% of subjects.
- Skin and Subcutaneous Tissue Disorders: Erythema and rash were noted in 18% and 8% of subjects respectively. In ACAM2000 subjects 1% of vaccinia-naïve and <1% of previously vaccinated subjects experienced at least one severe adverse event. With the exception of one case of contact dermatitis and one case of urticaria, erythema and rash accounted for all severe events.

  Generalized rashes (erythematous, papulovesicular, urticarial, folliculitis, nonspecific) are not uncommon following smallpox vaccination and are presumed to be hypersensitivity reactions occurring among persons without underlying illnesses. These rashes are generally self-limited and require little or no therapy, except among patients whose conditions appear to be toxic or who have serious underlying illnesses.

  Inadvertent inoculation at other body sites is the most frequent complication of vaccinia vaccination, usually resulting from autoinoculation of the vaccine virus transferred from the site of vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus. Accidental infection of the eye (ocular vaccinia) may result in ocular complications including, but not limited to, keratitis, corneal scarring and blindness.

  Major cutaneous reactions at the site of inoculation, characterized by large area of erythema and induration and streaking inflammation of draining lymphatics may resemble cellulitis. Benign and malignant lesions have been reported to occur at the smallpox vaccination site.

6.2 ACAM2000 Clinical Trial Experience

Two randomized, controlled, multi-center Phase 3 trials enrolled 2244 subjects that received ACAM2000 and 737 that received a comparison licensed live vaccinia virus vaccine, Dryvax®. Study 1 was conducted in male (66% and 63% for ACAM2000 and Dryvax®, respectively) and female (34% and 37% for ACAM2000 and Dryvax®, respectively) subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects). The majority of subjects were Caucasian (76% and 71% for ACAM2000 and Dryvax®, respectively) and the mean age was 23 in both groups with an age range from 18-30 years. Study 2 was conducted in male (50% and 48% for ACAM2000 and Dryvax®, respectively) and female (50% and 52% for ACAM2000 and Dryvax®, respectively) subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). The majority of subjects were Caucasian (78% for both groups) and the mean age was 49 years in both groups with an age range of 31 to 84 years.

6.2.1 Common Adverse Events Reported in ACAM2000 Clinical Program

Adverse events reported by ≥5% of subjects in either the ACAM2000 or the comparison treatment group during Phase 3 studies are presented by type of adverse events, by baseline vaccination status (vaccinia-naïve versus previously vaccinated) and by treatment group. Severe vaccine-related adverse events, defined as interfering with normal daily activities, in vaccinia-naïve subjects were reported by 10% of subjects in the ACAM2000 group and 13% in the comparison group. In the previously vaccinated subjects, the incidence of severe vaccine-related adverse events was 4% for the ACAM2000 groups and 6% for the comparison group.

Table 3 - Adverse Events Reported by ≥5% of Subjects in ACAM2000 or Dryvax®

	Study 1 Vaccinia-Naïve Subjects		Study 2 Previously Vaccinated Subjects	
	ACAM2000 N=873 n (%)	**Dryvax® N=289 n (%)**	**ACAM2000 N=1371 n (%)**	**Dryvax® N=448 n (%)**
At least 1 adverse event	**864 (99)**	**288 (100)**	**1325 (97)**	**443 (99)**
Blood and lymphatic system disorders	**515 (59)**	**204 (71)**	**302 (22)**	**133 (30)**
Lymph node pain[a]*	494 (57)	199 (69)	261 (19)	119 (27)
Lymphadenopathy	72 (8)	35 (12)	78 (6)	29 (6)
Gastrointestinal disorders	**273 (31)**	**91 (31)**	**314 (23)**	**137 (31)**
Nausea[a]	170 (19)	65 (22)	142 (10)	63 (14)
Diarrhea[a]	144 (16)	34 (12)	158 (12)	77 (17)
Constipation[a]	49 (6)	9 (3)	88 (6)	31 (7)
Vomiting[a]	42 (5)	10 (3)	40 (3)	18 (4)
General disorders and administration site conditions	**850 (97)**	**288 (100)**	**1280 (93)**	**434 (97)**
Injection site pruritus[a]	804 (92)	277 (96)	1130 (82)	416 (93)
Injection site erythema[a]	649 (74)	229 (79)	841 (61)	324 (72)
Injection site pain[a]	582 (67)	208 (72)	505 (37)	209 (47)
Fatigue[a]	423 (48)	161 (56)	468 (34)	184 (41)
Injection site swelling	422 (48)	165 (57)	384 (28)	188 (42)
Malaise[a]	327 (37)	122 (42)	381 (28)	147 (33)
Feeling hot[a]	276 (32)	97 (34)	271 (20)	114 (25)
Rigors[a]	185 (21)	66 (23)	171 (12)	76 (17)
Exercise tolerance decreased[a]	98 (11)	35 (12)	105 (8)	50 (11)
Musculoskeletal and connective tissue disorders	**418 (48)**	**153 (53)**	**418 (30)**	**160 (36)**
Myalgia[a]	404 (46)	147 (51)	374 (27)	148 (33)
Nervous system disorders	444 (51)	151 (52)	453 (33)	174 (39)
Headache[a]	433 (50)	150 (52)	437 (32)	166 (37)
Respiratory, thoracic, and mediastinal disorders	**134 (15)**	**40 (14)**	**127 (9)**	**42 (9)**
Dyspnea[a]	39 (4)	16 (6)	41 (3)	18 (4)
Skin and subcutaneous tissue disorders	**288 (33)**	**103 (36)**	**425 (31)**	**139 (31)**
Erythema[a]	190 (22)	69 (24)	329 (24)	107 (24)
Rash[a]	94 (11)	30 (10)	80 (6)	29 (6)

[a] Event was listed on a checklist included in subject diaries; therefore should be considered solicited. In addition to events listed above the following were also included as part of the checklist: chest pain and heart palpitations, but these events did not occur in ≥5% of subjects.

7 DRUG INTERACTIONS

7.1 Simultaneous Administration with Other Vaccines

There are no data evaluating the simultaneous administration of ACAM2000 with other vaccines.

7.2 Interference with Laboratory Tests

ACAM2000 may induce false-positive tests for syphilis. Positive RPR tests results should be confirmed using a more specific test, such as the FTA assay.

ACAM2000 may induce temporary false-negative results for the tuberculin skin test (purified protein derivative [PPD]) and possibly, blood tests for tuberculosis. Tuberculin testing should be delayed if possible for 1 month following smallpox vaccination.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal harm when administered to a pregnant woman. Congenital infection, principally occurring during the first trimester, has been observed after vaccination with live vaccinia smallpox vaccines, although the risk may be low. Generalized vaccinia of the fetus, early delivery of a stillborn infant, or a high risk of perinatal death has been reported.

The only setting in which vaccination of pregnant women should be considered is when exposure to smallpox is considered likely. If this vaccine is used during pregnancy, or if the vaccinee lives in the same household with or has close contact with a pregnant women, the vaccinee should be apprised of the potential hazard to the fetus. Healthcare providers, state health departments, and other public health staff should report to the National Smallpox Vaccine in Pregnancy Registry all cases in which persons who received ACAM2000, or were exposed to a woman who received ACAM2000 within 28 days after vaccination, during pregnancy, or within 42 days prior to conception. Civilian women should contact their healthcare provider or state health department for help enrolling in the registry. Clinicians or public health staff should report civilian cases through their state health department or to CDC, telephone 404-639-8253 or 877 554 4625. Military cases should be reported to the DoD, telephone 619 553-9255, Defense Switched Network (DSN) 553-9255, fax 619 767-4806 or e-mail NHRC-BirthRegistry@med.navy.mil.

8.3 Nursing Mothers

ACAM2000 has not been studied in lactating women. It is not known whether vaccine virus or antibodies are secreted in human milk. Live vaccinia virus can be inadvertently transmitted from a lactating mother to her infant. Infants are at high risk of developing serious complications from live vaccinia smallpox vaccination.

8.4 Pediatric Use

The safety and effectiveness of ACAM2000 have not been established in the age groups from birth to age 16. The use of ACAM2000 in all pediatric age groups is supported by evidence from the adequate and well-controlled studies of ACAM2000 in adults and with additional historical data with use of live vaccinia virus smallpox vaccine in pediatrics. Before the eradication of smallpox disease, live vaccinia virus smallpox vaccine was administered routinely in all pediatric age groups, including neonates and infants, and was effective in preventing smallpox disease. During that time, live vaccinia virus was occasionally associated with serious complications in children, the highest risk being in infants younger than 12 months of age. [See Warnings and Precautions (5.6)].

8.5 Geriatric Use

Clinical studies of ACAM2000 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There are no published data to support the use of this vaccine in geriatric (persons >65 years) populations.

11 DESCRIPTION

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is a live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health Strain) and grown in African Green Monkey kidney (Vero) cells and tested to be free of adventitious agents.

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

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 of diluent.

After reconstitution, each vial of ACAM2000 vaccine contains approximately 100 doses (0.0025 mL/dose). The concentration of vaccinia virus is 1.0-5.0 x 10^8 plaque-forming units (PFU)/mL or 2.5-12.5 x 10^5 PFU/dose determined by plaque assay in Vero cells. ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a stainless steel bifurcated needle that has been dipped into the vaccine.

12 CLINICAL PHARMACOLOGY

Smallpox vaccine does not contain smallpox virus (variola) and cannot spread or cause smallpox.

12.1 Mechanism of Action

Vaccinia virus is a member of the same taxonomic group (the Orthopox genus) as smallpox (variola) virus, and immunity induced by vaccinia virus cross-protects against variola virus. Vaccinia virus causes a localized virus infection of the epidermis at the site of inoculation, surrounding dermal and subcutaneous tissues, and draining lymph nodes. Virus may be transiently present in blood and infects reticuloendothelial and other tissues. Langerhans cells in the epidermis are specific targets for the early stage of virus replication. The formation of a pustule ('pock' or 'take') at the site of inoculation provides evidence of protective immunity. The virus replicates within cells and viral antigens are presented to the immune system. Neutralizing antibodies and B and T cells provide long-term memory. The level of neutralizing antibody that protects against smallpox is unknown but >95% of persons undergoing primary vaccination develop neutralizing or hemagglutination inhibiting antibodies to vaccinia.

12.2 Pharmacodynamics

12.2.1 Cutaneous Response

The cutaneous responses following smallpox vaccination are dependent on the immune status of the individual, potency of the vaccine, and vaccination technique. Two types of responses have been defined by the WHO Expert Committee on Smallpox, and described by the Advisory Committee on Immunization Practices (ACIP). The responses include: a) major cutaneous reaction, which indicates that virus replication has taken place and vaccination was successful; or b) equivocal reaction. Equivocal reactions may be a consequence of pre-existing immunity adequate to suppress viral multiplication, vaccination technique failure, or use of inactive vaccine or vaccine that has lost potency.

Successful vaccination in persons who are naïve to smallpox vaccination, termed primary vaccination, is represented by a major cutaneous reaction, defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

Subjects who have been previously vaccinated and are revaccinated may manifest a reduced cutaneous response compared to vaccinia-naïve subjects, but still exhibit an immune response to the vaccine. [See Dosage and Administration (2.4)]

12.2.2 Neutralizing Antibody and Cellular Immune Responses

Neutralizing antibodies are known to mediate protection against smallpox. Neutralizing antibodies against vaccinia develop in >95% of individuals following primary vaccination, rise rapidly (by day 15-20 after vaccination) and may be boosted on revaccination. Antibody titers are highly variable. Titers may remain high for longer periods following two or more vaccinations than after a primary vaccination. The level of the neutralizing antibody response following primary vaccination is generally in proportion to the intensity of the cutaneous reaction. The level of neutralizing antibody that is required to protect against smallpox has not been clearly established, although some studies indicate that persons with antibody titers > 1:32 are protected. Cellular immune responses are also elicited by vaccination and may contribute to protection and immunological memory.

12.2.3 Virus Shedding

Virus is shed from the vaccination site during the period starting with the development of a papule (day 2-5); shedding ceases when the scab separates and the lesion is re-epithelialized, about 14-21 days after vaccination. Steps should be taken in clinical use to reduce the risk of accidental infection of other sites in the vaccinated patient or of contact spread to other individuals [See Vaccination Instructions (2.3)].

14 CLINICAL STUDIES

Vaccine efficacy was assessed by comparing the immunologic response of ACAM2000 to another US-licensed live vaccinia virus smallpox vaccine, Dryvax®, in two randomized, multi-center active-controlled clinical trials; one study in subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects) and one study in subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). In both trials, the co-primary efficacy endpoints were the proportion of subjects with a successful vaccination/revaccination and the geometric mean neutralizing antibody titer (GMT) on Day 30. Successful primary vaccination was defined as a major cutaneous reaction on Day 7 or 10 (Days 6 to 11, with allowable visit window). Successful revaccination was defined as development of any cutaneous lesion on Day 7 (± 1 day) of a measurable size. Successful revaccination was determined by a panel of experts who reviewed digital photographs of the cutaneous lesions.

The statistical method used to compare the proportion of subjects who were successfully vaccinated in the two treatment groups was a test of non-inferiority of ACAM2000 to the active comparator intended to rule out a greater than 5% margin of superiority of the comparator for successful primary vaccination (Study 1) and a 10% margin of superiority of the comparator for successful revaccination (Study 2). Non-inferiority was to be declared if the lower bound of the 1-sided 97.5% confidence interval (CI) for the percent difference between ACAM2000 and the comparator exceeded -5% in naïve subjects and -10% in previously vaccinated subjects.

Analysis of the GMT was performed using a test of non-inferiority of neutralizing antibody titer between ACAM2000 and the comparator, intended to ensure that the ratio of the GMTs of ACAM2000: comparator vaccine was at least 0.5 (equivalent to the difference of the $\log_{10}$ (GMT) being at least -0.301).

In Study 1, a total of 1037 male and female vaccinia-naïve subjects, aged 18 to 30 years inclusive, primarily Caucasian (76%) were randomized in a 3:1 ratio to receive ACAM2000 (780 subjects) or comparator (257 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (258, 264, and 258 subjects, respectively). All subjects were to be evaluated for their cutaneous response and a random subset was selected for evaluation of neutralizing antibody response.

In Study 2, a total of 1647 male and female previously-vaccinated subjects, aged 31 to 84 years inclusive, primarily Caucasian (81%) were randomized in a 3:1 ratio to receive ACAM2000 (1242 subjects) or the comparator (405 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (411, 417, and 414 subjects, respectively). All subjects were evaluated for their cutaneous response and a random subset was to be selected for evaluation of neutralizing antibody response.

Table 4 presents the results of the primary efficacy analyses for both studies.

Table 4 - – Cutaneous Response (Vaccination Success) and Neutralizing Antibody Response in Subjects Given ACAM2000 Vs. Comparator Vaccine

	Study Population / Treatment Group			
	Study 1 Vaccinia-Naïve Subjects		**Study 2 Previously Vaccinated Subjects**	
	ACAM 2000	**Comparator**	**ACAM 2000**	**Comparator**
Cutaneous Response (Vaccination Success)				
Size of Evaluable Population[a]	776	257	1189	388
Number of Vaccination Successes (%)	747 (96)[b]	255 (99)	998 (84)[h]	381 (98)
97.5% 1-sided CI by normal approx. on percent difference between ACAM2000-Comparator	-4.67% [c]		-17% [i]	
Non-Inferiority to Comparator	Yes		No	
Neutralizing Antibody Response (based on $PRNT_{50}$[d] Titer on Day 30)				
Size of Evaluable Population[e]	565	190	734	376
GMT[f]	166	255	286	445
Log_{10} mean	2.2	2.4	2.5	2.6
97.5% 1-sided CI by ANOVA on difference between ACAM2000-Comparator	-0.307[g]		-0.275[j]	
Meets Non-Inferiority to Comparator	No		Yes	

[a] Subjects who received study vaccine and were evaluated for a local cutaneous reaction within the protocol-designated timeframe were included in the efficacy evaluable (EE) population.

[b] Results for vaccine lots, A, B and C were 95%, 98% and 96%.

[c] Since the critical value for the evaluation was declared to be -5%, ACAM2000 is considered to be non-inferior to Comparator for this parameter.

[d] $PRNT_{50}$ – Vaccinia 50% plaque reduction neutralization test.

[e] A randomly selected sample of subjects who received study vaccine and had samples collected for neutralizing antibody response at Baseline and at the designated time-point post-treatment were included in the antibody evaluable (AnE) population.

[f] GMT – Geometric mean neutralizing antibody titer.

[g] Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is not considered to be non-inferior to Comparator for this parameter.

[h] Results for vaccine lots, A, B and C were 79%, 87% and 86%.

[i] Since the critical value for the evaluation was declared to be -10%, ACAM2000 is not considered to be non-inferior to Comparator for this parameter.

[j] Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is considered to be non-inferior to Comparator for this parameter.

The primary determinant for an effective immune response in those naïve to vaccine is a major cutaneous reaction. ACAM2000 was non-inferior to comparator in this population with regard to eliciting a major cutaneous reaction. The measure of the strength of the generated antibody response was similar but did not meet the predefined criterion for non-inferiority. Among subjects who were previously vaccinated, development of a major cutaneous response after revaccination with vaccinia-based smallpox vaccines may not provide an accurate measure of the strength of the immune response because the pre-existing immunity modifies the scope of the cutaneous response. In previously vaccinated subjects, ACAM2000 was non-inferior to the comparator with regard to the strength of the neutralizing antibody immune response. Therefore, ACAM2000 was non-inferior to the comparator in the rate of major cutaneous reaction in those naïve to the vaccine, and the strength of the neutralizing antibody immune response in those previously exposed to vaccinia-based smallpox vaccines.

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16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is supplied in multiple-dose 3 mL clear glass vials containing lyophilized powder (freeze-dried vaccine). After reconstitution with 0.3 mL of diluent, the vial contains approximately 100 nominal doses of 0.0025 mL of vaccinia virus (live), 1.0 - 5.0×10^8 PFU/mL or 2.5-12.5x10^5 PFU/dose.

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

Bifurcated needles are supplied in boxes (5 x 5 x 1 in) containing 100 needles.

1 mL tuberculin syringes with 25 gauge x 5/8" needles are supplied for vaccine reconstitution.

16.2 Storage and Handling

ACAM2000 should be stored in a freezer with an average temperature of -15°C to -25°C (+5°F to -13°F).

Prior to reconstitution, ACAM2000 vaccine retains a potency of 1.0×10^8 PFU or higher per dose for at least 18 months when stored at refrigerated temperatures of +2-8°C (36-46°F).

During shipment, ACAM2000 should be maintained at a temperature of -10°C or colder.

After reconstitution, ACAM2000 vaccine may be administered during a 6 to 8 hour workday at room temperature (20-25°C, 68-77°F). Reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) no longer than 30 days, after which it should be discarded [*See Dosage and Administration (2.3)*]. Diluent for Smallpox Vaccine, (Vero Cells) Lyophilized, ACAM2000 should be stored at room temperature (15-30°C, 59-86°F). ACAM2000 contains live vaccinia virus that is transmissible, and should be handled as an infectious agent once vials are open. See 2.1 [Instructions for Vaccine Preparation] and 2.2 [Preparation / Handling Precautions and Instructions for Disposal] for details on handling and disposal.

17 PATIENT COUNSELING INFORMATION

Please refer patient to the Medication Guide prepared for ACAM2000 Smallpox Vaccine.

17.1 Serious Complications of Vaccination

Patients must be informed of the major serious adverse events associated with vaccination, including myocarditis and/or pericarditis, progressive vaccinia in immunocompromised persons, eczema vaccinatum in persons with skin disorders, auto- and accidental inoculation, generalized vaccinia, urticaria, erythema multiforme major (including Stevens-Johnson syndrome) and fetal vaccinia in pregnant women.

17.2 Protecting Contacts at Highest Risk for Adverse Events

Patients must be informed that they should avoid contact with individuals at high risk of serious adverse effects of vaccinia virus, for instance, those with past or present eczema, immunodeficiency states including HIV infection, pregnancy, or infants less than 12 months of age.

17.3 Self-inoculation and Spread to Close Contacts

Patients must be advised that virus is shed from the cutaneous lesion at the site of inoculation from approximately Day 3 until scabbing occurs, typically between Days 14-21 after primary vaccination. Vaccinia virus may be transmitted by direct physical contact. Accidental infection of skin at sites other than the site of intentional vaccination (self-inoculation) may occur by trauma or scratching. Contact spread may also result in accidental inoculation of household members or other close contacts. The result of accidental infection is a pock lesion(s) at an unwanted site(s) in the vaccinee or contact, and resembles the vaccination site. Self-inoculation occurs most often on the face, eyelid, nose, and mouth, but lesions at any site of traumatic inoculation can occur. Self-inoculation of the eye may result in ocular vaccinia, a potentially serious complication.

17.4 Care of the Vaccination Site and Potentially Contaminated Materials

Patients must be given the following instructions:

- The vaccination site must be completely covered with a semipermeable bandage. Keep site covered until the scab falls off on its own.
- The vaccination site must be kept dry. Normal bathing may continue, but cover the vaccination site with waterproof bandage when bathing. The site should not be scrubbed. Cover the vaccination site with loose gauze bandage after bathing.
- Don't scratch the vaccination site. Don't scratch or pick at the scab.
- Do not touch the lesion 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.
- After changing the bandage or touching the site, wash hands thoroughly with soap and water or >60% alcohol-based hand-rub solutions.
- To prevent transmission to contacts, physical contact of objects that have come into contact with the lesion (e.g. soiled bandages, clothing, fingers) must be avoided.
- Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.
- Soiled and contaminated bandages must be placed in plastic bags for disposal.
- The vaccinee must wear a shirt with sleeves that covers 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 vaccinee must change the bandage every 1 to 3 days. This will keep skin at the vaccination site intact and minimize softening.
- Don't put salves or ointments on the vaccination site.
- When the scab fall off, throw it away in a sealed plastic bag and wash hands afterwards.

17.8 Appendix IVd: Attachment 4 to US Health Affairs Memorandum 'Chronological Record of Medical Care and Symptom Diary after Smallpox Vaccination'

Note: The US Health Affairs Memorandum; Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program attaches the standard forms 600 (Rev6-97) Electronic Copy SVP Overprint (11-07) and the diary version from 1 Jan 08. This CTP replaces these forms with the latest standard forms 600 (Rev. 11/2010) Electronic Copy SVP Overprint (02-14, 7-09 and 2-08 respectively) and the diary version 07 Feb 08.

CHRONOLOGICAL RECORD OF MEDICAL CARE
Smallpox Vaccination Screening Form Page 1 of 2
To be completed by potential vaccine recipient

1. Today's Date (dd/mm/yyyy): _____ 2. GENDER: ☐ Male ☐ Female
3. Have you ever received the smallpox vaccine? ☐ Yes ☐ No ☐ Unsure
4. Have you ever had a serious problem after smallpox or other vaccination? ☐ Yes ☐ No ☐ Unsure
   If YES; Explain: _____
5. Do you have a current illness with fever? ☐ Yes ☐ No ☐ Unsure
6. Are you allergic to any of these products: polymyxin B, neomycin? ☐ Yes ☐ No ☐ Unsure
7. Are you being treated with eye drops or ointment? ☐ Yes ☐ No ☐ Unsure
8. Are you recovering from a recent surgery (including eye or dental)? ☐ Yes ☐ No ☐ Unsure
9. Could YOU or someone you LIVE WITH be pregnant? ☐ Yes ☐ No ☐ Unsure
10. Do you have a child in the home less than one year of age? ☐ Yes ☐ No ☐ Unsure
11. Are you currently breastfeeding? ☐ Yes ☐ No ☐ N/A
12. Do you have a heart or blood vessel condition, such as angina, earlier heart attack, coronary artery disease, congestive heart failure, cardiomyopathy, stroke, mini stroke, chest pain or shortness of breath on exertion or history of significant arrhythmia with or without corrective/ablative surgery? ☐ Yes ☐ No ☐ Unsure
13. Check EACH of the following conditions that apply to you: ☐ Smoke cigarettes now ☐ High blood pressure ☐ High cholesterol ☐ Diabetes or high blood sugar ☐ Heart condition before age 50 in mother, father, brother, sister
14. Are you currently taking any prescription medications for your blood pressure, cholesterol, or diabetes? ☐ Yes ☐ No ☐ Unsure

Before vaccinating against smallpox, we want to know if YOU or YOUR HOUSEHOLD CONTACTS have any of several medical conditions. Please answer the following questions to the best of your knowledge.

	Myself	Close Contact
15. Do you OR someone you currently live with NOW HAVE any of the following skin problems: psoriasis, skin infection, uncontrolled acne, shingles, chickenpox, burns, recent tattoo, recent piercing, or other conditions causing breaks in the skin?	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
16a. Do you OR someone you currently live with NOW HAVE or RECENTLY HAD a problem or take(s) medication that affects the immune system? For example: have or take medication for HIV, AIDS, leukemia, lymphoma, chronic liver problem, Crohn's disease, lupus, arthritis, or other immune disease; have had radiation or X-ray treatment (not routine X-rays) within the last 3 months; have EVER had a bone-marrow or organ transplant (or take medications for that); or have another problem that requires steroids, prednisone or a cancer drug for treatment.	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
16b. Are you concerned that you might have one or more risk factors for HIV? NOTE: If you think you might have an increased risk for HIV infection, HIV testing is available.	☐ Yes ☐ No ☐ Unsure	
17a. Have you OR someone you currently live with EVER HAD Eczema or Atopic Dermatitis? (Usually this skin condition involves an itchy, red, scaly rash that lasts more than 2 weeks. It often comes and goes). If YES or UNSURE for either you or your close contact, answer 17b-17f.	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
17b. A doctor has made the diagnosis of eczema or atopic dermatitis.	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
17c. There have been (dry) scaly, itchy rashes that have lasted more than 2 weeks.	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
17d. At least once, there is a history of an itchy rash in the folds of the arms or legs.	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
17e. There is a history of eczema and food allergy during childhood.	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure
17f. A doctor has made the diagnosis of asthma or hay fever (including parents, brothers, or sisters).	☐ Yes ☐ No ☐ Unsure	☐ Yes ☐ No ☐ Unsure

"FOR FEMALES ONLY:" If you might be pregnant, or likely to become pregnant, please tell us. You may need additional pregnancy testing.

18a. First day of last menstrual period: _____ 18b. Was your last menstrual period normal and on time? ☐ Yes ☐ No ☐ Unsure

19. Do you have other questions or have other concerns you would like to discuss? ☐ Yes ☐ No

Explain "other," "unsure'" or additional concerns (may use additional page): _____

PATIENT'S IDENTIFICATION (May use for mechanical imprint):

RECORDS MAINTAINED AT:

LAST NAME: RANK/GRADE:

FIRST NAME: STATUS:

FMP/SSAN: DEPT/SVS:

DATE OF BIRTH:

CHRONOLOGICAL RECORD OF MEDICAL CARE
Smallpox Vaccination Screening Form Page 2 of 2
To be completed by a healthcare provider

1. Provider Assessment Date (dd/mm/yyyy): _____
   (Note: If provider Assessment Date or Action Taken Immunization Date is blank, the Default date is "Today's Date" on page 1.)

2. Vaccine risk factors based on page 1 review and patient interview (check all that apply):

	Self	Close Contact
No restriction	☐	☐
Pregnancy	☐	☐
Immune suppression	☐	☐
Skin condition	☐	☐
Infant under 1 year old	☐	
Heart condition	☐	3+ RF ☐
Other	☐	☐ (Describe in #4)

3. Provider decision and plan, check all that apply:

   ☐ Vaccinate: Primary ☐ Vaccinate: Revaccination ☐ Do Not vaccinate; current within 10 yr interval

   ☐ Vaccination exemption; medical permanent (MP) (note in section #4)

   ☐ Vaccination exemption; medical temporary (MT); (see #2 above or note in section #4):

4. Provider comment on any concerns about contraindications, need to defer, need to consult, and/or relevant diagnosis:

Credentialed Provider Signature and Printed Name/Stamp:

VACCINE ADMINISTRATION: Vaccination Date (dd/mm/yyyy): _____

6. Location: ☐ Left Arm (15 jabs) ☐ Right Arm (15 jabs) ☐ Other location (describe):

   Lot #: VV04-003A Mfr: sanofi-pasteur

7. **IF IMMUNIZED,** check all that apply:

   ☐ Medication Guide given to patient ☐ Bandages provided if needed ☐ Females advised to avoid becoming pregnant for 4 weeks

   ☐ Patient advised about post-vaccination reaction, site care, and reasons for follow-up visit ☐ Patient understands information provided

Please assure that all actions taken and deferrals are updated into your Service's Immunization Tracking System (ITS) as soon as possible.

Vaccine administered by: (Signature and Printed Name/Stamp)

PATIENT'S IDENTIFICATION (May use for mechanical imprint):
RECORDS MAINTAINED AT:
LAST NAME: RANK/GRADE:
FIRST NAME: STATUS:
FMP/SSAN: DEPT/SVS:
DATE OF BIRTH:

Standard Form 600 (Rev. 11/2010) Electronic Copy SVP Overprint (02-14)

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Clinical/Sick-call Follow up Note

1. Today's Date (MM/DD/YYYY) ☐☐/☐☐/☐☐☐☐

2. Day 0 = Smallpox Vaccination Date ☐☐/☐☐/☐☐☐☐ 2b. Days post vax ☐☐

3. Vital Signs Temp ☐☐☐.☐ Pulse ☐☐☐ Resp ☐☐ BP ☐☐☐/☐☐☐

4. Chief Compliant (Default = routine check)

5. Was there a bandage on the vaccination site? ○ Yes ○ No

5a. IF YES: How many days did patient use a bandage? ☐☐

5b. Did patient see the vaccination site every day or two? ○Yes ○No

6a. Vaccination site appearance today (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab or crust
- ☐ local itching
- ☐ local rash
- ☐ nothing

6b. Vaccinee recall of appearance since vaccination (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab or crust
- ☐ local itching
- ☐ local rash
- ☐ nothing seen
- ☐ patient did not remember/observe

7. Check anything else experienced after the smallpox vaccination (Check all that apply)

- ☐ headache
- ☐ body rash
- ☐ itchy all over
- ☐ eye infection
- ☐ fever (temp in box)
- ☐ muscle aches
- ☐ feeling lousy
- ☐ swollen lymph nodes
- ☐ bandage reaction
- ☐ chest pain
- ☐ shortness of breath
- ☐ other (describe in box)

8. Any problems following vaccination? (Check all they apply)

- ☐ Restricted activity — How many days? ☐☐
- ☐ Limited duty — How many days? ☐☐
- ☐ Missed work — How many days? ☐☐
- ☐ Took medication (list in box) — How many days? ☐☐
- ☐ Visited clinic or emergency room
- ☐ Hospitalized
- ☐ Other (described in box)

9. Vaccination Site measures (if indicated)

Erythema length (mm) ☐☐☐ X width ☐☐☐

Vesicle length (mm) ☐☐☐ X width ☐☐☐

Note any other reactions, problems or medications following vaccination:

10. Does the patient believe anyone might have become ill as a result of the vaccination? ○ Yes ○ No ○ Unsure

If YES or UNSURE describe in box (or on continuation page)

11. Assessment and Plan (check all that apply:

- ☐ Fully Immunized ("major reaction, "take")
- ☐ Equivocal response
- ☐ Referred to Vaccine Healthcare Centers
- ☐ Re-vaccination indicated
- ☐ Follow-up for events described
- ☐ Medication prescribed (list)
- ☐ No further follow up planned
- ☐ Consultation Allergy/Immunology/Dermatology/Cardiology/other_____)
- ☐ Other action (describe in box) Report to VAERS if warranted.

11a. Other assessment/plan related to evaluation

12. Duty limitations

- ☐ Full duty
- ☐ No direct patient care
- ☐ Quarters for ___ days
- ☐ Urgent/Emergent referral
- ☐ Routine referral

Provider Signature and Printed Name/Stamp

Patient's identification (May use mechanical imprint)

Last Name

First Name MI

Social Security Number ☐☐☐ ☐☐ ☐☐☐☐

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Clinical/Routine Follow up Note

1. Today's Date (MM/DD/YYYY) ☐☐/☐☐/☐☐☐☐

2. Smallpox Vaccination Date ☐☐/☐☐/☐☐☐☐

3. Did you put a bandage on the vaccination site ○ Yes ○ No

3a. IF YES: How many days did you use a bandage? ☐☐

3b. Did you see the vaccination site every day or two? ○ Yes ○ No

4a. Vaccination site appearance today (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab or crust
- ☐ local itching
- ☐ local rash
- ☐ nothing

4b. Vaccinee recall of appearance since vaccination (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab or crust
- ☐ local itching
- ☐ local rash
- ☐ nothing seen
- ☐ patient did not remember/observe

4c. Check anything else experienced after the smallpox vaccination (Check all that apply)

- ☐ headache
- ☐ body rash
- ☐ itchy all over
- ☐ eye infection
- ☐ fever (temp in box)
- ☐ muscle aches
- ☐ feeling lousy
- ☐ swollen lymph nodes
- ☐ bandage reaction
- ☐ chest pain
- ☐ shortness of breath
- ☐ other (describe in box)

5. Any problems following vaccination? (Check all they apply)

- ☐ Restricted activity — How many days? ☐☐
- ☐ Limited duty — How many days? ☐☐
- ☐ Missed work — How many days? ☐☐
- ☐ Took medication (list in box) — How many days? ☐☐
- ☐ Visited clinic or emergency room
- ☐ Hospitalized
- ☐ Other (described in box)

6. Note any other reactions, problems or medications following vaccination:

7. Does the patient believe anyone might have become ill as a result of the vaccination? ○ Yes ○ No ○ Unsure
If YES or UNSURE describe in box (or on continuation page)

8. Provider evaluation and action (check all that apply:

- ☐ Fully Immunized ("major reaction, "take")
- ☐ Equivocal response
- ☐ Referred to Vaccine Healthcare Centers
- ☐ Re-vaccination indicated
- ☐ Follow-up for events described
- ☐ Medication prescribed (list)
- ☐ No further follow up planned
- ☐ Consultation Allergy/Immunology/Dermatology/Cardiology/other_____)
- ☐ Other action (describe in box) Report to VAERS if warranted.

Provider Notes:

Provider Signature and Printed Name/Stamp:

Last Name

First Name MI

Social Security Number

Patient's identification (May use mechanical imprint)

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Continuation Note

1. Today's Date (MM/DD/YYYY)

☐☐ / ☐☐ / ☐☐☐☐

Additional Notes on Problems, Issues or Concerns of Patient or Provider related to Vaccine Assessment or Follow-up. Subjective section may be filled out by either patient/vaccine or provider. Objective findings, Assessment and Plan should be completed by a provider.

Subjective: History of issues related to vaccination assessment or follow-up

Objective: Relevant exam, test or laboratory findings

Assessment: Integrated summary

Plan

Provider Signature and Printed Name/Stamp:

Last Name

First Name MI

Social Security Number

Patient's identification (May use mechanical imprint)

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

Symptom Diary After Smallpox Vaccination

a) Patient name: Last _____ First_____ MI _____ b) Social Security Number: _____-_____-_____

c) Date of Birth: Mo_____/Day_____/Yr_____ d) Age: _____years e) Gender: ☐ Male ☐ Female

f) Date of smallpox vaccine administration: Mo_____/Day_____/Yr_____ g) Clinic / site where vaccination was given:_____

h) Taken any steroids/pain/fever medications: ☐ 1-3 days before vaccine(_____) ☐ 0-30 days after vaccine(_____) ☐ None during this period (-3 to +30 days)

i) Ethnicity ☐ White/Caucasian ☐ Asian ☐ Black/African American ☐ Native Hawaiian/Other Pacific Islander
☐ Hispanic ☐ American Indian/Alaskan Native ☐ Do not want to provide ☐ Other (specify:_____)

THE FIRST 4 WEEKS AFTER SMALLPOX VACCINATION: Please **check any symptoms** present on each indicated day recording details below	Day 0 (vaccination)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Week 4
1. Symptoms (Y or N)																						
2. Fever (record temperature. eg.101.2F)																						
3. Chills (Y or N)																						
4. Swelling at vaccination site (Y or N)																						
5. Cough/ difficulty breathing (Y or N)																						
6. Rash or vaccine-type reaction on body (Y or N, if Y describe rash and where, below)																						
7. Bandage used (Y or N, type below)																						
8. Did you seek medical care because of vaccination? (describe below)																						
9. Did you take any medications because of vaccination?(specify below)																						
10. Did you miss work/school because of vaccination?																						
11. Joint pain (0-9scale) (0=no, 9=worse)																						
12. Muscle pain (0-9 scale)																						
13. Headache (0-9 scale)																						
14. Pain at vaccination site (0-9 scale)																						
15. Swelling/tender lymph nodes (0-9 scale)																						
16. Itching at vaccination site (0-9 scale)																						
17. Chest pain (0-9 scale)																						
18. Shortness of breath (0-9 scale)																						
19. Other symptoms, illnesses, new medications, etc.(describe below)																						
20. **Vaccination site appearance** (using letter codes below)																						

Date scab fell off: Mo_____/Day_____/Yr_____

If at any time you have questions about your vaccination please contact the DoD Vaccine Clinical Call Center at 1-866-210-6469 (24 hrs a day, 7 days a week) or email the Vaccine Healthcare Center at https://askvhc.wramc.amedd.army.mil

Use all the letter codes that apply to describe vaccination site for each day above:

1= red spot	2= bump	3=reddish blister	4=whitish blister	5=scab
6=ulcer, crater	w=warmth	sw=swollen>3 in.	st=streaks	dr=drainage

If medical care sought, where? Name of facility/MD: _____

Permission to acquire medical records? ☐ **Yes** ☐ **No**

Additional comments (use additional pages if necessary): _____

Signature of vaccinee:	**Date completed:**

DATA PRIVACY NOTICE: Data requested are being collected under the authority of The Privacy Act of 1974. 5 U.S.C. §552A. The SSN is being collected because it is a unique identifier that will better enable military staff to maintain contact with patients over time. Every effort will be made to safeguard the confidentiality of the information provided.

07 Feb 08

17.9 Appendix IVe: Attachment 5 to US Health Affairs Memorandum 'Smallpox Vaccine in Pregnancy Registry, Information Paper'

Note: The US Health Affairs Memorandum; Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program attaches the 'Smallpox Vaccine in Pregnancy Registry, Information Paper' from September 2007. This CTP replaces this paper with the latest version from 26-June-2012.

Smallpox Vaccine in Pregnancy Registry

INFORMATION PAPER:
When Pregnancy Is Discovered After Smallpox Vaccination

1. Purpose. This paper provides information for women who discover they are pregnant after receiving smallpox vaccination.

2. Current Recommendations on Vaccination and Pregnancy

Similar to other live virus vaccines, smallpox vaccine is not recommended for pregnant women in non-emergency situations. Further, it is recommended that women who receive the vaccine should avoid becoming pregnant for at least 4 weeks after vaccination.

Because it can be difficult to predict conception or diagnose early pregnancy, it is not surprising that some women may inadvertently receive smallpox vaccine shortly before or after becoming pregnant.

3. Historic Experience with Smallpox Vaccine in Pregnancy

Smallpox vaccine recommendations have changed over time. In the mid-20th century, when smallpox disease was still naturally occurring, billions of women around the world, both pregnant and not pregnant, received the vaccine. During smallpox outbreaks, health officials intentionally gave pregnant women smallpox vaccine to protect them from lethal infections.

There is no historic evidence that smallpox vaccine caused increased rates of spontaneous abortion (miscarriage). There is no historic evidence that the smallpox vaccine used in the United States caused birth defects.

Fetal vaccinia is a known, but extremely rare, complication that can occur after smallpox vaccine is given in pregnancy. Fetal vaccinia occurs when the virus used in smallpox vaccine infects the unborn baby (fetus). Cases of fetal vaccinia have been associated with stillbirth or infant death shortly after delivery. In the 20th century, 3 cases of fetal vaccinia were reported in the United States, and 47 cases were reported from other countries around the world. It is possible that other cases occurred, but were not reported. No cases of fetal vaccinia were reported after 173,000 pregnant women in New York City were vaccinated in 1947. It is estimated that 1 case of fetal vaccinia might occur for every 10,000 to 100,000 pregnant women who get smallpox vaccine for the first time.

4. Recent Experience with Smallpox Vaccine in Pregnancy

The National Smallpox Vaccine in Pregnancy Registry, established in 2003 and managed by the Department of Defense Birth and Infant Health Registry, follows women who inadvertently receive smallpox vaccine while pregnant. The Registry collects confidential information to better understand if smallpox vaccine in pregnancy is associated with problems for mothers or infants in the modern era.

In the United States, approximately 17% of all recognized pregnancies end in miscarriage, and 3% to 5% of infants are born with birth defects. It is natural for parents who suffer a pregnancy loss, or have a baby with a birth defect, to want to know the cause. Unfortunately, the causes of most miscarriages and birth defects are unknown.

Thus far, findings from the National Smallpox Vaccine in Pregnancy Registry indicate that pregnancy loss, preterm birth, and birth defects occur at rates similar to, or less than, rates seen in the general population. Women who inadvertently receive smallpox vaccine while pregnant may be reassured that current data support historic data, and do not suggest that they are at higher risk for poor pregnancy outcomes. In addition, there have been no cases of fetal vaccinia among Registry pregnancies.

5. Better Understanding Pregnancy Losses

It may be possible to know if smallpox vaccine was associated with a miscarriage or stillbirth by laboratory testing for vaccinia virus. In order to perform this testing, specimens must be brought to a special

laboratory and preserved (without formalin) at –70C in viral transport media. Women who would like to have this testing performed should discuss with their healthcare providers as soon as possible after a miscarriage is diagnosed.

6. Resources for Additional Information

The National Smallpox Vaccine in Pregnancy Registry was established to collect important confidential information from women who received smallpox vaccine in pregnancy. Professionals from the Registry can answer many questions from participants and their healthcare providers. The Registry may be contacted at:

National Smallpox Vaccine in Pregnancy Registry
c/o DoD Birth and Infant Health Registry,
Naval Health Research Center, Dept. 164, 140 Sylvester Rd., San Diego, CA 92106
Phone: 619-553-9255 (DSN 553)
Fax: 619-767-4806
Email: NHRC-BirthRegistry@med.navy.mil

Additional resources include:

Vaccine Healthcare Centers Network
DoD Vaccine Clinical Call Center 866-210-6469

Military Vaccine (MILVAX) Agency
Phone: 877-GET-VACC (877-438-8222)
or 703-681-4245 (DSN 761)

Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine
Madigan Army Medical Center, Tacoma, WA
Phone: 253-968-1710 or 1252 (DSN 782)

References

CDC. Recommendations for Using Smallpox Vaccine in a Pre-Event Vaccination Program. MMWR 2003;52(RR07):1-16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5207a1.htm

Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and Its Eradication. Geneva: World Health Organization 1988.

Levine MM, Edsall G, Bruce-Chwatt LJ. Live-virus vaccines in pregnancy: Risks and recommendations. Lancet 1974;2:34-8.

Naderi S. Smallpox vaccination during pregnancy. Obstet Gynecol 1975;46(2):223-6. (Note that the vaccine strain described here and used in Iran was different from the vaccine used in the United States.)

Ryan MAK, Gumbs GR, Conlin AS, Sevick CJ, Jacobson IG, Snell KJ, Spooner CN, Smith TC. Evaluation of Preterm Births and Birth Defects in Liveborn Infants of US Military Women Who Received Smallpox Vaccine. Birth Defects Res A Clin Mol Teratol 2008;82(7):533-9.

Ryan MAK, Seward JF, for the National Smallpox Vaccine in Pregnancy Registry Team. Pregnancy, birth, and infant health outcomes from the National Smallpox Vaccine in Pregnancy Registry, 2003-2006. Clin Infect Dis 2008;46:S221-6.

Stenchever MA, Droegemuller W, Herbst AL, Mishell DR. Comprehensive Gynecology, Mosby, 2001:414.

17.10 Appendix IVf: Attachment 6 to US Health Affairs Memorandum 'Vaccination Response Interpretation'

VACCINATION-RESPONSE INTERPRETATION

Inspect the vaccination site 6 to 8 days after vaccination. Interpret the response at that time. The World Health Organization (WHO) Expert Committee on Smallpox defined two types of responses:

a) major reaction: virus replication took place and vaccination was successful; or

b) equivocal reaction: a possible consequence of immunity adequate to suppress viral multiplication or allergic reactions to an inactive vaccine without production of immunity.

Major Reaction:

A vesicular (blistery) or pustular (pus-filled) lesion or area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

After primary (first) vaccination, the vaccination site usually progresses as follows:

- The inoculation site becomes reddened and pruritic 3 to 4 days after vaccination.
- A vesicle surrounded by a red areola then forms, which becomes umbilicated (collapsed center) and then pustular by days 7 to 11 after vaccination.
- The pustule begins to dry; the redness subsides; and the lesion becomes crusted between the second and third week. By the end of about the third week, the scab falls off, leaving a permanent scar that at first is pink in color but eventually becomes flesh-colored.
- After revaccination, skin reactions might be less pronounced with more rapid progression and healing than those after primary vaccination. Revaccination is successful if a pustular lesion or area of definite induration or congestion surrounding a central lesion (i.e., scab or ulcer) appears 6 to 8 days after revaccination.

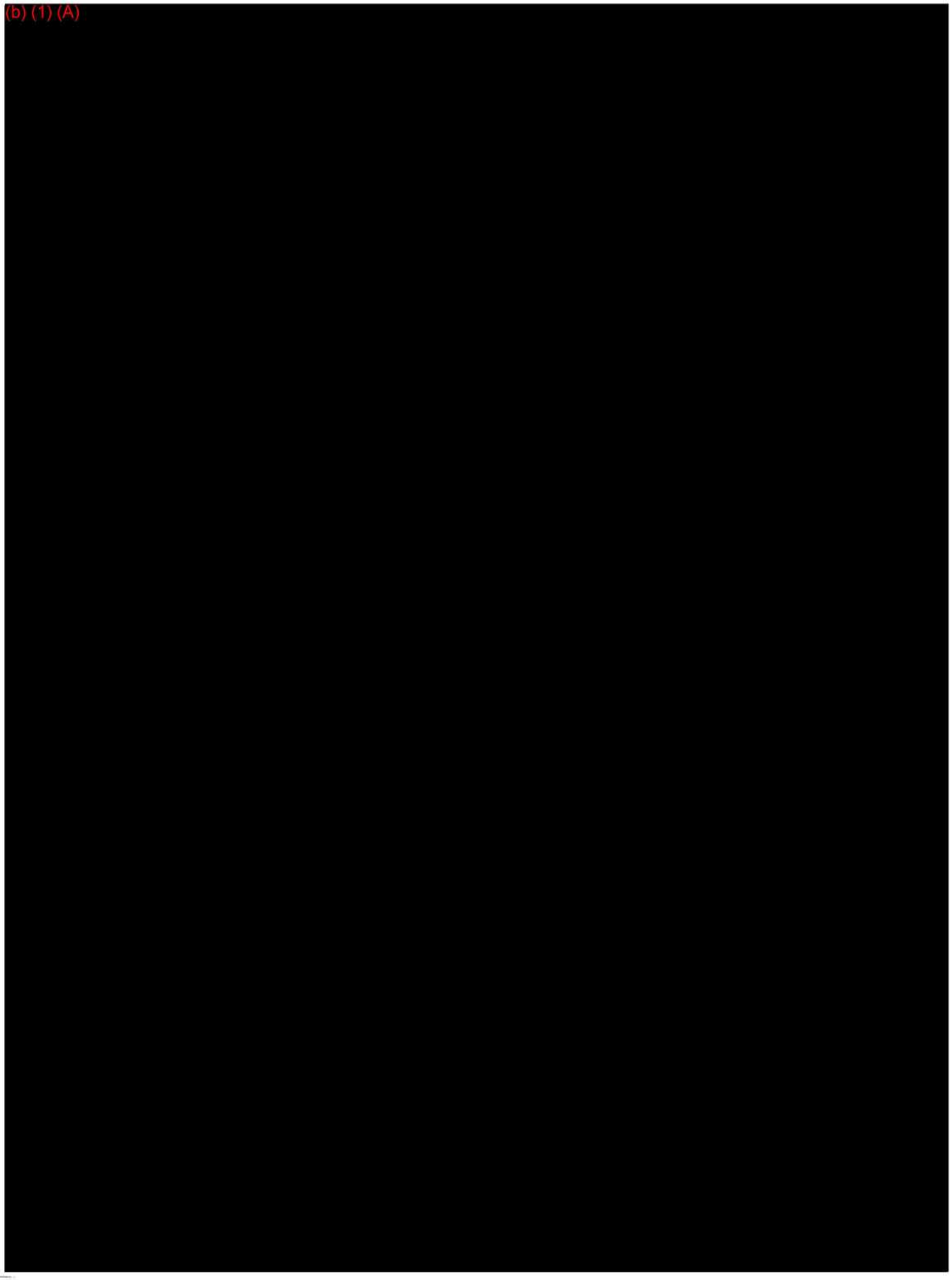
Equivocal Reaction:

Equivocal reactions, including accelerated, modified, vaccinoid, immediate, early, or immune reactions, are all responses other than major reactions. If an equivocal reaction is observed, check vaccination procedures and repeat vaccination using another vial or vaccine lot, if available. A response to smallpox vaccination may be blunted by immunity, insufficiently potent vaccine, or vaccination technique failure. If repeat vaccination using vaccine from another vial fails to elicit a major reaction, consult public-health authorities before attempting another vaccination of that person.

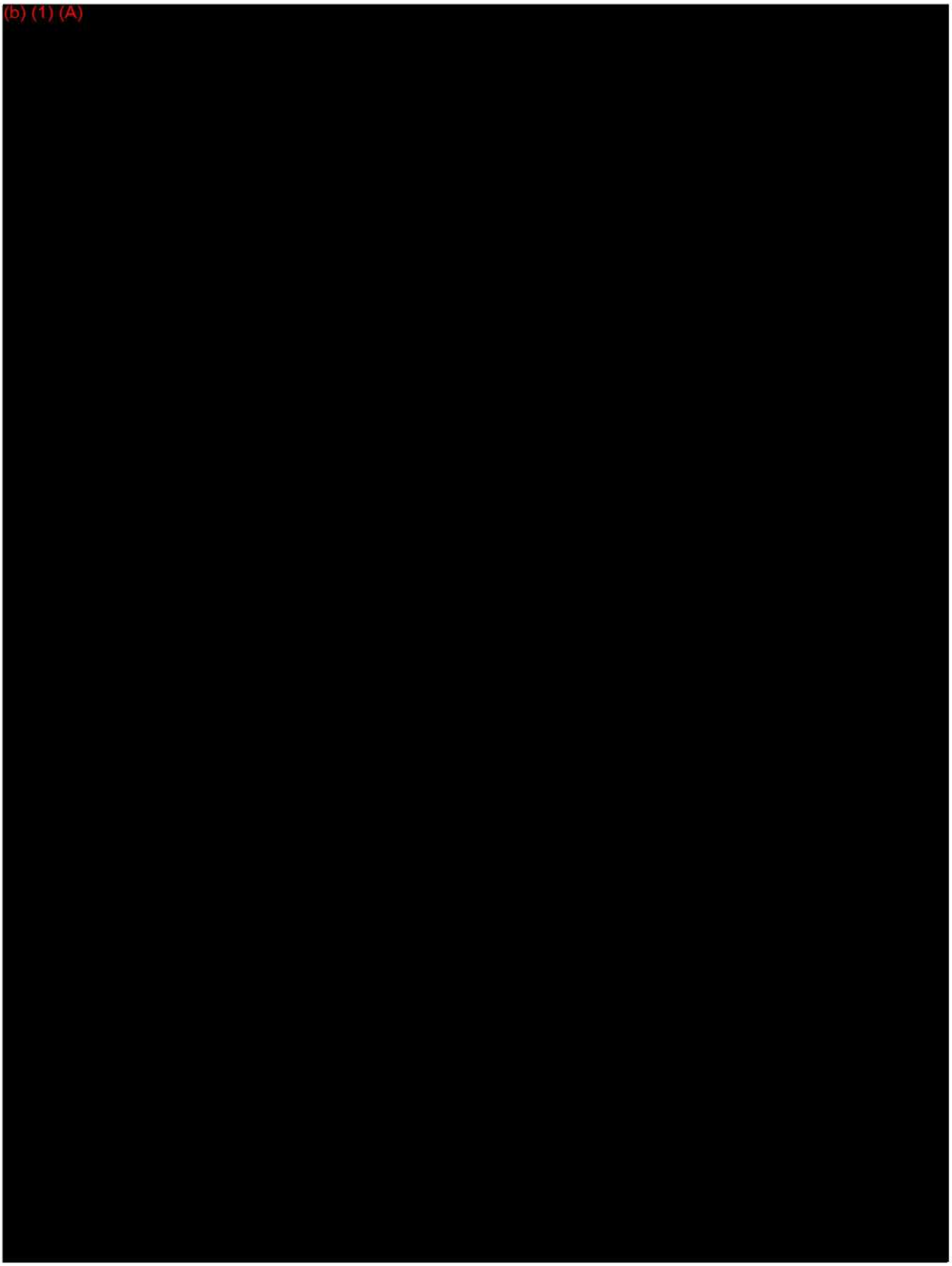
Sources: Fenner et. al, 1988 (pp 296, 312-314); ACIP, 2001.

Attachment G

17.11 Appendix IVg: Attachment 7 to US Health Affairs Memorandum 'Policy for Smallpox Vaccine and Persons with Cardiac Conditions'

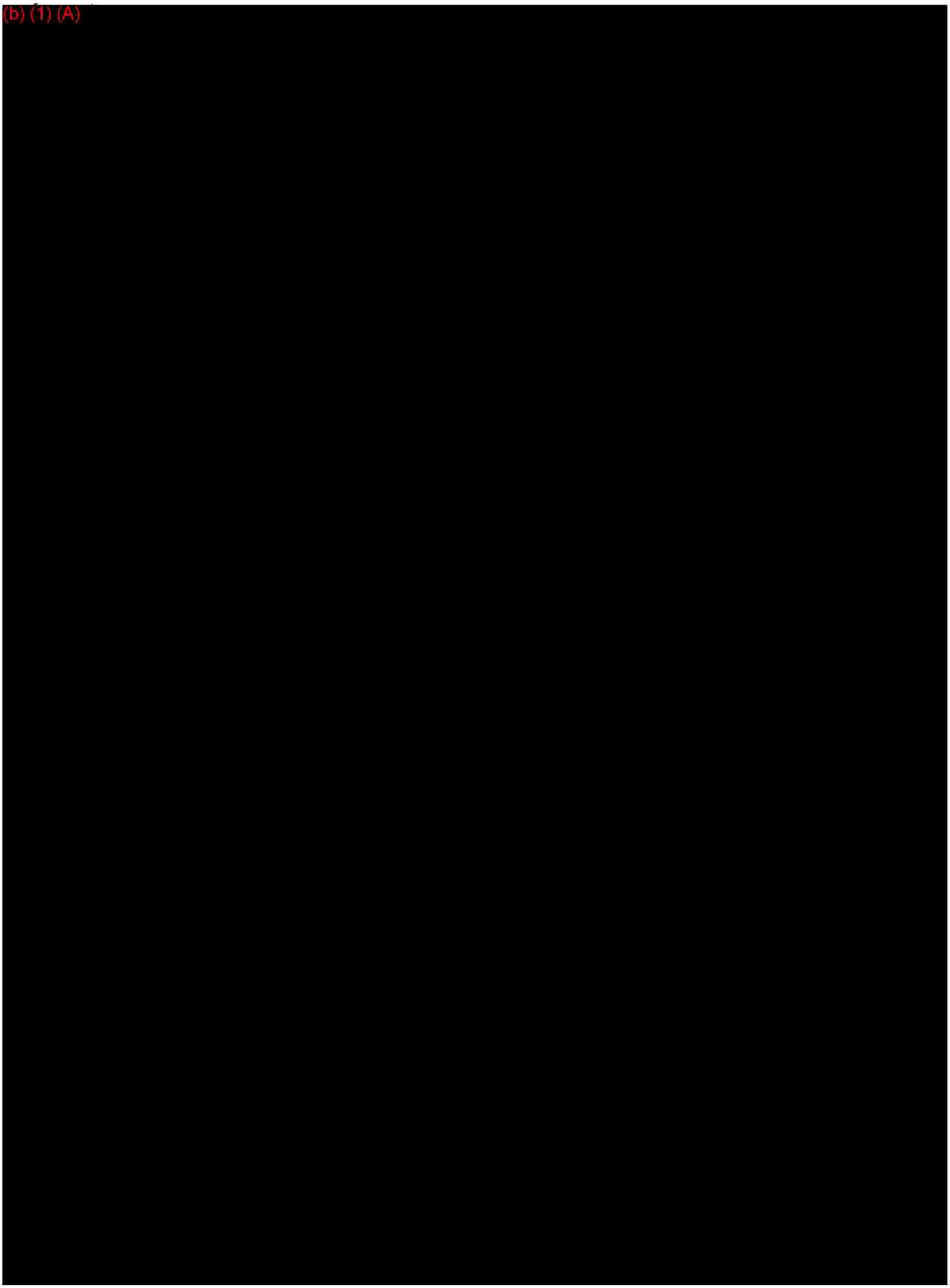

(b) (1) (A)

(b) (1) (A)

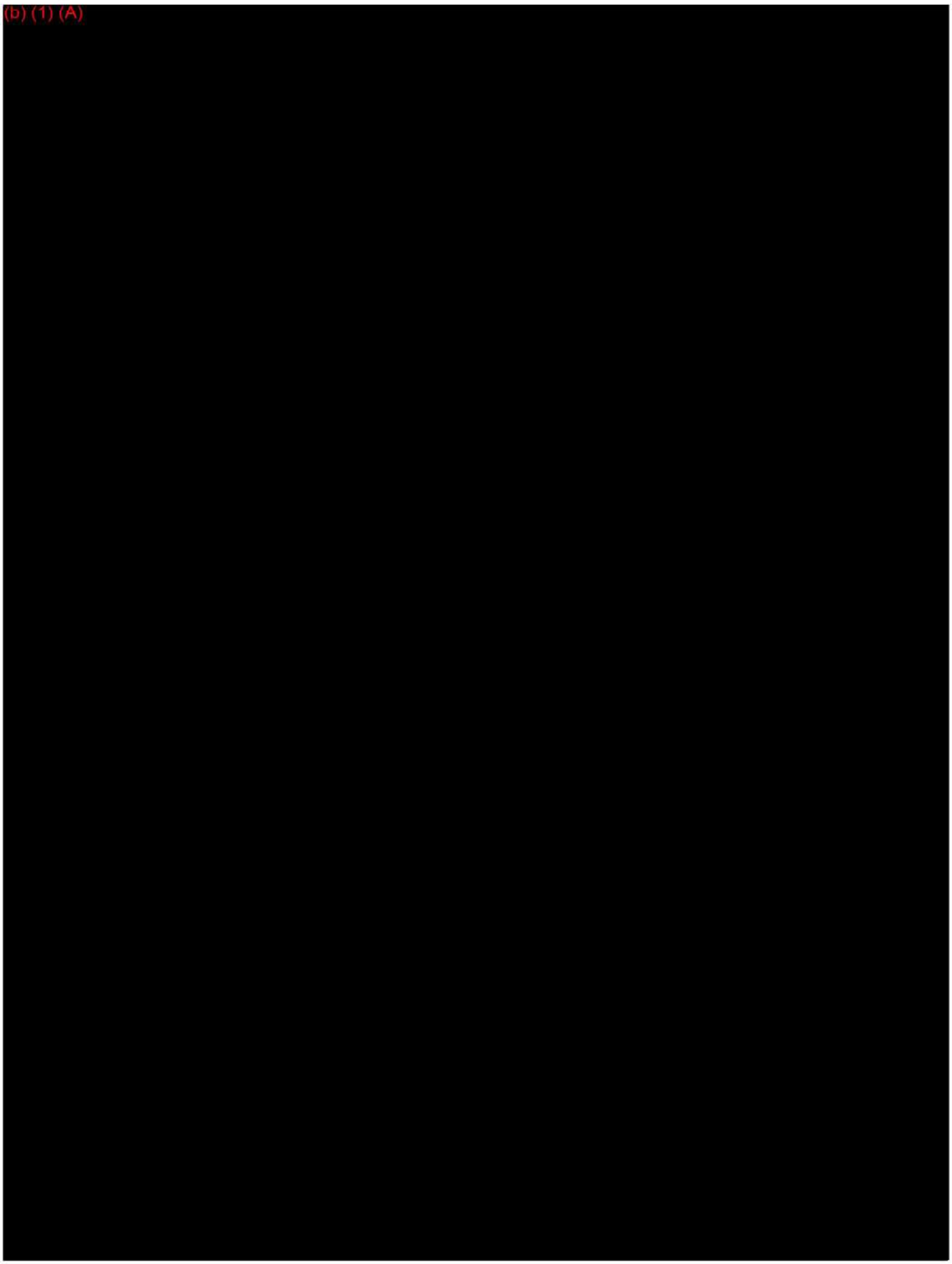


17.12 Appendix IVh: Attachment 8 to US Health Affairs Memorandum 'Establishment of Case Management Guidelines for Smallpox Vaccine Associated Myopericarditis'

(b) (1) (A)



(b) (1) (A)



17.13 Appendix IVi: Attachment 9 to US Health Affairs Memorandum 'Information Paper Vaccinia Immune Globulin Intravenous (Human) (VIGIV)'

Note: The US Health Affairs Memorandum; Update of Clinical Policy for the Department of Defense Smallpox Vaccination Program attaches 'Information Paper Intra-Venous Vaccinia Immune Globulin (IV-VIG)' from 9 November 2007. This CTP replaces this Information Paper with the 'Information Paper Vaccinia Immune Globulin Intravenous (Human) (VIGIV)' dated 25 June 2013.

INFORMATION PAPER

Military Vaccine Agency
25 Jun 2013

SUBJECT: Vaccinia Immune Globulin Intravenous (Human) (VIGIV)

1. Purpose. Define procedures for acquiring VIGIV

2. Facts.

a. The DoD requires smallpox vaccination of designated at-risk military personnel, DoD civilian personnel classified as emergency-essential per DoD Directive 1404.10, and members of CBRNE response teams (e.g., smallpox epidemic response teams, treatment teams, and public health teams). A small number of people may be at increased risk for side effects after receipt of, or exposure to, the smallpox vaccine. VIGIV is indicated for the treatment of certain adverse conditions induced by the smallpox vaccine.

b. The Deputy Director of the Military Vaccine (MILVAX) Agency will act as final releasing authority for DoD owned VIGIV.

c. Under routine circumstances, the need for VIGIV will be determined by the attending physician in collaboration with a Vaccine Healthcare Centers Network (VHCN) physician before administration. The VHCN will provide and coordinate professional consultation services to optimize both diagnosis of a potential vaccinia adverse event and clinical use of VIGIV.

3. Procedures

a. Clinician identifies an individual with adverse reaction who may benefit from treatment with VIGIV. This would include but is not limited to: aberrant infections induced by vaccinia virus that include accidental implantation in eyes, mouth, or other areas where vaccinia infection would constitute a special hazard; eczema vaccinatum; progressive vaccinia; severe generalized vaccinia; or vaccinia infections in people who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in people who have eczematous skin lesions because of either the activity or extensiveness of such lesions. VIGIV is not indicated for isolated vaccinia keratitis or post-vaccinial encephalitis.

b. Clinician will immediately begin the consultation process with the VHCN by calling the DoD Vaccine Clinical Call Center at 866-210-6469, available 24 hours a day, 7 days a week. The VHCN physician, or the MTF attending physician after collaboration with

the VHCN physician, will notify the MILVAX Agency (LTC Jorge Carrillo, 703-681-5699) with case specifics (indication for VIGIV, number of vials required, receiving POC, etc.).

c. The Deputy Director of the MILVAX Agency or his designee will coordinate the shipment of all VIGIV to CONUS and OCONUS locations.

d. The attending clinician must review the VIGIV package insert and be familiar with the indications, contraindications, complications, as well as all factors that affect the safe administration of this product. The clinician then obtains needed specialty consults and administers VIGIV if expected benefit outweighs potential risks. The VHCN physician will coordinate any pre- and post-infusion labs with the attending clinician.

4. References.

a. Advisory Committee on Immunization Practices. Smallpox Vaccinations and Adverse Reactions, MMWR 2003;52(RR04): 1-28: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5204a1.htm

b. Centers For Disease Control and Prevention. Surveillance Guidelines for Smallpox Vaccine (Vaccinia) Adverse Reactions, MMWR 2006;55(RR01);1-16

c. Vaccinia Immune Globulin Intravenous (Human), Cangene Corporation, Package Insert: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm179513.htm

d. Guideline for Obtaining Vaccinia Polymerase Chain Reaction (PCR) Assay Testing at: www.vhcinfo.org/documents/PCR_ALGORYTHM_2012b.pdf

e. Multiple resources (e.g., product insert, Vaccine Information Statements) assembled by Military Vaccine Agency: www.vaccines.mil/smallpox

(b) (1) (A)

Approved by: LTC (b) (1) (A)

17.14 Appendix IVj: Attachment 10 to US Health Affairs Memorandum 'Precision in ICD9 Coding of Medical Encounters'

INFORMATION PAPER

DASG-HCA
19 February 2005

SUBJECT: Consistency & Precision in Coding Medical Encounters After Immunization

1. Purpose. To describe procedures to increase the consistency and precision of coding applied to inpatient and outpatient visits for healthcare for symptoms and conditions that may occur after immunization.

2. Facts.

a. Background. Healthcare researchers depend on military healthcare providers to precisely describe encounters with patients using the codes of the International Classification of Diseases, 9th edition, known as ICD9.

b. Goal. To increase the consistency and precision of analyses of vaccine safety using automated databases, military treatment facilities (MTFs) should help clinicians and medical-record coders find the most precise ICD9 codes to describe a patient's visit. MTFs can encourage precision by distributing and posting lists of codes for common encounters related to immunization.

c. Expected Codes. The attached list describes codes for common or expected symptoms or conditions after immunization. This list is not exhaustive. Always use the most specific code(s) clinically appropriate to the patient seen. When in doubt, consult with the coding specialists in the Patient Administration Division. A complete list of the ICD9 coding system appears at www.cdc.gov/nchs/about/otheract/icd9/abticd9.htm.

d. Poisoning. According to the ICD9 system, "poisoning" codes from 960 to 979 exclude adverse effects ["hypersensitivity," "reaction," etc.] of correct substances properly administered. Classify such episodes according to the nature of the specific adverse effect that followed administration of that substance (e.g., a vaccine).

e. E codes. "E" codes are appropriate in specific circumstances. For example, adverse effects of bacterial vaccines properly administered should be coded as E948.8. Use E949 for adverse effects of viral vaccines properly administered.

f. Example. Consider the proper codes to identify a visit to treat injection-site inflammation after immunization. If the patient experiences muscle ache, headache, and swelling of the injection site, enter 729.1, 784.0, 729.81, and 995.2. This will allow visits for similar conditions to be grouped together, enhancing our ability to calculate how often they occur.

3. Revision. Coding conventions vary from time to time. Consult current references.

C(b) (1) (A)

Approved by (b) (1) (A)

Common Or Expected Symptoms Or Conditions After Immunization
ICD9 Coding System, February 2005

Anaphylaxis -- 995.0 – including allergic shock and anaphylactic reaction due to adverse effect of correct medicinal substance properly administered

Angioedema – 995.1 – also called angioneurotic edema

Dizziness and giddiness – 780.4 – including light-headedness, vertigo not otherwise specified (NOS)

Edema -- 782.3

Fainting – 780.2 – including syncope and collapse, blackout, (near) (pre)syncope, vasovagal attack

Fever – 780.6 – including chills with fever

Headache -- 784.0

Infection following infusion, injection, transfusion, or vaccination – 999.3

Itching – 698.9 – pruritis

Malaise and fatigue – 780.7

Mylagia and myositis, unspecified – 729.1

Other general symptoms – 780.9 – including chill(s) NOS

Pain in joint – 719.4 – including arthralgia

Rash and other nonspecific skin eruption – 782.1 – including exanthem.

Skin sensation disturbance – 782.0 – including burning or prickling sensation, hyperesthesia, hypoesthesia, numbness, paresthesia, tingling

Subcutaneous nodules -- 782.2 – including localized superficial swelling, mass, or lump

Swelling of limb – 729.81

Unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered -- 995.2 – including allergic reaction, hypersensitivity, and idiosyncrasy to correct substance properly administered

Unspecified erythematous condition – 695.9 – including erythema NOS

The following ICD9 codes are specific to smallpox vaccination:

Adverse effects of correct medicinal substance properly administered, smallpox vaccine -- E949.0

Encephalitis, postvaccinal -- 323.5

Generalized vaccinia -- 999.0

Infection following infusion, injection, transfusion, or vaccination – 999.3 (such as for inadvertent inoculation)

Keratitis or keratoconjunctivitis in exanthema -- 370.44

Keratitis superficial without conjunctivitis -- 370.2

17.15 Appendix V: CDC Fact Sheet 'Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir'

SMALLPOX FACT SHEET – *Information for Clinicians and Public Health Professionals*

Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir

Smallpox vaccination (vaccinia) is a generally safe and effective means to prevent smallpox. However, in a number of individuals, smallpox vaccination can result in untoward effects and adverse reactions. The majority of adverse reactions caused by the smallpox vaccine are mild to moderate complications that resolve on their own. Serious reactions are rare, but can be fatal.

There are two medications that may help persons who have certain serious reactions to the smallpox vaccine; vaccinia immune globulin (VIG) and cidofovir. VIG has been extensively used in the past and felt (but not shown in controlled studies) to be effective. Cidofovir may be effective based on studies in animals. Treatment with these medications may require the vaccine recipient to be in the hospital. They are investigational and may cause a number of serious side effects themselves.

Vaccinia Immune Globulin (VIG)

- Vaccinia immune globulin (VIG) is a product used to treat certain serious adverse reactions caused by smallpox vaccine. There are about 2,700 treatment doses of VIG (enough for predicted reactions with more than 27 million people). Additional doses of VIG are being produced this year.
- VIG was produced in the 1960s from plasma obtained from recently vaccinated donors. It contained a high titer of anti-vaccinia neutralizing antibody. Because it contained a high proportion of aggregated protein it was administered solely by the intramuscular route and could not be used intravenously.
- An effort is underway to produce new lots of VIG that will meet the standards for intravenous immune globulin. This IV-VIG will require new recommendations for both dosage and preferred method of administration. The new IV-VIG has a low level of aggregated protein, allowing it to be used by either the IM or IV route. Intravenous VIG will be most likely administered at a lower dose than the intramuscular preparation.

VIG Indications, Precautions and Contraindications

- Historically, VIG has been indicated for accidental implantation involving extensive lesions, eczema vaccinatum, generalized vaccinia, and progressive vaccinia.
- VIG is NOT recommended for mild instances of accidental implantation, mild or limited generalized vaccinia, erythema multiforme, or encephalitis post-vaccination.
- For more information on the adverse reactions mentioned above, go to www.cdc.gov/smallpox.

Concomitant Use of VIG with Vaccination

In some instances, VIG was given concomitantly with vaccination to "prevent" complications in a susceptible person. Not enough is known about the efficacy of this practice to recommend its use. Furthermore, there is currently an insufficient amount of VIG to use prophylactically when the benefits are uncertain.

Dosage

When it was used in the 1950s-1970s, the dosage of VIG varied. In general an initial dose of 0.6 ml/kg body weight was injected intramuscularly and subsequent administration determined by the course of illness.

In severe cases of eczema vaccinatum and progressive vaccinia as much as 1-10 ml/kg was used. These large doses were split into smaller units, and injected at multiple sites spread out over time.

Frequency of Use

Data from a CDC survey indicates that VIG was administered at a rate of 47 uses per 1 million primary vaccinees and 2 uses per million revaccinees.

Cidofovir

Another drug that may be used to treat certain serious smallpox vaccine reactions is cidofovir, an antiviral drug marketed as Vistide.

- Cidofovir is currently licensed for the treatment of CMV retinitis and has demonstrated antiviral activity against poxviruses in vitro, and against cowpox and vaccinia viruses in mice.
- However, its use for the treatment of vaccinia adverse reactions is restricted under an Investigational New Drug (IND) protocol. Under the IND, cidofovir would only be used when VIG was not efficacious.
- Renal toxicity is a known adverse reaction of cidofovir.

Obtaining VIG and Cidofovir

Indications for VIG/cidofovir release

- Vaccinia Immune Globulin (VIG) and cidofovir are indicated for the treatment of certain serious smallpox vaccine adverse events, including progressive vaccinia, eczema vaccinatum, generalized vaccinia (severe form or if underlying illness), and inadvertent inoculation (if judged to be severe due to the number of lesions, toxicity of affected individual, or significant pain). VIG is recommended as the first line of therapy. Cidofovir may be considered as a secondary treatment, and will only be released by CDC after all inventories of VIG have been exhausted, after a patient fails to improve with VIG treatment, or as a last effort for a patient who is otherwise near death.
- VIG and cidofovir are available for civilians through the CDC under Investigational New Drug (IND) protocols for treatment of specific smallpox vaccine reactions. Based on the anticipated number of adverse events resulting from the planned vaccination program for healthcare workers, CDC's supply of VIG should be adequate.
- Physicians at military facilities may request VIG by calling the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at 301-619-2257 or 888-USA-RIID and asking for the physician on call.

Process for obtaining VIG/cidofovir under Investigational New Drug Protocol (IND)

- Physicians should first contact their State Health Department when seeking consultation for civilian patients experiencing a severe or unexpected adverse event following smallpox vaccination or when requesting VIG or cidofovir. If further consultation is required, or VIG or cidofovir is recommended, the physician will be referred to the **CDC Clinical Information Line (CIL) at 1-877-554-4625**. The nurses staffing the CIL will take basic information and then expedite the call to the CDC Smallpox Vaccine Adverse Events Clinical Consultation Team. The CDC Clinical Consultation Team will provide in-depth consultation and will facilitate VIG or cidofovir release as appropriate.
- According to FDA regulations, VIG or cidofovir released from the CDC must be administered according to their investigational new drug protocols (IND). The IND mandates that the treating physician must become a co-investigator. The responsibilities of the co-investigator are primarily to complete follow-up forms describing the clinical status of the patient being treated with VIG

and/or cidofovir, including the prompt report of any significant adverse reaction in the recipient. Detailed information on the requirements of the IND will be shipped with the products.

- Details on the process for requesting VIG from USAMRIID for vaccinated military personnel with adverse reactions may be obtained at http://www.smallpox.army.mil/resource/vig.asp?ste=milvax.

Shipment of VIG/cidofovir

- VIG/cidofovir will be shipped by the National Pharmaceutical Stockpile (NPS). The CDC Smallpox Vaccine Adverse Events Clinical Consultation Team will coordinate the shipment of VIG/cidofovir with NPS. The cost of VIG and cidofovir and the cost of shipping will be covered by the U.S. Government. Arrival of shipments should be expected within 12 hours of the approval for release.

17.16 Appendix VI: Interpretation Support for Assessment of Screening ECGs

For a clearer and mutual understanding of inclusion criterion #14, the following provides clarifying explanations and examples pertaining to eligibility for vaccination.

- Examples of subjects **eligible for vaccination**:
- Non-specific ST and T wave changes are not considered clinically significant and subject can be vaccinated.
- Sinus bradycardia which does not require clinical intervention is not considered clinically significant and subject can be vaccinated.
- Subjects who present with atrial disease which do not require clinical intervention, e.g. a pacemaker or drug treatment, are allowed to be vaccinated, as these can be considered not clinically significant. Examples are premature atrial contractions or ectopic atrial beats
- Occasional PVCs which do not require clinical intervention are not considered clinically significant and subject can be vaccinated.
- First degree atrioventricular block or PR interval prolongations up to 220 ms are also acceptable as long as they do not require clinical intervention, i.e. do not represent an indication for a pacemaker, and therefore the condition can be classified as not clinically significant.
- Right or left axis deviation which does not require clinical intervention is not considered clinically significant and subject can be vaccinated.
- QTc prolongations < 500 ms which do not require clinical intervention are not considered clinically significant and subject can be vaccinated. QTc prolongations > 500 ms which do not require clinical intervention should be discussed with the Medical Monitor before vaccination.

Examples of subjects NOT eligible for vaccination:

- First degree atrioventricular block with PR interval prolongations above 220 ms, as well as second or third degree atrioventricular block could represent significant heart disease and subject should not be vaccinated.
- Incomplete left bundle branch blocks could represent significant heart disease and subject should not be vaccinated.

- Significant ventricular disease represented by complete intraventricular conduction defects (complete left or right bundle branch block) must be considered clinically significant and subjects presenting with any such condition should not be vaccinated.
- Left anterior or posterior intraventricular fascicular blocks or hemiblock or QRS prolongation above 115 ms could represent ventricular disease and subject should not be vaccinated.
- ST elevation consistent with ischemia, subject should not be vaccinated.
- Two PVCs in a row, subject should not be vaccinated.

17.17 Appendix VII: Volunteer Registry Data Sheet (USAMRDC 60-R)

12. U.S. Army Medical Research and Development Command Form 60-R

VOLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R)

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397

2. Principal and Routine Purposes: To document participation in research conducted or sponsored by the U.S. Army Medical Research and Materiel Command. Personal information will be used for identification and location of participants.

3. Mandatory or Voluntary Disclosure: The furnishing of the SSN is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide information may preclude your participation in the research study.

PART A - INVESTIGATOR INFORMATION
(To Be Completed By Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

1. Study Number:_____

2. Protocol Title:_____

3. Contractor (Laboratory/Institute Conducting Study):_____

4. Study Period: From:_____/_____/_____ To:_____/_____/_____
DD MM YY DD MM YY

5. Principal/Other Investigator(s) Names(s):
_____
_____
_____

6. Location/Laboratory:
_____/_____
_____/_____
_____/_____

PART B - VOLUNTEER INFORMATION
(To Be Completed By Volunteer)

PLEASE PRINT, USING INK OR BALLPOINT PEN

7. SSN:_____/_____/_____ 8. Name:_____

9. Sex: M___F___ 10. Date of Birth:____/____/____ 11. *MOS/Job Series:_____ 12: Rank/Grade:_____

13. Permanent Home Address (Home of Record) or Study Location:_____
(Street) or (P.O. Box/Apartment Number)

_____
(City) (Country) (State) (Zip Code)

Permanent Home Phone Number:_____

14. *Local Address (If Different From Permanent Address):_____
(Street) or (P.O. Box/Apartment Number)

_____
(City) (Country) (State) (Zip Code)

Local Phone Number:_____

15. *Military Unit: _____ Zip Code:_____

Organization:_____ Post:_____ Duty Phone Number:_____

VOLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R) (continued)

PART C - ADDITIONAL INFORMATION
(To Be Completed By Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

16. Location of Study:_____

17. Is Study Completed: Y:___ N:___

Did volunteer finish participation: Y:____ N:____ If YES, date finished____/____/____
DD MM YY

If NO, date withdrawn:____/____/____ Reason Withdrawn:_____
DD MM YY

_____

18. Did any Serious or Unexpected Adverse Incident or Reaction Occur: Y:____ N:_____ If YES, Explain:

_____

_____

_____

19. *Volunteer Follow-up:_____

Purpose: _____

Date: ____/____/____ Was contact made: Y:____ N:____ If NO action taken, explain:_____
DD MM YY

_____

20. *Hard Copy Records Retired: Place:_____ File NR:_____

21. *Product Information:

Product:_____

Manufacturer:_____

Lot #:_____ Expiration Date:_____

NDA # _____ IND/IDE #:_____

*Indicates that item may be left blank if information is unavailable or does not apply. Entries must be made for all other items.

When completed, a copy of this form should be sent to the address below:

(b) (1) (A)
[redacted]

17.18 Appendix VIII: Roles and Responsibilities

Principal Investigator

- Complies with protocol and all Federal and local regulations and policies and has ultimate responsibility for the conduct of the clinical trial and submission of the clinical study report.
- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles.
- Qualified through training, education and experience.
- Supervises clinical trial staff.
- Participates in the informed consent process.
- Screens individuals and reviews all of the screening tests to determine eligibility of person to participate in the clinical trial. Investigator or designee makes final eligibility decision.
- Permits auditing, institutional/sponsor monitoring and inspection by the FDA.
- Assures adequate resources, time, and patient population to meet clinical trial requirements.
- Assures proper medical care is provided for AEs.
- Documents protocol deviations.
- Reports all serious adverse events to the regulatory bodies (IRB) and sponsor (BN).
- Delegates investigational product accountability and administration.
- Evaluates AEs for diagnosis, relationship, and severity. Ensures documentation and safety reporting.

Clinical Trial Coordinator

- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles.
- Qualified by training, education and experience, and holds a current, unrestricted nursing license.
- Participates in the IMP accountability.
- Participates in the informed consent process.
- Reviews all of the screening tests to determine eligibility of individual to participate in the clinical trial.
- May administer IMP to clinical trial participants.
- Manages conduct of the clinical trial throughout the trial.
- Prepares the clinical trial site for conducting the trial.
- Follow-up all AEs.
- Accurate and timely completion of CRFs.
- Trains staff on protocol/protocol changes.
- Documents protocol deviations.

Physician

- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles.
- Qualified by training, education and experience, and holds a current, unrestricted medical license.
- Participates in the informed consent process.
- Performs all required clinical trial examinations and evaluations of testing.
- Reviews all of the screening tests to determine eligibility of individual to participate in the clinical trial.
- Follow-up and evaluates all AEs.

Research Nurse

- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles.
- Qualified by training, education and experience, and holds a current, unrestricted nursing license.
- Participates in the informed consent process.
- Reviews all of the screening tests to determine eligibility of individual to participate in the clinical trial.
- May administer investigational product to clinical trial participants.
- Schedules follow-up appointments.
- Follow-up all AEs.
- Accurate and timely completion of CRFs
- Documents protocol deviations

Research Monitor

- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles.
- Qualified through training, education and experience
- Safety advocate for clinical trial participants.
- Reviews Safety Management Plan.
- Reviews all SAEs, protocol violations and annual reports.
- The research monitor may discuss the clinical trial protocol with the investigators, interview human subjects, and consult with others outside of the clinical trial about the research. The research monitor shall have authority to stop a research protocol in progress, remove individual human subjects from a clinical trial protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

Medical Monitor

- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles.
- Qualified through training, education and experience.
- Designated by the sponsor's representative.
- Reviews all AEs and SAEs
- Available to discuss inclusion/exclusion questions and any medical question which arises from the protocol.

Data Entry Technician

- Complies with GCP, HIPAA, Declaration of Helsinki and the Belmont Principles
- Qualified through training, education and experience.
- Ensures the accuracy, quality, and integrity of the data.
- Reviews electronic case report forms (eCRF) for consistency and clarity, generates and resolves data queries and provides feedback to PI, protocol nurse coordinator and protocol team.

17.19 Appendix IX: Amendment 8 to Clinical Trial Protocol Edition 7.0 dated 01-Jun-2016

FY12-19, HP-12-19, POX-MVA-006

A randomized, open-label Phase III non-inferiority trial to compare indicators of efficacy for MVA BN® smallpox vaccine to ACAM2000® in 18-42 year old healthy vaccinia-naïve subjects

Amendment 8 to Clinical Trial Protocol

Edition 7.0 dated 01-Jun-2016

Date of Amendment 8: 29-Sep-2016

17.19.1 Rationale

The reason for the protocol amendment is that the IRB Office required further updates to the submitted Clinical Trial Protocol Edition 7.

17.19.2 Changes

General changes:

- Update of Section 1 Signature Pages to reflect one Principle Investigator (PI) following (b) (1) (A) [redacted]. References to Lead PI changed to PI throughout the document. Update of Section 1.4 Responsibilities.
- Update of Section 2.6 Clinical Profile of MVA-BN with respect to the latest available clinical data.
- The whole protocol has been reviewed and updated for clarity and formal consistency.

Major changes are as follows:

Changes/ added terms are highlighted in **bold** letters in the text (table below), removed terms are marked using ~~strikethrough~~.

Clinical Trial Protocol Edition 7.0, dated 01-Jun-2016 **Previously written:**	**Clinical Trial Protocol Edition 8, dated 29-Sep-2016** **Changed to:**
Page 24, 1.5 Protocol Synopsis / Sample size, **Page 73, 5.1 Recruitment Procedure**	**Page 23, 1.5 Protocol Synopsis / Sample size,** **Page 72, 5.1 Recruitment Procedure**
Up to ~~600~~ subjects may be screened to be able to vaccinate 440 eligible vaccinia-naïve subjects (220 per group) in order to achieve at least 175 subjects per group in the Per Protocol Set (PPS).	Up to **750** subjects may be screened to be able to vaccinate 440 eligible vaccinia-naïve subjects (220 per group) in order to achieve at least 175 subjects per group in the Per Protocol Set (PPS). Reason for change: To enable enough subject screening visits to reach the sample size target of 440 vaccinated subjects.

Clinical Trial Protocol Edition 7.0, dated 01-Jun-2016 **Previously written:**	**Clinical Trial Protocol Edition 8, dated 29-Sep-2016** **Changed to:**
Page 30, 1.5 Protocol Synopsis / Exclusion criteria no 27 **Page 76, 5.3 Exclusion criteria no 27**	**Page 29, 1.5 Protocol Synopsis / Exclusion criteria no 27** **Page 75, 5.3 Exclusion criteria no 27**
Having received any vaccinations or planned vaccinations with a live vaccine within 28 days prior to or after trial vaccination	Having received any vaccinations or planned vaccinations with a live vaccine **(except trial vaccine)** within 28 days prior to or after trial vaccination. Reason for change: For clarity/emphasis.
Page 43, 2.6 Clinical Profile of MVA-BN® **Page 44 & 45, 2.6.1 Safety Overview of MVA-BN®**	**Page 42, 2.6 Clinical Profile of MVA-BN®** **Page 43 & 44, 2.6.1 Safety Overview of MVA-BN®**
Table 1 'Suspected Adverse Drug Reactions Reported in Completed Clinical Trials'.	Data within the body text of Section 2.6 and Table 1 of Section 2.6.1 have been updated with the latest available clinical data. Reason for change: Actualization of MVA-BN® clinical data
Page 70, 4.2.5 Withdrawal from Further Trial Vaccinations (Group 1)	**Page 69, 4.2.5 Withdrawal from Further Trial Vaccinations (Group 1)**
~~Administration of a licensed vaccine not foreseen by the clinical trial protocol.~~	Reason for change: Bullet point deleted as the decision for withdrawal from further trial vaccinations, specifically when Group 1 subjects have received other licensed vaccines, lies with the Investigator (or upon subject request).

Clinical Trial Protocol Edition 7.0, dated 01-Jun-2016 **Previously written:**	**Clinical Trial Protocol Edition 8, dated 29-Sep-2016** **Changed to:**
Page 98, 8.3.1 Reporting of Serious Adverse Events	**Page 96, 8.3.1 Reporting of Serious Adverse Events**
All unanticipated problems involving risk to subjects or others and SAEs related to trial participation ~~and all subject deaths~~ will be promptly reported to the HQ USAMRMC IRB by phone ([redacted]), by e-mail ([redacted]), or by facsimile ([redacted]), or sent to the U.S. Army Medical Research and Materiel Command, ATTN: [redacted]	All unanticipated problems involving risk to subjects or others and SAEs related to trial participation will be promptly reported to the HQ USAMRMC IRB by phone ([redacted]), by e-mail ([redacted]), or by facsimile ([redacted]), or sent to the U.S. Army Medical Research and Materiel Command, ATTN: [redacted]. Reason for change: Correction of IRB information.
Page 109, 10.3 Approval by an IEC/IRB	**Page 106, 10.3 Approval by an IEC/IRB**
Prior to initiation of the trial, the PI or designee will submit the trial protocol, sample ICD, recruiting message/poster and/or e-mail, and other requested documents to the ~~HQ USMRMC~~ Institutional Review Board (IRB) for review and approval.	Prior to initiation of the trial, the PI or designee will submit the trial protocol, sample ICD, recruiting message/poster and/or e-mail, and other requested documents to the Institutional Review Board (IRB) for review and approval. Reason for change: Correction of IRB information.
Pages 114 & 115, 13.4 Compensation	**Pages 111 & 112, 13.4 Compensation**
Subjects will receive $50 compensation for each trial blood draw. Subjects will be paid for trial blood draw within an appropriate	Subjects will receive $50 compensation for each trial blood draw. Subjects will be paid for trial blood draw within an appropriate

Clinical Trial Protocol Edition 7.0, dated 01-Jun-2016 **Previously written:**	**Clinical Trial Protocol Edition 8, dated 29-Sep-2016** **Changed to:**
time frame. Compensation for this protocol will comply with 24 USC 30 and DoDI 3206.02. ~~All military must be designated as off duty status on the day of vaccination in order to receive the additional $200, day of vaccination, compensation. These additional funds are to compensate for the additional time necessary on vaccination day.~~ In addition, subjects will be compensated for travel expenses required to get to and from the clinical trial site.	time frame. Compensation for this protocol will comply with 24 USC 30 and DoDI 3206.02. In addition, subjects will be compensated for travel expenses required to get to and from the clinical trial site. Reason for change: IRB request after consideration that soldiers may not be classified as off-duty status on the vaccination administration visit days.