CONFIDENTIAL

A Phase 2b Study to Determine the Efficacy of Candidate Influenza Vaccine MVA-NP+M1 in Adults aged 18 years and over

Investigational Product:	**MVA-NP+M1**
Protocol Number:	**FLU009**
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Sponsor's Authorised Representative:	**Dr Thomas G. Evans** Chief Medical Officer

Signature Tom Evans MD Date 20 MAY 2019

Printed Name Tom Evans MD

Principal Investigator Agreement:

I, the undersigned, have reviewed this protocol and agree to conduct this protocol in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), the ethical principles set forth in the Declaration of Helsinki, and with local regulatory requirements.

Signature Date

Printed Name

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AUC	Area under the curve
CEF	Chicken embryo fibroblasts
CRO	Contract research organisation
DMC	Data monitoring committee
DMSO	Dimethyl sulfoxide
EDTA	Ethylenediaminetetraacetic acid
ELISpot	Enzyme linked immunosorbent spot
eDiary	Electronic diary
GMO	Genetically modified organism
HA/H	Haemagglutinin
HIV	Human immunodeficiency virus
ICH GCP	International Council on Harmonisation Good Clinical Practice
ICS	Intracellular cytokine staining
IEC	Independent ethics committee
IFN-γ	Interferon gamma
ILI	Influenza like illness
IRB	Institutional review board
MedDRA	Medical dictionary for regulatory activities
M1	Matrix 1
MVA	Modified vaccinia virus Ankara
NA/N	Neuraminidase
NP	Nucleoprotein
pfu	Plaque forming units
QIV	Quadrivalent influenza vaccine
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
$TCID_{50}$	Tissue culture infectious dose

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STUDY ABSTRACT

Protocol Title	A Phase 2b Study to Determine the Efficacy of Candidate Influenza Vaccine MVA-NP+M1 in Adults aged 18 years and over
Protocol Number	FLU009
Primary Objective(s)	To assess the effect of MVA-NP+M1 on the reduction of laboratory confirmed influenza when given as an adjunct to licensed quadrivalent influenza vaccine (QIV) in adults
Secondary Objective(s)	• To assess the impact of MVA-NP+M1 on incidence and severity of influenza-like symptoms in adults aged 18 years and over when given as an adjunct to licensed QIV • To assess the safety of MVA-NP+M1 or placebo when given as an adjunct to licensed QIV in adults aged 18 years and over
Exploratory Objective(s)	To assess the immunogenicity of MVA-NP+M1 when given as an adjunct to licensed QIV in adults aged 18 years and over
Design	This is a Phase 2b, multicentre, randomised, single-blind study in up to 6000 adults to compare the efficacy, safety and immunogenicity of MVA-NP+M1 when given as an adjunct to a standard, licensed adult dose of QIV. The study will be conducted on an outpatient basis and will run over two consecutive influenza seasons. It is aimed to recruit approximately 2200 participants in Season 1 and 2800-3800 participants in Season 2.
Number and Location of Clinical Study Site(s)	Up to 10 Sites in Australia
Study Population	Healthy adults 18 years or over who are receiving a licensed QIV vaccine
Treatment Groups	MVA-NP+M1 vs. saline placebo Single dose of 1.5 x 10^8 plaque forming units MVA-NP+M1 or saline placebo given by intramuscular administration 2,500-3,000 per study group with approximately 1,100 per study group enrolled in Season 1
Length of Follow-up	Each participant will be followed for a total of approximately 210 days.
Primary Endpoint(s)	Incidence of laboratory confirmed influenza-like illness

1 INTRODUCTION

1.1 Background

Seasonal influenza has a significant annual global impact accounting for an estimated 1 billion illnesses and 250,000 to 500,000 deaths [1] with an estimated annual economic cost of $87.1 billion in the US alone [2]. Influenza pandemics also occur occasionally with significant health and economic burden [3]. In addition, the unpredictable risk of sporadic outbreaks of human infections with avian influenza (H5N1) could trigger a new pandemic if the virus acquires the ability to transmit from person to person [4] and make influenza a major global public health issue. The major demographic groups at highest risk of influenza infection, severe disease and death remain young children, older individuals, pregnant women and those with co-morbid conditions such as asthma, chronic respiratory disease, diabetes and immunosuppressive conditions.

Vaccination remains the most cost-effective strategy available to combat influenza. Current influenza vaccines work by inducing strain-specific antibodies against the highly polymorphic surface proteins (haemagglutinin [HA/H], neuraminidase [NA/N]) of the influenza virus. Inactivated or live vaccines are made up of proteins from viruses or live viruses, respectively, covering four influenza virus strains (H1N1, H3N2 and two strains of influenza B). The composition of virus strains used in the production of vaccines is based on a prediction of strains likely to circulate in the population in the upcoming influenza season. As the circulating virus strains change, current vaccines need to be reformulated annually to match new strains arising through genetic drift in the surface proteins of these seasonal viruses. As these surface proteins to which vaccine-induced antibodies are targeted are highly polymorphic, there is little protection against strains of a new subtype and limited protection even across strains within the same subtype. Approximately one year in 20, vaccine efficacy is much lower than expected owing to antigenic drift away from the vaccine strain [5]. This need for constant redesign and remanufacture increases the vaccine cost, places limitations on supply [6] and critically delays vaccine production when new strains arise until the HA and NA sequences have been identified leaving large populations susceptible to infection and illness from the new strains. The efficacy of current vaccines is also limited in the face of antigenic mismatch between circulating strains and those in the vaccine and it is also substantially reduced in older adults. Vaccination in older adults, who are a major target group for vaccination, prevents laboratory-confirmed influenza in only 30 to 40% compared to 70 to 90% in young adults [7]. There is therefore a major demand for improved vaccination strategies that can provide protection against a broad spectrum of virus strains particularly for older groups.

In situations where individuals are exposed to a newly arisen influenza virus strain against which they lack protective neutralising antibodies, cross-reactive T-cells against conserved internal antigens of influenza have been shown to be associated with limiting viral shedding, reduced duration of symptoms and minimising severity of symptomatic illness [8, 9]. A vaccine against influenza that induced protective T-cell responses against conserved internal antigens could therefore provide lasting immunity against not only human seasonal influenza, but also other subtypes currently found in avian species or swine which have the potential to cause a new pandemic. Since adults have been primed by prior exposure to influenza, a vaccine

expressing conserved internal antigens of influenza such as nucleoprotein (NP) and Matrix 1 (M1) could be used to boost cross-reactive T-cell responses to protective levels, providing durable broad immunity to all subtypes of influenza A.

The internal proteins of the influenza virus are more conserved compared to the external surface glycoproteins. There are two reasons for selecting NP and M1 as a target for T-cell inducing vaccines. First, there is very little polymorphism of NP and M1 between influenza A isolates. NP is 92% identical between H3N2 and H1N1 strains, and 91% identical between H3N2 and H5N1 strains. M1 is 95% identical between H3N2 and H1N1 strains, and 93% identical between H3N2 and H5N1 strains. This low level of variation appears to allow strong T-cell cross-reactivity. In the local population more than 70% of individuals generate a T-cell response to these two antigens [10]. Second, analysis of T-cell response to all the proteins of influenza have shown that the T-cell response to NP and M1 is the strongest and 80% of individuals have responses to these two proteins. Recent studies have also shown that T-cells specific to M1 and NP are associated with protecting individuals against influenza by limiting viral shedding, reduced duration of symptoms and minimising severity of symptomatic illness [8, 9].

Recombinant viral vectored vaccines have been used in humans to induce high frequencies of $CD4^+$ and $CD8^+$ T-cell responses to a wide range of antigens. One such recombinant viral vector is Modified Vaccinia Ankara (MVA) which has been used to generate strong T-cell responses to a wide range of antigens, including antigens from plasmodium, tuberculosis, hepatitis C, human immunodeficiency virus (HIV) and influenza. MVA-NP+M1 is a recombinant, replication-deficient MVA vector expressing the influenza antigens NP and M1 as a fusion protein [11].

MVA is an attractive candidate orthopox vaccine vector for safety and immunogenicity reasons. The successful worldwide eradication of smallpox using vaccination with vaccinia virus highlighted vaccinia as a candidate vaccine vector. Although millions of humans have been vaccinated with conventional replication-competent vaccinia virus, its small but definite risk to both researchers and future patients led to the development of several attenuated strains of vaccinia during smallpox eradication. MVA was originally derived from the vaccinia strain Ankara by over 500 serial passages in primary chicken embryo fibroblasts (CEF cells). MVA has six major genomic deletions compared to the parental Ankara genome and is severely compromised in its ability to replicate in mammalian cells. No replication has been documented in non-transformed mammalian cells.

MVA has an excellent safety record. It was administered intradermally to approximately 120,000 people during the smallpox eradication campaign [12]. MVA is currently in development as a vector for multiple diseases including HIV-1 [13, 14], tuberculosis [15], hepatitis C virus [16], influenza [11] and melanoma [17]. MVA vectored vaccines developed at the University of Oxford have been administered to over 4500 individuals including infants, young children, elderly adults, HIV-infected adults and children and patients with cancer in Europe and Africa without any safety concerns. Clinical studies have shown intramuscular administration, as compared to intradermal, to be associated with fewer and short-lived local adverse events and no reduction in immunogenicity [18].

1.2 Non-clinical Studies

MVA NP+M1 has been shown to be immunogenic in BALB/c mice. Biodistribution studies were not conducted with MVA-NP+M1. Distribution studies in mice, however, showed no evidence of replication of the virus or presence of disseminated infection 1 week after intradermal and intramuscular injections using similar MVA vaccines (MVA85A, MVA ME-TRAP, MVA AMA1 and MVA MSP1). A distribution study was therefore not thought to be necessary for MVA-NP+M1. Previous toxicology studies in mice showed no evidence of systemic MVA-related toxicity after administration (either intradermal or intramuscular). A low level of local irritation at the vaccination site after intradermal administration is normally noted in these toxicology studies.

Single and repeat dose toxicology studies were performed on BALB/c mice using the MVA-NP+M1 manufactured in CEF and revealed that repeated administration of MVA-NP+M1 had no effect on mortality, cage side observations or bodyweights. Mice gained weight and had normal food consumption during the study. Clinical observations, vaccination site reactogenicity, clinical chemistry, clinical haematology, gross necropsy, organ weights and histopathology indicated no overt toxicity related vaccine administration (see the Investigator's Brochure).

The MVA viral vector manufactured using the AGE1.CR.pIX® avian cell line has been previously used with a different insert for an Ebola preventive vaccine (MVA-EBOZ). A Good Laboratory Practice-compliant non-clinical toxicology study was conducted to evaluate the local and systemic toxicity of the MVA85A vaccine manufactured using the AGE1.CR.pIX® avian cell line. The MVA85A was used as a surrogate test article to support the use of a MVA-EBOZ vaccine produced in the AGE1.CR.pIX® avian cell line and to demonstrate the safety of the vaccine for the first in human study.

1.3 Clinical Experience with MVA-NP+M1

Administration of the MVA-NP+M1 vaccine is supported by data from eight clinical studies, see Table 1-1. The first six studies used MVA-NP+M1 manufactured in CEF; a total of 145 participants received MVA-NP+M1 in these studies.

Two studies have since been conducted with the vaccine manufactured using the AGE1.CR.pIX® cell line. The first was a small Phase 1 bridging study (FLU008) to ensure the product was safe and elicited comparable or superior immune responses than those induced by the same vaccine made in CEF cells. This was followed by a Phase 2 study (FLU007) of elderly participants who either received the licensed quadrivalent influenza vaccine (QIV) followed by either placebo (N=430) or MVA-NP+M1 (N=430).

Full details of the clinical experience with MVA-NP+M1 can be found in the Investigator's Brochure.

Table 1-1 Summary of MVA-NP+M1 Clinical Studies

Study	Phase	Vaccine	Purpose	Age (years)	Route	Dose of MVA-NP+M1	N
MVA-NP+M1 manufactured in CEF							
FLU001	1	MVA-NP+M1	Safety and immunogenicity of two routes of administration and dose effect	18-50	ID	5 x 10^7 pfu	12
		MVA-NP+M1		18-50	IM	5 x 10^7 pfu	8
		MVA-NP+M1		18-50	IM	2.5 x 10^8 pfu	8
		MVA-NP+M1		50-59	IM	1.5 x 10^8 pfu	10
		MVA-NP+M1		60-69	IM	1.5 x 10^8 pfu	10
		MVA-NP+M1		70+	IM	1.5 x 10^8 pfu	10
FLU002	2a	MVA-NP+M1	Safety and efficacy of influenza challenge	18-50	IM	1.5 x 10^8 pfu	15
FLU003	1	MVA-NP+M1 / Seasonal influenza vaccine	Safety and immunogenicity when co-administered with seasonal vaccine	50+	IM	1.5 x 10^8 pfu	9
FLU004	1	ChAdOx1-NP+M1 / MVA-NP+M1	Dose escalation to assess the boosting effect of MVA-NP+M1 after adenovirus prime	18-50	IM	1.5 x 10^8 pfu	3
FLU005	1	ChAdOx1-NP+M1 / MVA-NP+M1 *(8 weeks apart)*	Safety and immunogenicity of different prime-boost combinations of MVA-NP+M1 and adenovirus in different age groups	18-50	IM	1.5 x 10^8 pfu	12
		ChAdOx1-NP+M1 / MVA-NP+M1 *(52 weeks apart)*		18-50	IM	1.5 x 10^8 pfu	8
		MVA-NP+M1 / ChAdOx1-NP+M1 *(8 weeks apart)*		18-50	IM	1.5 x 10^8 pfu	13
		ChAdOx1-NP+M1 / MVA-NP+M1 *(52 weeks apart)*		18-50	IM	1.5 x 10^8 pfu	12
		ChAdOx1-NP+M1 / MVA-NP+M1 *(8 weeks apart)*		>50+	IM	1.5 x 10^8 pfu	12
FLU006	1	MVA-NP+M1 / Co-administered with seasonal influenza vaccine (Viroflu®)	Safety and immunogenicity when co-administered with seasonal vaccine	18-50	IM	1.5 x 10^8 pfu	3[b]
MVA-NP+M1 manufactured in AGE1.CR.pIX®							
FLU008	1	MVA-NP+M1	Bridging study to assess safety and immunogenicity of MVA-NP+M1 manufactured on new cell line	18-50	IM	1.5 x 10^8 pfu	6
FLU007	2	MVA-NP+M1 / Co-administered with seasonal QIV	Safety and efficacy in the elderly when co-administered with seasonal vaccine	≥65	IM	1.5 x 10^8 pfu	430

Abbreviations: CEF=chicken embryo fibroblasts; ID=intradermal; IM=intramuscular; N=number of participants; pfu=plaque forming units; QIV=quadrivalent influenza vaccine

[a] Simian adenovirus vectored vaccine ChAdOx1 NP+M1

[b] FLU006 was stopped early due to futility as recruitment was slower than had been expected.

1.3.1 Safety and Immunogenicity Summary

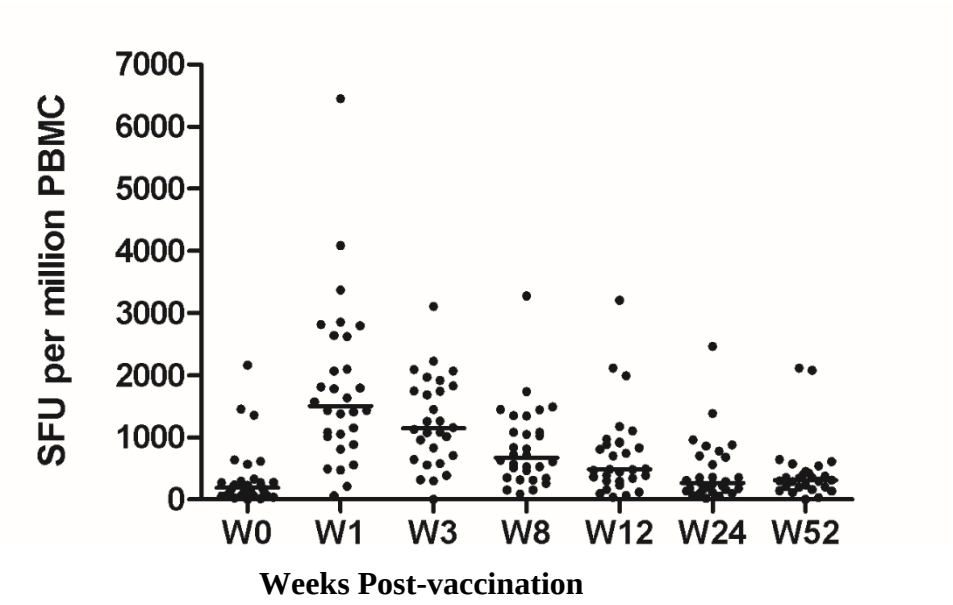
The vaccine has been shown to have a good safety profile with no vaccine related serious adverse events (SAEs). A dose dependent increase in adverse events was observed, and a dose of 1.5 x10^8 plaque forming units (pfu) was found to be the optimal balance between immunogenicity and reactogenicity across age groups [11]. There was no apparent difference between the vaccine manufactured in CEF and using AGE1.CR.pIX®. The vaccine also had a good safety profile when co-administered with the standard seasonal influenza vaccine.

Vaccination with MVA-NP+M1 results in a rapid increase in influenza-specific cross-reactive interferon gamma (IFN-γ)-secreting effector T-cells (determined by enzyme-linked immunosorbent spot (ELISpot) assay) across age groups which are maintained at protective levels over the course of a year [11]. In the older age groups, MVA-NP+M1 can boost pre-existing levels of influenza-specific T-cells and maintain them for up to at least 6 months post-vaccination [19]. The immunogenicity of MVA-NP+M1 in older adults (aged 50+) receiving a dose of 1.5 x10^8 pfu (Study FLU001) is shown in Figure 1-1.

MVA-NP+M1 in combination with licensed inactivated influenza vaccine induced influenza-specific T-cells and in addition, increase the magnitude and breadth of the antibody response induced by the inactivated influenza vaccine [20].

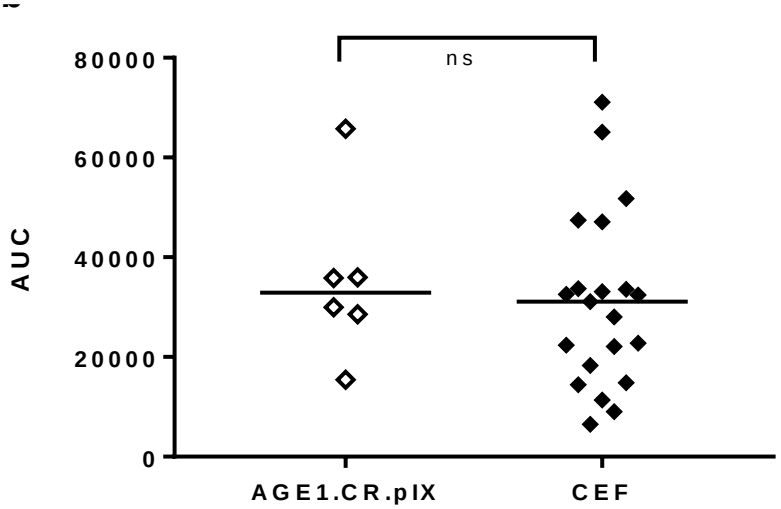
There was no statistically significant difference between T-cell responses when data from participants receiving MVA-NP+M1 manufactured using AGE1.CR.pIX® was compared with historical data from MVA-NP+M1 manufactured in CEF (FLU005), as shown in Figure 1-2.

Figure 1-1 Immunogenicity of MVA-NP+M1 in Older Adults (FLU001)



Abbreviations: PBMC=peripheral blood mononuclear cells; SFU=spot forming units; W=weeks

Figure 1-2 Area under the Curve Responses for Participants Vaccinated using MVA-NP+M1 (1.5×10^8 pfu) Manufactured on AGE1.CR.pIX® and Chicken Embryo Fibroblasts



Abbreviations: AUC=area under the curve; CEF=chicken embryo fibroblasts
Individual and median values are shown
Comparison performed using the Mann-Whitney test on data from FLU008 compared to historical data from Coughlin et al. (FLU005) [21]

1.3.2 Efficacy Summary

The efficacy of MVA-NP+M1 has been tested in two studies. In a small Phase 2a challenge study of MVA-NP+M1 alone (FLU002), MVA-NP+M1 vaccinated participants experimentally challenged with live influenza virus trended to less severe symptoms and shorter duration of viral shedding compared to unvaccinated controls [22]. A second Phase 2 study (FLU007), collecting symptom endpoints is now unblinded and undergoing further analysis.

1.4 Rationale for Study

Vaccination remains the most cost-effective strategy available to combat influenza. Current influenza vaccines work by inducing strain-specific antibodies against the highly polymorphic surface proteins of the influenza virus. The need for constant redesign and remanufacture increases the vaccine's cost, places limitations on supply and critically delays vaccine production when new strains arise. There is therefore a major demand for improved vaccination strategies that can provide protection against a broad spectrum of virus strains.

Previous studies have demonstrated the safety of MVA-NP+M1 across different age groups, including older adults and in combination with seasonal influenza vaccine; the immunogenicity of MVA-NP+M1 in older adults given alone and in combination with licensed inactivated seasonal influenza vaccine; and the effect of MVA-NP+M1 in limiting the severity of influenza illness in adults.

This study will therefore investigate the immunogenicity and efficacy in terms of viral and symptom endpoints in a large number of healthy adults aged 18 and over when given as an

adjunct to standard QIV. This MVA-NP+M1, produced using the novel immortalised duck retinal cell line AGE1.CR.pIX®**,** also addresses the scalability issues of CEF manufactured vaccines.

2 STUDY OBJECTIVES AND DESIGN

2.1 Objectives and Endpoints

The study objectives and corresponding endpoints are provided below.

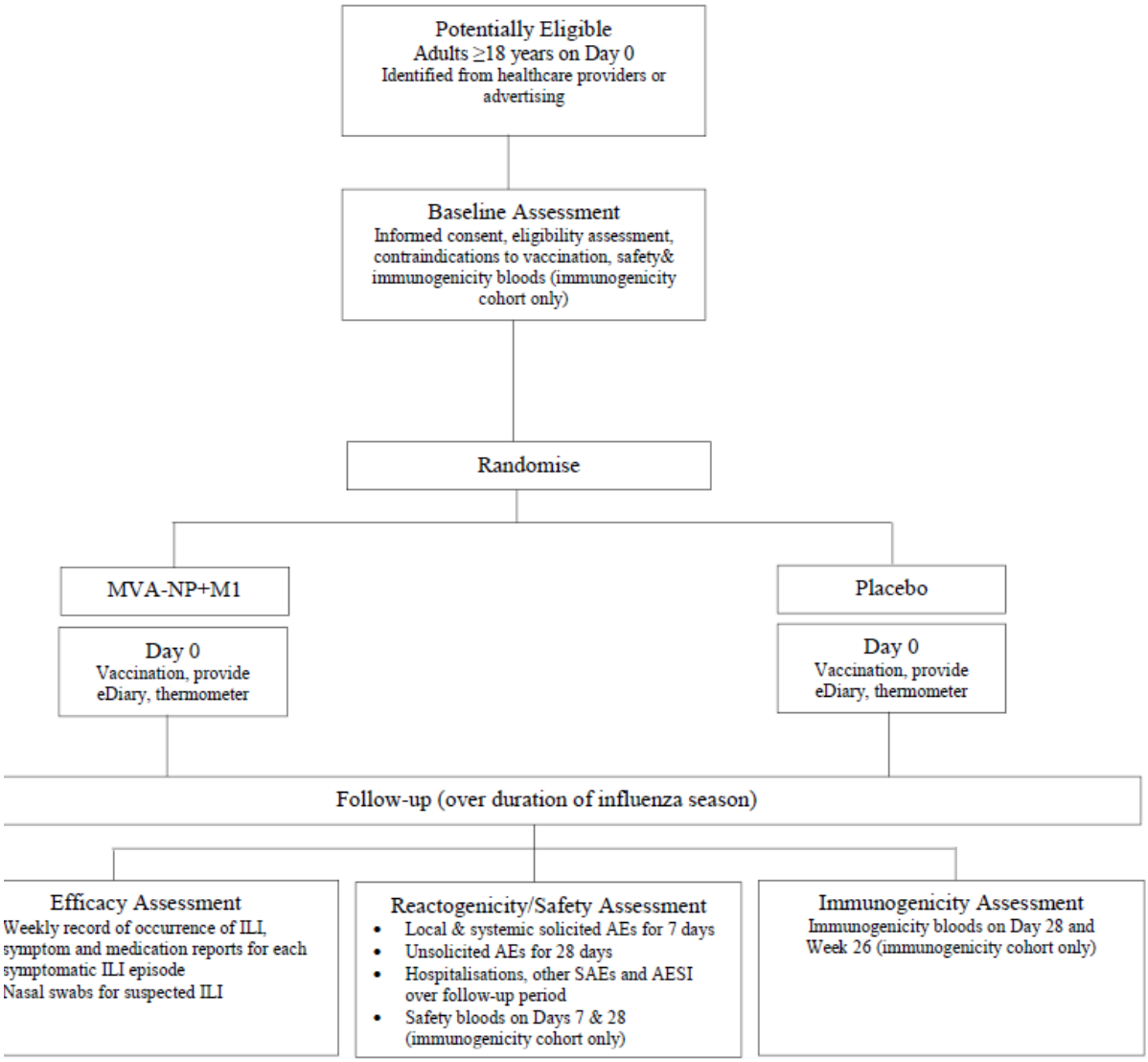
Note: that licensed QIV refers to a standard adult dose of QIV (15 μg per HA component) rather than a high dose QIV.

Objectives	Endpoints
Primary To assess the effect of MVA-NP+M1 on the reduction of laboratory confirmed influenza when given as an adjunct to licensed QIV in adults.	Primary Incidence rate of laboratory confirmed influenza using reverse transcription polymerase chain reaction (RT-PCR) on deep nasal/mid-turbinate swab samples.
Secondary	Secondary
• To assess the impact of MVA-NP+M1 on incidence and severity of influenza-like symptoms in adults aged 18 years and over when given as an adjunct to licensed QIV	• Incidence and severity of influenza-like illness (ILI) • Duration of ILI
• To assess the safety of MVA-NP+M1 or placebo when given as an adjunct to licensed QIV in adults aged 18 years and over	• Occurrence of solicited local and systemic reactogenicity signs and symptoms for 7 days following vaccination • Occurrence of SAEs during the whole study duration
• To assess the immunogenicity of MVA-NP+M1 when given as an adjunct to licensed QIV in adults aged 18 years and over	• Frequency of influenza-specific T-cells measured by IFN-γ/granzyme B ELISpot • Geometric mean titre of influenza-specific neutralising antibodies

2.2 Design

This is a Phase 2b, multicentre, randomised, single-blind study in up to 6000 adults to compare the efficacy, safety and immunogenicity of MVA-NP+M1 when given as an adjunct to a standard, licensed adult dose of QIV. The study will be conducted on an outpatient basis and will run over two consecutive influenza seasons. It is aimed to recruit approximately 2200 participants in Season 1 and 2800-3800 participants in Season 2. The study design is shown in Figure 2-1.

Figure 2-1 Study Flow Diagram



Abbreviations: AEs=adverse events; eDiary=electronic diary; ILI=influenza-like illness; SAE=serious adverse event

The majority of participants will participate in the main cohort of the study. These participants will attend the clinic for a single screening/vaccination visit on Day 0 and will be followed up over the duration of the influenza season into which they are recruited.

Approximately 50 participants will participate in an immunogenicity cohort; it is anticipated this will be at one centre only. In addition to the visits and procedures outlined for the main cohort, these participants will attend for a further three clinic visits on Days 7(+3 days) and 28 (±7 days) and Week 26 (±1 week) (approximate end of the influenza season).

Following screening and confirmation of eligibility on Day 0, all participants will be randomised in a 1:1 ratio to the two treatment groups shown in Table 2-1. Participants in the immunogenicity cohort only will also have pre-vaccination safety laboratory and immunogenicity blood samples taken.

Table 2-1 Treatment Groups and Number of Participants

	Group 1	**Group 2**
Study treatments	MVA-NP+M1	Placebo
Dose	1.5 x 10^8 pfu	None
Volume	0.5 mL	0.5 mL
Route of administration	Intramuscular injection	Intramuscular injection
Vaccination days	Day 0	Day 0
Number of participants; *Main cohort* *Immunogenicity cohort*	2500-3000 *2475* *25*	2500-3000 *2475* *25*

Vaccinations (1.5 x 10^8 pfu MVA-NP+M1 or saline placebo) will be administered by intramuscular injection using the Z-track technique on Day 0. Participants will be observed for at least 30 minutes post-vaccination in case of immediate adverse events and to comply with GMO licence regulations. All participants will be provided with an oral thermometer, tape measure and electronic diary card (eDiary) and instructed how to complete the eDiary at home.

Participants will record their oral temperature and any solicited adverse events for 7 days post-vaccination and unsolicited adverse events for 28 days post-vaccination. Participants will be asked to record whether or not they have a respiratory illness and / or ILI every week during the influenza season, starting on 01 May and ending on or before 15 October in line with official Australian influenza season. Respiratory illness or Influenza Like Illness (ILI) for this protocol that triggers a nasal swab collection (to maximize the likelihood of recovering virus positive samples) is defined as the presence of one or more of the following symptoms; fever or feverishness, cough, sore throat, congestion, chest pain, myalgia, and shortness of breath. Any episode with any one of these symptoms should undergo nasal sampling. The ILI regulatory definition used in the statistical section is defined as either fever or feeling feverish AND either a cough or sore throat.

Participants who are vaccinated early in the influenza season and complete the 28 day period for reporting unsolicited adverse events prior to 01 May will not be required to record any further data after Day 28 in the eDiary until this ILI reporting period starts. These participants will be telephoned ~7 days in advance of 01 May by way of reminder to start recording symptoms weekly.

The actual influenza season start and end dates used for final analysis will be determined by the Australian surveillance network and will be specified in the statistical analysis plan (SAP).

For every respiratory /ILI episode, patients will be asked to record the severity of their symptoms daily and any medications taken to treat the symptoms. If they experience such symptoms, they should attend the clinic on two occasions, the first within 72 hours of the onset of symptoms, for deep nasal/mid-turbinate swabs to be taken. Both swabs must be taken within 96 hours of symptom onset. These will be analysed for laboratory-confirmed influenza using RT-PCR.

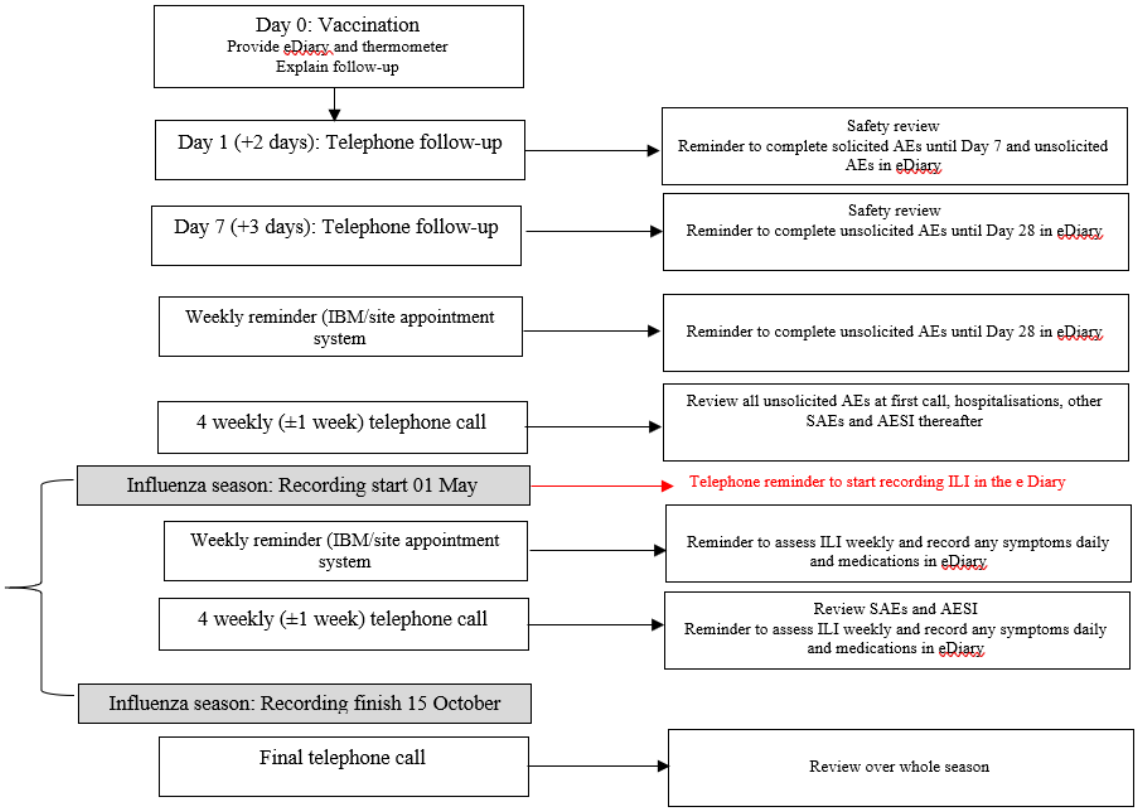
Weekly reminders to complete their diary will be sent to each participant through the IBM system or through site appointment systems, depending on where they are enrolled, over the duration of the influenza season. The study team will also contact participants by telephone every 4 weeks (±1 week) over the duration of the influenza season to remind participants to complete the ILI assessment in their diary and to enquire if they have had any hospitalisations, other SAEs or adverse events of special interest (AESI) (and other unsolicited adverse events at the first contact only for the main cohort).

Main Cohort:

Follow-up procedures for the main cohort are outlined in Figure 2-2 (participants who are vaccinated early in the influenza season and have completed Day 28 assessments prior to the start of the ILI reporting period on 01 May) and Figure 2-3 (participants who are vaccinated later in the influenza season and have Day 28 just prior to, or after, the start of the ILI reporting period on 01 May). The study team will contact participants by telephone on Day 1 (+2 days) post-vaccination and Day 7 (+3 days) post-vaccination for safety follow-up. If the participant has persistent, vaccine-related Grade 3 adverse events during the first 4 weeks post-vaccination they may be asked to attend a further clinical assessment.

At the end of the influenza season, all participants will be contacted by telephone to inform them of the end of the follow-up period and confirm all information has been collected.

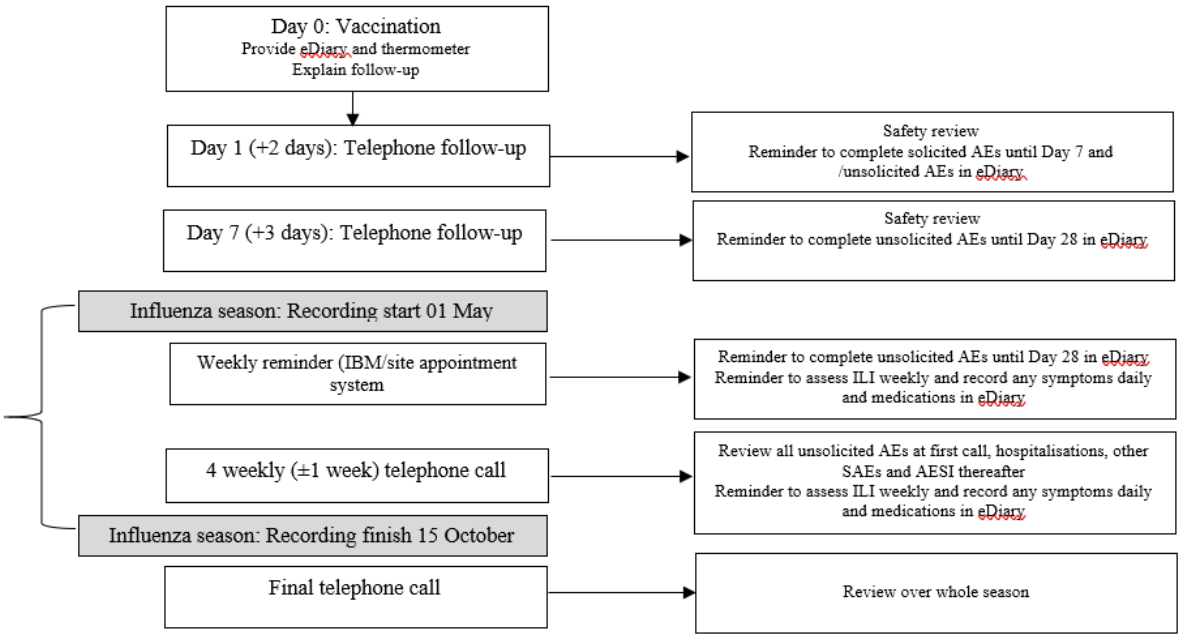
Figure 2-2 Follow-up Procedures for the Main Cohort (Participants Vaccinated early in the Influenza Season)



Applies to participants who have Day 28 prior to the start of the ILI reporting period on 01 May. Participants are not required to complete the eDiary in the period after Day 28 until 01 May

Abbreviations: AE=adverse event; eDiary=electronic diary; ILI=influenza-like illness; SAE=serious adverse event

Figure 2-3 Follow-up Procedures for the Main Cohort (Participants Vaccinated later in the Influenza Season)



Abbreviations: AE=adverse event; eDiary=electronic diary; ILI=influenza-like illness; SAE=serious adverse event

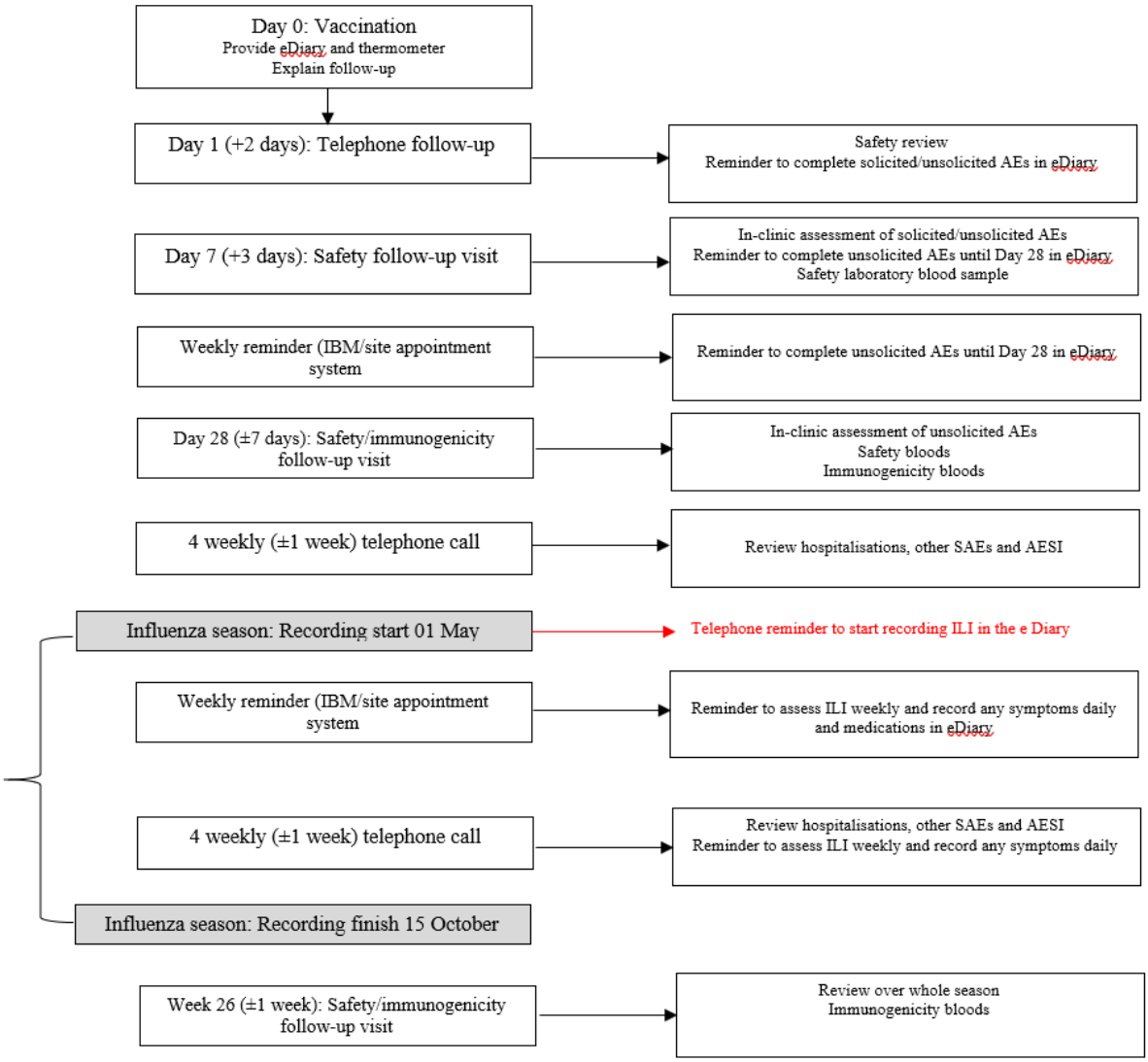
Immunogenicity Cohort:

Follow-up procedures for the immunogenicity cohort are outlined in Figure 2-4 (participants who are vaccinated early in the influenza season and have completed Day 28 assessments prior to the start of the ILI reporting period on 01 May) and Figure 2-5 (participants who are vaccinated later in the influenza season and have Day 28 just prior to, or after, the start of the ILI reporting period on 01 May).

The study team will contact participants by telephone on Day 1 (+2 days) post-vaccination for safety follow-up. Participants will attend the clinic for the following visits:

- Day 7 (+3 days) for assessment of solicited and unsolicited adverse events and safety laboratory blood samples
- Day 28 (±7 days) for assessment of unsolicited adverse events and safety laboratory and immunogenicity blood samples
- Week 26 (±1 week) (end of the influenza season) for immunogenicity blood samples and to confirm all information has been collected

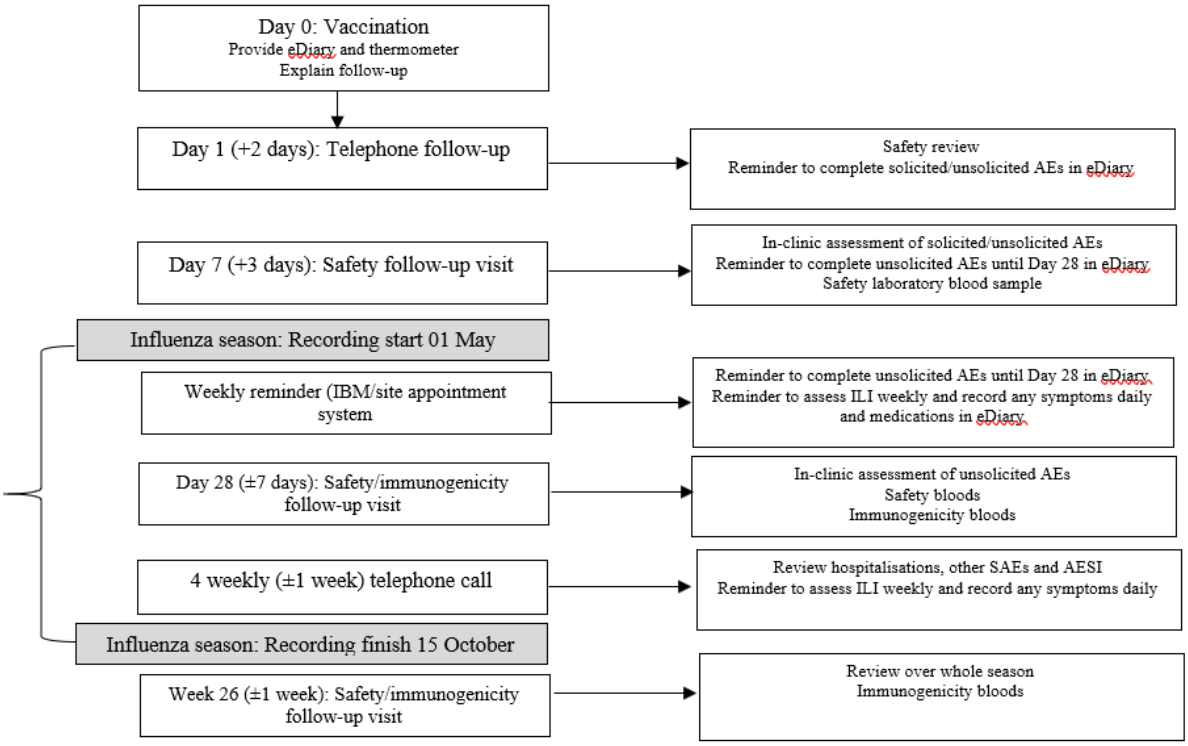
Figure 2-4 Follow-up Procedures for the Immunogenicity Cohort (Participants Vaccinated early in the Influenza Season)



Applies to participants who have Day 28 prior to the start of the ILI reporting period on 01 May. Participants are not required to complete the eDiary in the period after Day 28 until 01 May

Abbreviations: AE=adverse event; eDiary=electronic diary; ILI=influenza-like illness; SAE=serious adverse event

Figure 2-5 Follow-up Procedures for the Immunogenicity Cohort (Participants Vaccinated later in the Influenza Season)



Abbreviations: AE=adverse event; eDiary=electronic diary; ILI=influenza-like illness; SAE=serious adverse event

2.3 Data Monitoring Committee and Study Pausing and Stopping Rules

A data monitoring committee (DMC) will be appointed to review the study data and make recommendations concerning the continuation, modification, or termination of the study as detailed in Section 5.1.4.

The following study pausing or holding rules will apply for the study:

1. One or more study treatment-related SAE(s) or study treatment-related AESI occurs.

OR

2. Anaphylaxis or bronchospasm occur within 4 hours of vaccination, indicative of an immediate hypersensitivity reaction to vaccination.

OR

3. >10% of participants experience a Grade 3 or higher event judged related to study treatment, excluding local vaccination site reactions that decrease to <Grade 3 within 24 hours.

OR

4. An adverse event pattern of concern occurs.

If the Principal Investigator, local Medical Monitor, or Sponsor pauses the study, the decision will be recorded in a memorandum to the study file and will trigger DMC review, see Section 5.1.4.

The DMC may recommend resumption of enrolment with changes to the protocol if it judges that such changes will reduce safety risks. However, the final decision to resume study activities, amend the protocol, or terminate the study will be made by the Sponsor. The study site will be allowed to resume activities only upon receipt of written notification from the Sponsor. Decisions regarding pausing and resumption of the study will be communicated to the institutional review board (IRB)/independent ethics committee (IEC) by the Principal Investigator and to the applicable national regulatory authority by the Sponsor (or designee).

3 STUDY PROCEDURES

3.1 Schedule of Assessments

A schedule of assessments is provided in Table 3-1 for the main cohort and Table 3-2 for the immunogenicity cohort. A list of evaluations by visit/call day is provided in Appendix 1.

Table 3-1 Schedule of Assessments (Main Cohort)

	Screening / Vaccination	**Follow-up**			
Visit/Call Day	**D0**[a]	**D1(+2)**	**D7(+3)**	**D28(±7)**	**D29-EOS**[b]
Informed consent	X				
Inclusion and exclusion criteria	X				
Medical history reviewed	X				
Physical examination	X				
Urine pregnancy test (women of childbearing potential)	X				
Randomisation	X				
Vaccination	X[c]				
Post-vaccination observation period (30 mins)	X				
eDiaries, tape measure and thermometers provided	X				
Telephone contact		X[d]	X[d]	X (4 weekly)[e]	
IBM/site appointment system reminder		X(weekly)[f]			
eDiaries completed for local reactogenicity		X (daily)			
eDiaries completed for systemic reactogenicity		X (daily)			
eDiaries completed for unsolicited adverse events		X (daily)			
eDiaries completed for ILI symptoms		X (weekly 01 May to 15 October)[g]			
Nasal swabbing		X (if required)[h]			

Abbreviations: D=day; eDiaries=electronic diaries; EOS=end of study; ILI=influenza-like illness; mins=minutes; SAE=serious adverse event

Note: SAEs will be recorded for the duration of the study.

[a] Screening and Vaccination can occur on a separate day as long as QIV Vaccination is within the 28 day window

[b] Participants will be followed up over the followed-up over the duration of the influenza season into which they are recruited.

[c] MVA-NP+M1 or placebo by intramuscular injection.

[d] To review adverse events. If the participant has persistent, vaccine-related Grade 3 adverse events during the first 4 weeks post-vaccination they may be asked to attend a further clinical assessment.

[e] To remind participants to complete the ILI assessment in their diary and to enquire if they have had any hospitalisations or SAEs (plus other unsolicited adverse events at the first call only); final call performed at the end of the influenza season.

[f] Reminders to be sent out weekly to complete the eDiary. Reminders will not be sent between Day 28 and the start of the ILI reporting period on 01 May for participants vaccinated early in the influenza season who have Day 28 assessments prior to the start of the ILI reporting period.

[g] Assessment of ILI weekly. In the event of an episode, the severity of symptoms will be recorded daily and any medications taken to treat the symptoms. For participants vaccinated early in the influenza season and who have Day 28 assessments prior to the start of the ILI reporting period, a telephone reminder will be sent 7 days prior to the 01 May.

[h] If influenza symptoms are experienced, participants should attend the clinic on two occasions, the first within 72 hours of the onset of symptoms for deep nasal/mid-turbinate swabs to be taken. Both swabs must be taken within 96 hours of symptom onset.

Table 3-2 Schedule of Assessments (Immunogenicity Cohort)

	Screening	Vaccination	Follow-up			
Visit/Call Day	**~<120**	**0**	**D1(+2d)**	**D7(+3d)**	**D28(±7d)**	**W26(±1w) [a]**
Informed consent	X or	X[b]				
Inclusion and exclusion criteria	X or	X[b]				
Medical history taken/reviewed	X or	X[b]				
Physical examination	X or	X[b]		(X)		
Urine pregnancy test (women of childbearing potential)		X				
Randomisation		X				
Vaccination		X[c]				
Post-vaccination observation period (30 mins)		X		(X)		
eDiaries, tape measure and thermometers provided		X				
Telephone contact			X[d]		X (4 weekly)[e]	
IBM/site appointment system reminder			X (weekly)[f]			
In clinic assessment of local reactogenicity				X		
In clinic assessment of systemic reactogenicity				X		
In clinic assessment of unsolicited adverse events				X	X	
eDiaries completed for local reactogenicity			X (daily)			
eDiaries completed for systemic reactogenicity			X (daily)			
eDiaries completed for unsolicited adverse events		X	X (daily)			
eDiaries completed for ILI symptoms			X (weekly 15 May to 15 October)[g]			
Nasal swabbing			X (if required)[h]			
Haematology/biochemistry (mL)		12		12	12	
Exploratory immunology (mL)		50			50	50
Blood volume per visit (mL)		**62**		**12**	**62**	**50**
Cumulative blood volume (excluding repeats) (mL)		**62**	**62**	**74**	**136**	**186**

Abbreviations: D/d=day; eDiaries=electronic diaries; ILI=influenza-like illness; mins=minutes; SAE=serious adverse event; W/w=week; (X)=Performed if considered necessary

Note: SAEs will be recorded for the duration of the study.

[a] Participants will be followed up over the duration of the influenza season into which they are recruited. A final clinic visit will be performed at the end of the influenza season.

[b] Participants recruited through general advertising may have consent taken and a separate screening visit up to 120 days before vaccination. Participants recruited through their local healthcare provider will have screening procedures on Day 0 (as for the main cohort).

[c] MVA-NP+M1 or placebo by intramuscular injection.

[d] To review adverse events.

[e] To remind participants to complete the ILI assessment in their diary and to enquire if they have had any hospitalisations or SAEs; final assessment performed at the end of the influenza season at the ~Day 182 in-clinic assessment.

[f] Reminders to be sent out weekly to complete the eDiary. Reminders will not be sent between Day 28 and the start of the ILI reporting period on 15 May for participants vaccinated early in the influenza season who have Day 28 assessments prior to the start of the ILI reporting period.

[g] Assessment of ILI weekly. In the event of an episode, the severity of symptoms will be recorded daily and any medications taken to treat the symptoms. For participants vaccinated early in the influenza season and who have Day 28 assessments prior to the start of the ILI reporting period, a telephone reminder will be sent 7 days prior to the 15 May.

[h] If influenza symptoms are experienced, participants will attend the clinic on two occasions, the first within 72 hours of the onset of symptoms for deep nasal/mid-turbinate swabs to be taken. Both swabs must be taken within 96 hours of symptom onset.

3.2 Participant Selection

3.2.1 Recruitment and Informed Consent

Potential participants for the main cohort of the study will be identified by their local healthcare provider's practice (either directly or through database searches) or through study specific advertising. The practice will send study specific information to potentially eligible participants with an invitation to take part in the study. Interested participants with suitable existing medical history will be invited to participate in the study.

Other methods may also be used to recruit participants for the immunology cohort, such as advertising or referrals. All recruitment materials must be approved by the Sponsor and IRB/IEC.

Only patients who plan to receive a licensed QIV vaccine on the day of or in the 28 days before randomisation will be eligible.

Informed consent for the study will be obtained before any protocol specific procedures are performed as detailed in Section 8.3. Participants participating in the immunogenicity cohort will be asked to consent to have blood samples collected for laboratory safety tests and immunology assessments. Blood tests will not be a condition of participation in the main study and any participants initially recruited to the immunogenicity cohort who then does not wish to have blood tests will be offered participation in the main study without blood tests.

3.2.2 Assignment of Participant Identification Number

After informed consent is obtained, participants will be screened to assess eligibility for the study. For identification purposes, each participant for whom informed consent has been obtained will be assigned a unique 7-digit participant identification number (PID) by the site staff. The PID consists of three digits to represent site number assigned by the Sponsor, followed by a 4-digit number assigned by the site. (For example, if the clinical study site number is 120, the first participant to be screened would receive the number 120-0001, where all except "-0001" were pre-assigned by the Sponsor.) This participant identification number will be used throughout the study.

Eligibility for entry into the study will be based on the inclusion and exclusion criteria described in Section 3.2.3. The Investigator must document confirmation of eligibility prior to randomisation. For participants determined to be ineligible for the study, the reason for screening failure will be captured on the screening log and reported in the Monitoring Visit Reports.

3.2.3 Eligibility Criteria

All participants will be assessed for eligibility against the following inclusion and exclusion criteria:

3.2.3.1 Inclusion Criteria

Participants must meet <u>all</u> of the following criteria at the time of randomisation:

1. Healthy male or female adults aged 18 years and over

2. Receipt of a standard-dose licensed influenza QIV vaccine on the day of, or within 28 days prior to, randomisation
3. A female participant is eligible for this study if she is not pregnant or breast feeding and one of the following:
    a. Of non-childbearing potential (i.e. women who have had a hysterectomy or tubal ligation or are postmenopausal, as defined by no menses in greater than or equal to 1 year)
    b. Of childbearing potential but agrees to practice effective contraception 8 weeks post-vaccination and has a negative urine pregnancy test pre-vaccination. Acceptable methods of contraception include one or more of the following:
        i. Male partner who is sterile prior to the female participant's entry into the study and is the sole sexual partner for the female participant
        ii. Implants of levonorgestrel
        iii. Injectable progestogen
        iv. An intrauterine device with a documented failure rate of <1%
        v. Oral contraceptives
        vi. Double barrier methods including diaphragm or condom
        vii. Abstinence as long as it is line with the usual and preferred lifestyle of the participant
4. Participant is willing and has capacity to provide written informed consent for participation in the study (in the Investigator's opinion)
5. Able and willing (in the Investigator's opinion) to comply with all study requirements
6. Willing to allow the Investigators to discuss the participant's medical history with their healthcare provider
7. Present and able to visit the clinic in the event of an influenza symptom episode during the influenza season

3.2.3.2 Exclusion Criteria

Participants must have <u>none</u> of the following at the time of randomisation:

1. Any other significant disease, disorder or finding (including blood test results), which, in the opinion of the Investigator, would either put the participant at risk because of participation in the study, or may influence the result of the study
2. Receipt of any investigational product within 6 months prior to study, or prior participation in a clinical study of any Influenza vaccine and agreement not to participate in another clinical study for the duration of study follow-up
3. Prior receipt of an investigational vaccine likely to impact on interpretation of the study data

4. Active infection with HIV, Hepatitis B or Hepatitis C (from patient history or medical records)
5. History of severe allergic reactions (e.g. anaphylaxis)
6. History of auto-immune disease e.g. Guillain-Barré syndrome. Those with mild autoimmune-related diseases such as well-controlled diabetes, well-controlled thyroid disease or mild arthritic diseases can be enrolled.
7. Not willing to comply with study procedures
8. Immunosuppressed or taking immunosuppressive medications. Subjects with diseases that require immunosuppressive medication such as anti-TNF compounds, high dose glucocorticoids or daily glucocorticoids likely to suppress the adrenal axis should not be enrolled.
9. Use of warfarin or other blood thinning medications. Subjects on anticoagulants that may result in significant hematoma or bleeding at the injection site (e.g. thrombin inhibitors, fractionated heparin etc.) should be excluded but those on platelet inhibitors such as aspirin or clopidogrel can be enrolled.
10. Tattoos or birthmarks at the vaccination site
11. Participant bruises easily, has haematoma or keloid scarring
12. Receipt of a licenced inactivated vaccine (e.g. pneumococcal vaccine) within 2 weeks prior to vaccination
13. Receipt of an off licensed live vaccine (e.g. herpes zoster vaccine) within 4 weeks prior to vaccination

3.2.4 Screening/Baseline Assessments

Participants enrolled in the main cohort will be screened for eligibility and vaccinated on Day 0. However, vaccination can be performed on a different day to screening as long as QIV vaccination falls within the required 28-day window.

Participants enrolled in the immunogenicity cohort may have a separate screening visit up to 120 days before Day 0.

The following will be performed at screening:

- Collection of baseline information
  - Demographic information including age, ethnicity, gender
  - Height, weight
  - Medical history, including any allergies
  - Prior medications (recent [within the last 4 weeks] and currently ongoing)
  - Any co-morbidities
- Physical examination
- Description (brand) and timing of QIV received by the patient

- Urine pregnancy test sensitive to 25IU human chorionic gonadotrophin (pre-vaccination on Day 0 in women of childbearing potential)

Results and findings that make the participant ineligible will be discussed with the participant and they will be referred for follow-up care with their healthcare provider if necessary.

Participants will not be vaccinated, or will have vaccination deferred in the event of the following;

- Acute disease at the time of vaccination. Acute disease is defined as the presence of a moderate or severe illness with or without fever. All vaccines can be administered to persons with a minor illness such as diarrhoea, mild upper respiratory infection with or without low-grade febrile illness, i.e. temperature of ≤37.5°C/99.5°F
- Temperature of >37.5°C (99.5°F) at the time of vaccination

3.3 Study Randomisation

Eligible participants will be randomised to the study based on a randomly-generated sequence of numbers (randomisation schedule) managed by IBM Clinical Development. The randomisation schedule will be prepared by a statistician who will not be involved in the study's statistical analyses. Participants will be randomised on Day 0 after informed consent has been provided and eligibility confirmed.

Participants in the main cohort will be stratified by age <65 years and ≥65 years of age at the time of randomisation. Investigators will aim to enrol approximately 70% of participants in the <65 years old strata.

Participants recruited into the immunogenicity cohort will be randomised separately from the main cohort with no stratification.

All participants will be randomised in a 1:1 ratio to one of two treatment groups:

Group 1: 1.5 x 10^8 pfu MVA-NP+M1

Group 2: 0.5 mL 0.9% -saline placebo

Discontinued participants will not be replaced.

3.4 Investigational Product Administration

Vaccination will take place after consent and screening/baseline assessments have been completed and the participant has been randomised. All participants will receive either MVA-NP+M1 or placebo, according to randomisation as described in Section 3.3. Details of the study treatments are provided in Section 4.

All investigational vaccine administrations will be made into the deltoid muscle by intramuscular injection using a suitable sterile needle and syringe and employing the Z-track technique. The skin and subcutaneous tissues will be pulled and held to one side before the needle is inserted deep into the muscle tissue in the identified vaccination site. The vaccine is injected slowly, followed by a 10 second delay, at which time the needle is removed and the

tissues are quickly permitted to resume their normal position. This provides a Z-shaped track, which makes it difficult for the injected vaccine to seep back into subcutaneous tissues.

If MVA-NP+M1 or placebo are given on the same day as the QIV the two vaccines must not be given to the same deltoid muscle.

All vaccinations will be made by a suitably qualified health professional. A second study team member will be present to account for each vaccination given.

The suitably qualified healthcare professional will wear gloves, eye protection and an apron or laboratory coat/gown during the procedure. The vaccination site will be covered with an occlusive sterile dressing to minimise dissemination of the recombinant virus into the environment. This should absorb any virus that may leak out through the needle track. The sterile dressing will be removed 30 minutes after vaccination. The dressing will be discarded as genetically modified organism (GMO) waste.

Allergic reactions to vaccination are possible, therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and a medically qualified study team member trained to recognise and treat anaphylaxis must be present in the clinic during the entire vaccination procedure and post-vaccination observation period.

3.5 Participant Follow-up and Contact

3.5.1 Follow-up over Influenza Season

All participants who are assigned a participant identification number and receive study vaccine will be followed up over the duration of the influenza season to which they are recruited, unless they withdraw consent, are lost to follow-up (see Section 3.5.2) or the study is terminated early.

Participants will be followed up twice over the first week on Day 1 (+2 days) by telephone call and on Day 7 (+3 days) by either telephone call (main cohort) or in-clinic visit (immunogenicity cohort). Weekly reminders to complete their diary will be sent to each participant through the IBM system or through site appointment systems, depending on where they are enrolled, over the duration of the influenza season. The study team will also contact participants by telephone every 4 weeks (±1 week) over the duration of the influenza season to remind them to complete the ILI assessment in their diary and to enquire if they have had any hospitalisations or SAEs (plus other unsolicited adverse events at the first call only for the main cohort). Three attempts will be made for each follow-up phone call made during the study, if the participant cannot be contacted at any of these occasions this will be recorded and attempts will be made again at the next scheduled call.

Participants will receive a digital thermometer to record their temperature over the first 7 days post-vaccination and an eDiary to be used during the follow-up period. The eDiary is a web-based tool to:

1. Directly collect solicited adverse events over the first 7 days post-vaccination and influenza symptoms and medications over the duration of the influenza season (between 01 May and 15 October). These data will be integrated into the clinical database and directly used for analysis

2. Record unsolicited adverse events (all adverse events up to Day 28; hospitalisations and other SAEs only thereafter) and concomitant medications to enable the site staff to engage in a conversation with the participant during the scheduled telephone calls during the follow-up period. The eDiary will be considered source documentation for these data and relevant information should be collected and recorded on the unsolicited adverse event and concomitant medication electronic case report forms (eCRFs)

Participants will be trained in the use of the eDiary and will receive an instruction manual to take home.

3.5.2 Loss to Follow-up

If the study site's team members are unable to establish contact with a participant who either misses a scheduled study visit or fails to complete the eDiary, the study site must make every possible effort to re-establish contact and document such efforts. If contact is re-established, then the participant will resume participation in the study.

If contact with the participant cannot be re-established by the end of the influenza season, then a determination of "lost to follow-up" should be made.

3.6 Study Evaluations

3.6.1 Efficacy Evaluations

Participants will be asked to record in the eDiary whether or not they have respiratory symptoms indicating potential influenza every week during the influenza season. These symptoms include fever or feverishness, cough, sore throat, congestion, chest pain, myalgia, and shortness of breath. The regulatory definition of ILI is defined as **feeling feverish** or having a **fever** (temperature ≥37.8 C) and at least one of the following symptoms: a **cough,** and/or **sore throat**. For every respiratory episode, participants will be asked to record the severity of their symptoms daily and any medications taken to treat the symptoms.

If they experience any influenza symptom(s), participants should attend the clinic on two occasions, the first as soon as possible and at least within 72 hours of the onset of symptoms for deep nasal/mid-turbinate swabs to be taken. Both swabs must be taken within 96 hours of symptom onset.

Swabs will be taken with a flexible aluminium or plastic fine-shafted swab with a polyester, Dacron, or rayon tip. For deep nasal swabs the swab will be inserted into the nostril and back into the nasopharynx and will be slowly withdrawn with a rotating motion. For Mid-Turbinate swabs the swab is inserted in to the nostril to the point of resistance at the turbinate's and slowly withdrawn in a rotating motion. Both methods should result in a well-coated swab. The tip of the swab will be transferred into a vial containing transport media labelled with the participant's details.

Four swabs will be collected (one from each nostril at two visits within 96 hours) at each occurrence of any influenza symptom. However, if the participant experiences extreme discomfort during the first swab visit then there can be exceptions made in returning for the second swab. It will always be preferable to collect swabs at two timepoints, however, if it

becomes evident that the collection of swabs is detrimental to influenza symptom reporting and participants returning later in the season for swabbing then the collection a single swab can take precedence to ensure participants continue to report influenza symptoms.

These will be analysed at the study central laboratory for laboratory-confirmed influenza using RT-PCR.

3.6.2 Immunogenicity Laboratory Evaluations

Samples for immunogenicity analysis will only be taken from participants in the immunogenicity cohort. At each scheduled timepoint, a 50 mL blood sample will be taken and handled according to the Laboratory Manual.

Assessment of immune response to MVA-NP+M1 will be performed based on the percentage of CD4+ and CD8+ T-cells that produce any of the cytokines or functional markers or a combination of these simultaneously following stimulation with peptide pools derived from and representing the entire amino acid sequence of the mycNP+M1 encoded in the vaccine. Response will be measured using the ex vivo IFN-γ/Granzyme B ELISpot assay. The immune response will also be assessed by flow cytometry in the multi-colour intracellular cytokine staining (ICS) assay.

The antibody assays will include microneutralisation and hemagglutination inhibition titres using standard methodologies for the four strains that are in the licensed vaccine.

3.6.3 Safety Evaluations

3.6.3.1 Adverse Events

3.6.3.1.1 Solicited Adverse Events

Solicited adverse events are events the participant is specifically asked about. These adverse events are commonly observed soon after receipt of vaccines and relate to local and systemic signs and symptoms. Solicited adverse events will be collected for 7 days post-vaccination[1]. These will be recorded daily in the eDiary for all participants. Participants in the immunogenicity cohort will also have an in-clinic assessment on Day 7 (+3 days). Solicited adverse events will also be reviewed during the telephone calls on Day 1 (+2 days) (all participants) and Day 7 (+3 days) (main cohort only).

For this study, solicited adverse events to be collected include:

- Vaccination site reactions: pain, induration, warmth, erythema (redness)
- Systemic adverse events: feverishness, chills, myalgia, fatigue, headache, nausea, arthralgia, malaise

[1] In the event that they persist longer than 7 days then an adverse event will be recorded

Participants will be asked to record the presence of these symptoms and grade the severity as described in Section 5.3.1. Oral temperature will be measured using the thermometer provided and the diameter of induration will be measured with the tape measure provided.

3.6.3.1.2 Unsolicited Adverse Events

Unsolicited adverse events are other events meeting the criteria for adverse events (see Section 5.2) apart from those the participant is specifically asked about. Unsolicited non-serious adverse events will be collected for 28 days post-vaccination. Hospitalisations, other SAEs and AESI will be collected for the duration of the influenza season.

Participants will collect unsolicited adverse events in the eDiary and these will be reviewed during telephone calls with the participant and relevant information (event term, start and end date, severity, causality, outcome and seriousness) collected and entered into the eCRF as described in Section 5.2, Section 5.3.2, Section 5.4 and Section 5.5.

3.6.3.2 Laboratory Safety Tests

Laboratory safety tests will be performed for participants in the immunogenicity cohort only. 5 mL blood samples will be taken for haematology and biochemistry pre-vaccination on Day 0 and on Days 7 (+3 days) and 28 (±7 days). Results from laboratory safety tests obtained on the study must be reviewed by the Investigator (or a designee who is a medically qualified study team member) and managed in accordance with the study site procedures. The clinical significance of all results outside of the normal range will be determined by the Investigator and may be reported as an adverse event at the discretion of the Investigator. Additional laboratory safety tests may be performed if the Investigator deems them to be necessary to fully evaluate an adverse event. In the event that the Investigator elects to order non-protocol-specified laboratory tests, the Investigator must record the rationale for the tests and a determination of clinical significance of the result in the source documents. The Investigator must keep the local Medical Monitor informed of adverse events of clinical significance.

Abnormal results and findings will be discussed as applicable with the participant, and the participant will be referred for follow-up with their healthcare provider if necessary.

3.6.3.2.1 Haematology

For each assessment, a sample of venous blood will be collected in a tube containing ethylenediaminetetraacetic acid (EDTA) according to local laboratory procedures.

The following will be measured: full blood count: haemoglobin, haematocrit, erythrocytes, mean cell volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.

3.6.3.2.2 Biochemistry

For each assessment, a sample of venous blood will be collected in a heparinised tube according to local laboratory procedures.

The following will be measured: sodium, potassium, urea, creatinine, albumin and liver function tests (alanine transaminase, alkaline phosphatase and bilirubin).

3.6.3.3 Physical Examination

A skin, respiratory, cardiovascular, abdominal and lymphatic system examination will be performed at screening for all participants. A symptom-directed exam will be repeated, if required on Day 7 (+3 days) for participants in the immunogenicity cohort only. Results will be recorded as normal, abnormal and not clinically significant or abnormal and clinically significant.

3.6.3.4 Concomitant Medications

Concomitant medication includes prescription and non-prescription drugs or other treatments, and any vaccines other than the study vaccine.

Recently used and ongoing medications will be reviewed and recorded during screening.

Concomitant medications used by participants post-vaccination will coincide with the collection period of adverse events. All medications taken will be recorded in the eDiary and will be discussed with the participant at the scheduled telephone calls during the study. All medications taken in the first 28 days will be recorded in the eCRF. Thereafter, only the following will be recorded:

- All medications taken to treat SAEs
- All new vaccinations
- All antibiotic use
- Any new medication to treat respiratory illness

The name of the medication, treatment start and stop dates (or 'ongoing'), and indication must be recorded on the concomitant medication eCRF. The indication recorded on the concomitant medication eCRF must correspond to a medical term/diagnosis recorded on the adverse event eCRF, or to a pre-existing condition noted in the participant's medical history, or be noted as prophylaxis, e.g. dietary supplement.

4 STUDY TREATMENTS

Detailed instructions on the receipt, storage, accountability, preparation and disposal of the study treatments can be found in the Pharmacy Manual. A study vaccine manager will be responsible for the study treatments and must be a designated study team member, such as the study pharmacist. A Delegation of Authority Log will be maintained by the study site and will identify the individual(s) authorised to prepare and administer the study vaccine.

4.1 Description of Study Treatments

Participants will receive either the study vaccine, MVA-NP+M1, or placebo, according to randomisation).

4.1.1 MVA-NP+M1

Participants randomised to Group 1 will receive MVA-NP+M1, a MVA virus recombinant, replication-deficient, vector expressing the conserved influenza antigens NP and M1 as a fusion protein.

MVA-NP+M1 is manufactured under Good Manufacturing Practice conditions. It is provided in polymer vials as a liquid for injection. It will be certified by a Qualified Person, labelled and sent to PCI Pharma Services distribution centre in Australia for storage and distribution to clinical sites.

Each vial of MVA-NP+M1 contains 700 µL volume in formulation buffer containing 10% sucrose, 0.1% pluronic acid, 25 mM TRIS to a target final concentration of 1.2 x 10^9 tissue culture infectious dose ($TCID_{50}$)/mL. On the vaccination day, MVA-NP+M1 will be allowed to reach room temperature and administered within 1 hour of removal from the fridge.

The dose of MVA-NP+M1 to be used in this study will be 1.5 x 10^8 pfu (4.3 x 10^8 $TCID_{50}$), based on previous Phase 1 and Phase 2a clinical studies which have shown the vaccine is well tolerated and immunogenic at this dose, see Section 1.2. In FLU001, participants up to the age of 85 years received doses of 1.5 x10^8 pfu and 2.5 x 10^8 pfu MVA-NP+M1 in FLU001 and the former was shown to be less reactogenic and better tolerated.

4.1.2 Placebo

Participants randomised to Group 2 will receive a placebo injection of 0.9% saline (sourced by Fisher Clinical Services) instead of MVA-NP+M1. Each vial of saline will only be used for a single participant.

4.2 Blinding

This study is single blind.

The participant will be blinded to which study vaccine (MVA-NP+M1 or placebo) they are administered. The Investigator and all study staff acting to determine or record safety, as well as all laboratory staff will also remain blinded ("observer blind"). The pharmacist and any study staff administering the study vaccine will not be blinded. The volume and site of vaccination will be the same for both Group 1 and Group 2. Identical syringes and needles will be used for preparation and administration of each study vaccine. Study vaccine will be prepared out of sight of the participant.

4.3 Receipt and Storage

MVA-NP+M1 will be shipped to a distribution centre in the study region. It will then be shipped to the study sites at 2°C to 8°C with a continuous temperature-monitoring device.

Upon receipt, the pharmacist or study vaccine manager must immediately inspect all vials for damage. Any damage or discrepancies from the packing list must be documented and promptly discussed with the Sponsor and the Study Monitor to determine the appropriate action. The temperature monitors should be downloaded according to the accompanying instructions in the shipment. Temperature records must be sent to the Local Sponsor and the site will receive

written confirmation that the vials are clinically released before they are used. If the temperature monitor has been out of range then the shipment should be placed into quarantine and the Sponsor and Study Monitor contacted immediately to determine whether the study vaccine may be used.

Vials of MVA-NP+M1 in the outer carton (to protect from light) must be stored between 2 and 8^{o}C in a continuously monitored refrigerator. The vials of saline placebo will be stored at room temperature.

All study treatments must be kept in a secured location with no access for unauthorised personnel.

At the start of the study, a sufficient number of MVA-NP+M1 and placebo vials will be shipped to each study site to vaccinate approximately 20% of the planned participants based on recruitment projections. Further study vaccine supplies may be requested following the re-supply process in the Vaccine Management Manual.

4.4 Accountability

The pharmacist or study vaccine manager is required to maintain accurate accountability records for the study vaccine. Instructions and forms to be completed and kept for accountability will be provided to the pharmacist or study vaccine manager. If the pharmacist or study vaccine manager wishes to use site-specific accountability forms, these must be reviewed and approved in advance by the Sponsor. Upon completion of the study, all accountability records will be copied and the copies returned to the Sponsor or its designee. The originals must be maintained at the study site with the rest of the study records.

The number of vials of MVA-NP+M1 and placebo received and dispensed must be recorded on a participant by participant basis, including the applicable batch number. At the end of the study, all MVA-NP+M1 will be returned to the local country depot for destruction.

The brand of QIV used by each participant must also be documented.

4.5 Preparation

MVA-NP+M1 will be allowed to reach room temperature before use. It will be kept at room temperature after removal from the refrigerator and administered within 1 hour.

0.9% Saline placebo will be stored at room temperature.

0.5 mL volume of MVA-NP+M1 or 0.9% Saline placebo will be withdrawn from the vial/ampoule using a sterile needle and syringe prior to use according to the procedure in the Pharmacy Manual.

4.6 Disposal of Unused Investigational Product

MVA-NP+M1 will be returned to the local country depot for destruction. 0.9% Saline placebo will be destroyed locally according to the sites own policy. This destruction will be recorded with an original copy kept at site and a copy send to the Sponsor Trial Master File.

4.7 Compliance

Vaccine administration will take place at the study site and will be performed by a suitably qualified healthcare professional. The precise date and time of vaccination shall be documented in the eCRF. The study will be monitored by a Study Monitor approved by the Sponsor. During these visits, all procedures will be monitored for compliance with the protocol. Source documents will be reviewed and compared with the data entries in the eCRFs to ensure consistency.

5 SAFETY

5.1 Responsibilities for Ensuring the Safety of Study Participants

The national Regulatory Authority, the study Sponsor, the Institution through which the research is performed and all members of the Principal Investigator's study site team share responsibility for ensuring that participants in this study are exposed to the least possible risk of adverse events that may result from participation in this protocol.

5.1.1 Principal Investigator

The Principal Investigator has a personal responsibility to closely monitor study participants and an inherent authority to take whatever measures necessary to ensure their safety. The Principal Investigator has the authority to terminate, suspend or require changes to a clinical study for safety concerns and may delay an individual's study vaccine administration or pause study vaccine administration in the whole study if they have some suspicion that the study vaccine might place a participant at significant risk. The Principal Investigator determines severity and causality for each adverse event.

Responsibilities of the Principal Investigator may be assigned to a designee who is a medically qualified team member, however the accountability for the specific task remains with the Principal Investigator.

5.1.2 Study Sponsor

The Sponsor also has an institutional responsibility to ensure participant safety. This responsibility is vested in the local Medical Monitor and a DMC.

5.1.3 Local Medical Monitor

The local Medical Monitor is the Sponsor's representative and is a credentialed physician or surgeon in their country of residence with the necessary expertise to act in such capacity. The local Medical Monitor reviews the safety of the product for protocols in a specific region and, in conjunction with the Sponsor, determines expectedness of study treatment-related SAEs. The local Medical Monitor, in consultation with the Sponsor, may assess the causality for adverse events and may upgrade the causality determined by the Principal Investigator.

5.1.4 Data Monitoring Committee

A DMC will be appointed to review the study data and make recommendations concerning the continuation, modification, or termination of the study. The DMC will perform the following:

- Scheduled evaluation of study conduct and progress and review of the cumulative safety and efficacy data. Scheduled meetings will take place as follows:
  - Kick off meeting before the first participant is enrolled
  - A meeting at the end of the first influenza season to review safety and efficacy data and perform a futility analysis (with re-powering if required), see Section 7.7.1

- Perform unscheduled review of data if one of the study pausing or holding rules is met, see Section 2.3

There will be a minimum of three appropriately qualified committee members of whom one will be the designated chair. The DMC will operate in accordance with the study-specific charter, which will be agreed prior to the start of enrolment.

The chair of the DMC may be contacted for advice and independent review by the Investigator or Sponsor in any other situation where the Investigator or Sponsor feels independent advice or review is important.

The DMC will be convened if any of the pausing or holding rules is met. The DMC will be notified within 24 hours of the Investigators' being aware of any study treatment-related SAEs. The DMC has the power to place the study on hold if deemed necessary.

If, following review of data by the DMC, a recommendation to resume study enrolment and vaccine administration is made, the DMC will record their judgment in a memorandum to the study file and notify the Sponsor. The DMC memorandum will be forwarded to the local Medical Monitor and Principal Investigators.

5.1.5 Institutional Review Boards and Ethics Committees

The IRB/IEC has institutional responsibility for the safety of participants in clinical studies. The IRB/IEC has the authority to terminate, suspend or require changes to a clinical study.

5.1.6 National Regulatory Authority

Since the national regulatory authority receives all expedited safety reports for the study it also has the authority to terminate, suspend or require changes to a clinical study.

5.2 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an investigational product in humans, whether or not considered product-related. An adverse event (also referred to as an adverse experience) can be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product and does not imply any judgment about causality. An adverse event can arise with any use of the investigational product (e.g. off-label use, use in combination with another product) and with any route of administration, formulation, or dose, including an overdose.

Medical conditions that exist prior to administration of the study vaccine (pre-existing conditions) will be recorded in the participant's medical history to establish baseline. Day-to-day fluctuations in pre-existing conditions that do not represent a clinically significant change in the participant's status will not necessarily be reported as adverse events.

Any adverse change from the participant's baseline condition (determined from screening evaluations conducted to confirm study eligibility) that occurs following the administration of the study vaccine will be considered an adverse event. This includes the occurrence of a new adverse event or the worsening of a baseline condition, whether or not considered related to

the study vaccine. Intermittent conditions such as headaches in adults or irritability in infants may be present on study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following receipt of study vaccine. Adverse events include but are not limited to: adverse changes from baseline that represent increases in severity, adverse changes in the general condition of the participant, signs and symptoms noted by the participant, concomitant disease with onset or increased severity after study vaccine administration, and clinically significant changes in laboratory safety parameters occurring after study vaccine administration.

The reporting period for all adverse events is specified in Section 3.6.3.1. Solicited adverse events will be reported using pre-defined terms. Unsolicited adverse events will be reported using a recognised medical term or diagnosis that accurately reflects the event. Adverse event evaluations will be reviewed by the Principal Investigator or by a designated medically qualified practitioner. Adverse event information is to be completed by members of the study team designated in writing by the Principal Investigator. The onset and resolution dates of the event and action taken in response to the event will be documented.

5.3 Assessing Severity

The safety concepts of severity and seriousness are distinct concepts (see also Section 5.5). Severity refers to a degree of clinical manifestation. Seriousness refers to defined outcomes from an adverse event. A severe adverse event is not always serious and a serious adverse event is not always severe.

5.3.1 Solicited Adverse Events

With the exception of the Day 7 (+3 days) in-clinic assessment for participants in the immunogenicity cohort, the severity of solicited adverse events will be made by the participant. Severity will be assigned using the definitions in Appendix 3.

5.3.2 Unsolicited Adverse Events

For all unsolicited adverse events, the Principal Investigator is responsible for assessing the severity of the event and the causal relationship of the event to the study vaccine.

The **severity** of all adverse events, including clinical findings and abnormal laboratory values, will be classified using the definitions in Appendix 3, or for those events without a classification in the toxicity table as one of the following grades:

- Mild: Events are generally regarded as noticeable but have no impact on normal activities; they may or may not require over-the-counter treatment managed by the participant
- Moderate: Events generally have some impact on an individual's normal activities and may require general symptomatic medical intervention by a healthcare professional or by the participant
- Severe: Events may be incapacitating, leading to suspension of normal daily activities, and would generally require more immediate medical evaluation and intervention by a healthcare professional

All Severe adverse events will be notified to the Medical Monitor to be assessed on life threatening severity (as per Appendix 3). If the Medical Monitor deems the event to be of such severity then this can be upgraded at their discretion to a grade 4 in the eCRF.

A change in severity of an adverse event will not be recorded as a new adverse event. Only the highest severity level that occurs during the entire period of the adverse event will be recorded on the eCRF with the onset and resolution dates encompassing the entire duration of the event.

5.4 Assessing Causal Relationship (Relatedness)

Solicited adverse events of vaccination site reactions will be considered causally related to study treatment.

For all other adverse events, the Investigator and the Sponsor (the local Medical Monitor) will determine a **causal relationship** to the study vaccine. A number of factors will be considered in making this assessment, including: 1) the temporal relationship of the event to the administration of the study vaccine 2) whether an alternative aetiology has been identified and 3) biological plausibility.

Causality of all adverse events should be assessed by the Investigator using the following question:

"Is there a reasonable possibility that the adverse event may have been caused by the study vaccine?"

- **YES (related):** There is a reasonable possibility that the study vaccine contributed to the adverse event
- **NO (not related):** There is no reasonable possibility that the adverse event is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the adverse event

The Principal Investigator and the local Medical Monitor both determine causality. It is expected that communication and consultation may occur in the assessment of the causality of adverse events.

Every effort should be made by the Investigator to determine the existence of any pre-existing conditions (e.g. headache in adults or rashes in infants on study Day 0 with onset prior to study vaccination) that must be taken into consideration when assessing causal relationship of an adverse event. Pre-existing conditions should be recorded in the eCRF as baseline history and substantiated by appropriate source documentation. Intermittent conditions such as headaches in adults or irritability in infants may not be present on study Day 0 but may represent an adverse event if the intensity or duration of the event is worse than usual following study vaccine.

5.5 Assessing "Seriousness" and Serious Adverse Events

Seriousness refers to the outcome of an adverse event. Seriousness is determined by both the Principal Investigator and the local Medical Monitor. If either Principal Investigator or local Medical Monitor determines an event to be serious, it will be classified as such. If any of the following outcomes are present then the adverse event is serious:

- It results in **death** (i.e. the adverse event caused or led to the fatality). Serious does not describe an event which hypothetically might have caused death if it were more severe
- It was immediately **life-threatening** (i.e. the adverse event placed the participant at immediate risk of dying. It does not refer to an event which hypothetically may have led to death if it were more severe)
- It required inpatient **hospitalisation** or prolonged hospitalisation beyond the expected length of stay. Hospitalisations for scheduled treatments and elective medical/surgical procedures related to a pre-existing condition that did not increase in severity or frequency following receipt of study vaccine, are **not** serious by this criterion. Hospitalisation is defined as a hospital admission or an emergency room visit for a period greater than 24 hours
- It resulted in a persistent or significant **disability/incapacity** (i.e. substantial reduction of the participant's ability to carry out activities of daily living)
- It resulted in a **congenital anomaly or birth defect** (i.e. an adverse finding in a child or foetus of a participant exposed to the study vaccine prior to conception or during pregnancy)
- Other **medically important conditions** that may not result in death, threaten life or require hospitalisation (i.e. the adverse event does not meet any of the above serious criteria) may be considered an SAE when, based on appropriate medical judgment, they may jeopardise the participant and require medical or surgical intervention to prevent one of the serious outcomes listed in these criteria (e.g. allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalisation, or the development of drug dependency or drug abuse)

An **SAE** is an adverse event meeting the outcome criteria for seriousness regardless of relationship to the study vaccine.

5.6 Definition of Adverse Reaction

An adverse reaction is an adverse event judged to be related to study vaccine.

5.7 Assessing Expectedness of Adverse Events

Expected adverse events are adverse events consistent with the applicable product information provided by the Sponsor (the Investigator's Brochure for an investigational product). The Sponsor, in conjunction with the local Medical Monitor, determines expectedness of related SAEs.

5.8 Definition of Suspected Unexpected Serious Adverse Reaction

When an adverse event is judged to be related to study vaccine and is judged to be both serious and unexpected, and is in a participant who received active vaccine, it is a suspected unexpected serious adverse reaction (SUSAR) and is subject to expedited reporting.

5.9 Definition of an Adverse Event of Special Interest

AESI for this study are listed in Appendix 2Appendix 2. AESI should be recorded and reported using the same procedures as for SAEs. They should therefore be recorded over the duration of the influenza season to which the participant is recruited and reported to the Sponsor according to the process in Section 5.10.

5.10 Reporting of Serious Adverse Events

5.10.1 Reporting to the Sponsor

All SAEs, which include SUSARs, are reported to the Sponsor for the entire study period. SUSARs are reported even after the study is over, if the Sponsor, local Medical Monitor or Principal Investigator becomes aware of them. The study site will be provided with specific reporting procedures including the SAE paper form and any supplemental reporting forms to be used. SAEs will be reported on the SAE paper form and the AE eCRF using a recognised medical term or diagnosis that accurately reflects the event.

SAEs will be assessed for severity, causal relationship to the study vaccine, and expectedness by the Investigator and the local Medical Monitor according to their roles (as described in Section 5.1.1 and Section 5.1.3). The onset and resolution dates of the event and medical care taken in response to the event will be documented. If the event has not resolved by the end of the influenza season the participant is enrolled into, it will be documented as “ongoing” on the eCRF, however, follow-up of the SAE must continue until resolved or the condition has stabilised. Information recorded on the eCRF must be substantiated in the source documents.

The SAE form for that event must be completed by the Principal Investigator, within one business day of the study site becoming aware of the event. The SAE form should be completed with all information known at the time. and scanned and emailed to safety@clinical.net.au.

Fatal or life-threatening SAEs that the Investigator suspects are related to the study vaccine should be telephoned to the local Medical Monitor immediately upon the Investigator’s awareness of the event. If the local Medical Monitor is required by the protocol or chooses to suspend enrolment s/he shall immediately create a written memorandum for record to the study file and telephonically notify the Sponsor of this act.

Contact information for all safety personnel are contained in the Team Contact List, which will be stored at the study site in the Site Regulatory Binder and maintained by the study Sponsor.

Investigators must not wait to collect additional information to fully document the event before notifying the local Medical Monitor of an SAE. The initial notification should include the following (at minimum):

- Protocol number and name and contact number of the Investigator

- Participant identification number (and initials and date of birth, if available)
- Date participant received investigational product
- SAE(s) and date of event onset
- Current status of participant

The Sponsor will notify the DMC of all SUSARs within 24 hours of becoming aware of an event and will provide all follow-up information in a timely manner.

5.10.2 Expedited Reporting

SUSARs are subject to expedited reporting. The process will be further described in the Study Specific Safety Management Plan.

The Sponsor has authorised the CRO to execute its responsibilities for expedited safety report submission to the appropriate regulatory authorities within specific time periods of being notified of the event (within 7 or 15 calendar days depending the character of the SUSAR); therefore, it is important that the Investigator submit additional information requested as soon as it becomes available.

5.11 Other Events Requiring Immediate Reporting

The Investigator must report the following events to the Sponsor within 24 hours of becoming aware of the event:

- Withdrawal of consent during the study for safety reasons
- Protocol deviation affecting the safety of a participant or involving the vaccination process
- Adverse event thought to be an allergic reaction to the study vaccine
- Any event that, in the opinion of the Investigator, precludes further administration of the study vaccine
- Pregnancy

5.12 Adverse Event Treatment, Follow-up, and Outcome

Treatment of any adverse events will be determined by the Investigator using his/her best medical judgment and according to current clinical practice guidelines. All applied measures as well as follow-up will be recorded in the appropriate eCRF.

The Investigator will continue follow-up on adverse events, including laboratory abnormalities and solicited adverse events, until the event has resolved, is otherwise satisfactorily explained, or the participant completes the study. The resolution date will be recorded on the eCRF as the last date on which the participant experienced the adverse event. If an adverse event resolution date is uncertain the Principal Investigator should estimate the completion date based on medical judgment and interview of the participant. Approximate dates of resolution from phone or other communications may be taken as adverse event resolution dates. Some examples of estimation of adverse event resolution are: 1) an asymptomatic laboratory abnormality on one

visit that has not been followed-up between visits but has resolved by the next visit may be assumed to have resolved by the midpoint of the inter-visit interval; 2) A resolved adverse event that was treated may be assumed to have been resolved by the end of treatment.

Adverse events that are still present at the end of the study should be recorded as ongoing.

Information recorded on the eCRF must be substantiated in the source documents. If an adverse event evolves into a condition that becomes "serious," it will be designated as serious on the adverse event eCRF and a supplemental SAE Report form will be completed.

Follow-up for SAEs must continue until resolution and the outcome reported to the Sponsor, even if this extends beyond the SAE reporting period (the end of the influenza season into which the participant is enrolled).

For analysis purposes, the outcome for SAEs will be determined on or before the end of the second influenza season.

Outcome of all adverse events will be classified as one of the following:

- Resolved
- Resolved with sequelae
- Ongoing
- Death

If at any time after completion of the SAE reporting period the Investigator becomes aware of a serious adverse event that is suspected by the Investigator to be related to the study vaccine, the event must be reported to the Sponsor.

5.13 Follow-up of Participants Who Become Pregnant

If a participant becomes pregnant during the study, she should be encouraged to continue in the study for safety follow-up. Follow-up should continue for pregnancy outcome including premature terminations, and data are to be included in the safety reports.

The Investigator must notify the local Medical Monitor of the pregnancy immediately (even if already known to have resulted in spontaneous or elective abortion) by scanning and emailing, or faxing, the Pregnancy Notification Form to the local Medical Monitor. At a minimum, the estimated date of conception, the estimated due date, and the date the participant received the study vaccine should be provided.

If a participant becomes pregnant, she will not have any interventions done as normally mandated by the protocol (applies only to participants in the immunogenicity cohort). The participant will undergo all other evaluations according to Table 3-1 or Table 3-2.

The health status of the mother and child, the date of delivery, and the child's sex, birth weight and multiparity should be reported to the local Medical Monitor after delivery, using a Pregnancy Notification Form. If delivery occurs before the end of the influenza season, the participant should continue to be followed for SAEs until this time unless withdrawal of consent has occurred. If delivery occurs after the end of the influenza season, the Investigator should attempt to maintain contact with the participant to obtain information after delivery.

Pregnancy will not be recorded as an adverse event. If the pregnancy results in a miscarriage or a planned termination, the event (spontaneous abortion or elective abortion) will be reported as an adverse event or SAE per the Investigator's judgment (e.g. if it was a medically important or life-threatening event that meets the definition of an SAE).

A congenital anomaly or birth defect (i.e. an adverse finding in a child or foetus of a participant exposed to the study vaccine before conception or during pregnancy) must be reported as a SAE.

If it is determined after completion of the study that a participant became pregnant during the study, the participant should notify the Investigator. The pregnancy must be reported to the local Medical Monitor and the status of the mother and child after delivery will be obtained and reported, when possible.

6 DATA COLLECTION, MONITORING AN RECORD RETENTION

6.1 Source Documentation

Source documents are defined as the results of original observations and activities of a clinical investigation, including medical notes. The Investigator must permit the Study Monitor, the IEC/IRB, the Sponsor's auditors and representatives from regulatory authorities direct access to all source documents for confirmation of the accuracy and reliability of data contained within the eCRFs (source document verification). Participant confidentiality will be protected at all times.

Source documentation includes, but is not limited to, the following and will be identified in a source data location log:

- Screening/enrolment log
- Medical notes - which should be updated after each visit
- Informed consent form
- Laboratory reports (for the immunology cohort)
- Visit dates
- Study vaccine accountability forms

6.2 Data Management

Data recorded on source documents will be entered on eCRFs using an electronic data capture system approved by the Sponsor. Data collection must be completed for each participant who signs an informed consent form and receives at least one vaccination.

eCRFs should be completed in accordance with instructions. The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be transcribed directly into the eCRFs using a secure internet connection. The eCRFs should be filled out completely by the Investigator or designee as stated on the delegation of responsibilities form. The eCRF system will be Food and Drug Administration Code of Federal Regulations 21 Part 11 compliant.

The eCRFs must be reviewed, signed and dated by the Investigator when complete.

Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data. A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or Study Monitor. Clinical Data Managers and Study Monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

External immunogenicity data will be transferred electronically to the CRO. Discrepancies will be queried to the site and/or the laboratory until the electronic data and the database are reconciled.

All updates to queried data will be made by authorised study site personnel only and all modifications to the database will be recorded in an audit trail. Once all the queries have been resolved, eCRFs will be locked by password protection. Any changes to locked eCRFs will be approved by the Investigator.

Once the full set of eCRFs has been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then only be made only by written agreement of the Sponsor.

Unsolicited adverse events and medical history terms will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be coded according to the World Health Organization drug code.

The clinical database (in SAS® format) will be transferred to the Sponsor at the end of the study.

6.3 Monitoring

The study will be monitored in accordance with the principles of International Council on Harmonisation Good Clinical Practice (ICH GCP) by a Study Monitor approved by the Sponsor. During these visits, all procedures will be monitored for compliance with the protocol. Source documents will be reviewed and compared with the data entries in the eCRFs to ensure consistency. The frequency of monitoring visits will be determined, in part, by the rate of participant recruitment.

The monitoring visits also provide the Sponsor with the opportunity to ensure that timely patient accrual and the other Investigator's obligations and all applicable requirements are being fulfilled.

6.4 Record Retention

All study records (source documents, signed informed consent forms, IRB/IEC correspondence and approval letters, study treatment management records) will be kept secured for a minimum of 2 years following the marketing of the investigational product. Additional storage will be according to the guidance of the applicable national regulatory authority or authorities. The Investigator will ensure that study records are not disposed of or removed from the study site without prior notification and approval from the Sponsor or its designee.

7 STATISTICAL CONSIDERATIONS

The planned statistical analyses for this study are outlined below. A more detailed SAP (including plans for any interim analysis, futility analysis, subgroup analysis, and sensitivity analysis) and including methods for imputing missing data, where applicable, will be created and finalised prior to database lock for preparation of the final study report (see Section 7.7.2).

7.1 Participant Analysis Sets

- The Safety Analysis Set will consist of all randomised participants who received at least one vaccination (according to the vaccination actually received)
- The Efficacy Analysis Set will consist of all randomised participants who received the study vaccine according to the randomised treatment group (i.e. intent-to-treat)
- The Immunology Analysis Set will consist of all randomised participants according to their randomised treatment group who received the study vaccine, provided the pre-vaccination and at least one post-vaccination blood sample evaluable for immunological analysis and did not have any major protocol deviations that would impact on the results of the immunological analysis

7.2 Disposition, Demographics and Protocol Compliance

All data will be listed. Summaries will be provided for the Safety Analysis Set, unless stated otherwise.

Participant disposition (participants screened, screen failed [with reason], randomised, vaccinated and completed or withdrawn [with reason]) will be summarised by treatment group.

Demographic parameters (age, sex, and race/ethnicity) and other baseline characteristics will be summarised by treatment group for all participants in the Safety Analysis Set. Medical history will be summarised by system organ class (SOC) and preferred term.

Protocol deviations recorded during monitoring will be centrally collated, categorised according to deviation type and assigned as major or minor. Summaries will be generated by category.

7.3 Efficacy Analyses

Efficacy analyses will be performed on the Efficacy Analysis Set. The primary endpoint, the incidence rate of laboratory confirmed influenza using RT-PCR on nasal swab samples, will be compared between vaccine groups using Fisher's Exact Test. Secondary efficacy endpoints assessing the incidence and severity of influenza-like symptoms will be performed by comparing the incidence of ILI (using the regulatory definition of ILI defined as **feeling feverish** or having a **fever** (temperature ≥37.8 C) and at least one of the following symptoms: a **cough,** and/or **sore throat**) by Fisher's test exact and symptom severity as an area-under-the-curve (AUC) using a Mann-Whitney U Test.

7.4 Immunogenicity and Other Immunology Analyses

Immunogenicity data will be summarised for all time points as collected and as available for the Immunogenicity Analysis Set. Data will be transformed as appropriate prior to analysis, and all transformation processes will be clearly described in the SAP.

7.4.1 Immune Response Determined by Intracellular Cytokine Staining Assay

Dimethyl sulfoxide (DMSO)-subtracted cytokine response, as well as DMSO cytokine response (to better understand the distribution of background noise in the assay) will be used to summarise percentage CD4+ and CD8+ T cell response by treatment group and stimulation antigen. Summaries will include the assessment of response at all pre- and post-vaccination immunogenicity time points, as well as change from pre-vaccination to each post-vaccination time point, by treatment group.

The number (percentage) of participants designated as a responder according to the SAP will be summarised at each time point for ICS, and across all available time points compared to baseline cytokine expression, for all vaccinated participants by treatment group.

7.4.2 ELISpot Assay

Median DMSO-subtracted antigen response will be used to summarise responses. Summaries will include the assessment of response at all pre- and post-vaccination immunogenicity time points, as well as change from pre-vaccination to each post-vaccination time point.

The number (percentage) of participants designated as a responder according to the SAP will be summarised at each time point, and across all available time points, for all vaccinated participants by treatment group.

7.5 Safety Analyses

Safety analyses will be performed using the Safety Analysis Set.

7.5.1 Adverse Events

The number (percentage) of participants with unsolicited adverse events post-vaccination will be summarised by MedDRA system organ class and preferred term. Additional summaries will present the number (percentage) of participants with adverse events by severity and by relationship to investigational product; each participant will be counted once per preferred term at the greatest severity or most related state recorded for that term.

Separate summaries of the number (percentage) of participants with solicited adverse events will also be presented. Solicited adverse events will also be summarised by severity; each participant will be counted once per term at the greatest severity and most related state recorded for that term.

Separate listings will be provided for participants with SAEs and for participants with AESI and adverse events leading to discontinuation. SAEs may also be summarised by system organ class and preferred term.

7.5.2 Injection Site Reactions

The number (percentage) of participants recording vaccination site reactions in the eDiary in the first 7 days post-vaccination will be summarised by treatment group, timepoint post-vaccination and severity.

7.5.3 Clinical Laboratory Parameters

The number (percentage) of participants with post-vaccination clinical laboratory values as newly abnormal following study vaccination and meeting toxicity mild criteria (Grade 1) or above as specified in the Toxicity Table (Appendix 3) summarised using shift tables at each post-vaccination timepoint and overall. Newly abnormal results will be separately listed with the normal range and baseline value.

7.6 Sample Size Considerations

Sample size calculations based on various incidence rates in the control arm, relative vaccine efficacies for those in the MVA-NP+M1 arm, and alpha levels (two-sided) are provided in Table 7-1.

Table 7-1 Sample Size Calculations (80% power, two-sided alpha levels)

Rate of Influenza in Control Arm	Relative Vaccine Efficacy	Total Sample Size Required		
		α=0.10	α=0.15	α=0.20
2%	30%	11478	9658	8360
	35%	8188	6890	5964
	40%	6082	5118	4430
	50%	3652	3074	2660
3%	30%	7586	6382	5524
	35%	5412	4554	3,942
	40%	4022	3384	2930
	50%	2416	2034	1760
4%	30%	5640	4746	4108
	35%	4026	3386	2932
	40%	2992	2516	2178
	50%	1798	1512	1310

All calculations assume 80% power and given this is a proof of concept study an alpha of 0.1 is chosen for powering analyses. Based on the projected range of incidence rates in the control arm, a total sample size of approximately 5000 to 6000 participants over two influenza seasons is expected to provide approximately 80% power to detect a meaningful vaccine efficacy (approximately 35%) in the MVA-NP+M1 arm.

After the first influenza season, which will enrol approximately 2,200 participants, a sample size recalculation may be performed on the basis of the observed relative vaccine efficacy of

MVI-NP+M1 during the first influenza season. This will be described in more detail in the SAP.

7.7 Plan for Statistical Summaries and Analyses

7.7.1 Preliminary Data Reviews

The DMC will review cumulative safety and efficacy data from the first influenza season. This review of safety and efficacy data may include a formal futility analysis, as well as a potential sample size recalculation based on the observed relative vaccine efficacy in the MVA-NP+M1 vaccine group. Any plans for a potential futility analysis and/or sample size recalculation will be established *a priori* (prior to any unblinding of study data) and will be clearly described within the SAP and DMC Charter.

All unblinded-by-group summaries will be prepared for the DMC by an unblinded statistician not associated with the study conduct or development of the SAP for the final analysis. All procedures associated with this review, including objectives, data handling, and elements to be included for review will be documented in the DMC minutes.

7.7.2 Final Study Report

The final study report will include all available efficacy, immunogenicity (including exploratory analyses) and safety data; clinical assessments; and concomitant medications from the duration of the study.

Modifications or additions to the analyses described in Section 7.2 to Section 7.5 will be included in the SAP. Any decisions to deviate from the planned analyses described in the protocol and in the statistical analysis plan will be described in detail in the final study report.

7.8 Computer Methods

Statistical analyses will be performed using SAS® version 9.4 or later under a Windows operating system.

8 ETHICS

8.1 Regulatory Considerations

The study will be conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH GCP, and local regulatory requirements as applicable. The study site(s) should have recruitment and retention guidelines appropriate for different age groups (e.g., infants, adolescents, adults).

The protocol and informed consent form will be reviewed and approved by an IRB/IEC prior to any protocol-specified procedures being conducted. The Investigator is responsible for ensuring that the protocol is reviewed by an IRB/IEC with the appropriate composition (per clinical study site guidelines). The Investigator will inform the IRB/IEC as to the progress of the study at applicable intervals as defined by IRB/IEC policy.

There are potential known and unknown risks associated with vaccination. With any vaccine, including licensed ones, there is a rare risk of anaphylaxis which can be fatal. Participants will therefore be observed in the clinic for at least 10 minutes post-vaccination. Vaccination may also cause Guillain-Barré syndrome causing severe weakness, which may also be fatal.

Intramuscular injection of influenza vaccines frequently causes the local and systemic signs and symptoms that are being collected as adverse events. These will be solicited from the participant to ensure they are nor occurring more frequently or are more severe than expected.

With any new treatment there is always a possibility of an unexpected adverse events. Pausing and holding rules have been defined for the study (see Section 2.3) and the DMC will perform a review of safety data if one of these is met. There are also routinely scheduled reviews of safety and efficacy data throughout the study.

To maintain confidentiality, participant identification numbers will be used to identify laboratory samples, source documents, eCRF, study reports etc. All study records will be maintained in a secured location. Clinical information will not be released without written permission from the participant except as necessary for monitoring or auditing of the study by the Sponsor or its designee or applicable regulatory authorities.

After the study has been unblinded, the participant should be informed by the Investigator whether they received MVA-NP+M1 or placebo.

8.2 Institutional Review Board or Independent Ethics Committee

All the documents the IRB/IEC may need to fulfil its responsibilities, such as the protocol, protocol amendments, informed consent form, information concerning participant recruitment, payment or compensation procedures, etc. will be submitted to the IRB/IEC by the Investigator. The IRB's/IEC's written, unconditional approval of the appropriate version of the study protocol and the informed consent form will be in the possession of the Investigator/study site staff prior to the conduct of any protocol-specified procedures.

Modifications to the protocol may not be implemented without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the participants or when the

modification involves only logistical or administrative aspects of the study. Such logistical or administrative modifications will be submitted to the IRB/IEC in writing by the Investigator, and a copy of the correspondence to verify the submission will be maintained.

The Investigator must inform the IRB/IEC of modifications to the informed consent form or any other documents previously submitted for review/approval and any new information that may adversely affect the safety of the participants or the conduct of the study, provide an annual update and/or request for re-approval, and advise the IRB/IEC when the study has been completed.

Any study site-generated documents or forms to be provided to the participant (e.g. information cards, letters from the Investigator), and all forms of study advertising (flyers, brochures, print advertisements, radio or television scripts, etc.) must be approved by the Sponsor or its designee prior to the study site submitting them to the IRB/IEC. Approval from the IRB/IEC must be obtained prior to providing the documents or forms to the participant.

8.3 Informed Consent

Written, informed consent will be obtained prior to any protocol-specified procedures being conducted. The written consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. Informed consent will be documented in writing on a version-controlled consent form approved by the IRB/IEC.

The informed consent process will be conducted in a private space, whether at the study site, at home, or at another location, to maintain confidentiality. The consent process will be conducted in the participant's language of choice. All relevant information should be provided in both oral and written form in a way that is understandable to the participant. Ample time and opportunity must be given for the participant to inquire about details of the study. The potential participant should be encouraged to take the informed consent form home to discuss with family and friends before deciding whether or not to participate in the study.

An assessment of a participant's understanding of the key study concepts (e.g. procedures, risks) should be conducted prior to signing the consent form.

The Investigator or the Investigator's qualified designee will explain the nature of the study and inform the participant that participation is voluntary and that the participant can leave the study at any time, without penalty or loss of benefits to which they are otherwise entitled. The participant must be informed about the study's purpose including why the participant was selected to participate, study goals, expected benefits and risks, potential risks, and that some potential risks are unforeseeable. The participant must be provided with a description of the procedures and the estimated duration of time required for participation in the study, as well as alternative interventions or courses of treatment, if applicable.

The participant must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they are, where further information may be obtained, and who to contact in the event of a study-related injury. Participants must be told who to contact for answers to any questions related to the study. The extent of the

confidentiality of participant records must be defined and the participant must be informed that applicable data protection legislation applies.

The participant must be informed that the Study Monitor(s), auditor(s), IRB/IEC members, and the applicable regulatory authorities will be granted direct access to the participant's original study medical records for verification of protocol-specified procedures and/or data, without violating the confidentiality of the participant to the extent permitted by the applicable laws and regulations. The participant must be informed that his/her signature on the informed consent form indicates that he/she has decided to participate in the study, having read and discussed the information presented.

Modifications made by the Investigator to an informed consent form templates provided to the Investigator by the Sponsor or its designee will be reviewed and approved by the Sponsor or its designee prior to being submitted to the IRB/IEC.

The original, signed informed consent form for each participant will be maintained by the Investigator as part of the participant's study records. A copy of the signed informed consent form will be provided to each participant/.

Informed consent is an ongoing process. At every clinic visit it will be verbally reconfirmed that the participant is voluntarily consenting to the study and understands the significant aspects of the study (e.g. purpose, risks, duration).

Participants in the immunogenicity cohort only will be asked to consent to have blood samples collected in addition to the procedures for the main cohort. Blood tests will not be a condition of participation in the main study and all participants initially recruited to the immunology cohort who then do not wish to have blood tests will be offered participation in the main study without blood tests.

9 STUDY COMPLETION

The end of the study is defined as the date of database lock.

The Investigator will notify the IRB/IEC when the study has been completed.

10 PUBLICATION

The final study report will be made available to the Principal Investigator for purposes of publications. The Principal Investigator and study staff must send all manuscripts, abstracts, and presentations using data from this study to the Sponsor for review prior to their submission. The Sponsor reserves the right to delete any part or parts of such materials deemed to be confidential or proprietary.

11 CHANGES IN THE PROTOCOL

The protocol may not be modified without written approval from the Sponsor. All changes to the protocol must be submitted to the IRB/IEC and must be approved by the IRB/IEC prior to their implementation except when necessary to eliminate immediate hazards to the participants or when the modification involves only logistical or administrative aspects of the study.

12 REFERENCES

1. WHO, *Influenza fact sheet No. 211*. 2014.
2. Molinari, N.A., et al., *The annual impact of seasonal influenza in the US: measuring disease burden and costs.* Vaccine, 2007. **25**(27): p. 5086-96.
3. Dawood, F.S., et al., *Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study*. Lancet Infect Dis, 2012. **12**(9): p. 687-95.
4. Babakir-Mina, M., et al., *Influenza virus A (H5N1): a pandemic risk?* New Microbiol, 2007. **30**(2): p. 65-78.
5. Kilbourne, E.D., et al., *The total influenza vaccine failure of 1947 revisited: major intrasubtypic antigenic change can explain failure of vaccine in a post-World War II epidemic*. Proc Natl Acad Sci U S A, 2002. **99**(16): p. 10748-52.
6. Bardenheier, B.H., et al., *Influenza vaccine supply, 2005-2006: did we come up short?* BMC Health Serv Res, 2007. **7**: p. 66.
7. Hannoun, C., F. Megas, and J. Piercy, *Immunogenicity and protective efficacy of influenza vaccination.* Virus Res, 2004. **103**(1-2): p. 133-8.
8. Hayward, A.C., et al., *Natural T Cell Mediated Protection Against Seasonal and Pandemic Influenza: Results of the Flu Watch Cohort Study.* American Journal of Respiratory and Critical Care Medicine, 2015.
9. Sridhar, S., et al., *Cellular immune correlates of protection against symptomatic pandemic influenza.* Nat Med, 2013. **19**(10): p. 1305-12.
10. Lee, L.Y., et al., *Memory T cells established by seasonal human influenza A infection cross-react with avian influenza A (H5N1) in healthy individuals.* J Clin Invest, 2008. **118**(10): p. 3478-90.
11. Berthoud, T.K., et al., *Potent CD8+ T-cell immunogenicity in humans of a novel heterosubtypic influenza A vaccine, MVA-NP+M1*. Clin Infect Dis, 2011. **52**(1): p. 1-7.
12. Hochstein-Mintzel, V., et al., *[An attenuated strain of vaccinia virus (MVA). Successful intramuscular immunization against vaccinia and variola (author's transl)]*. Zentralbl Bakteriol Orig A, 1975. **230**(3): p. 283-97.
13. Goepfert, P.A., et al., *Phase 1 safety and immunogenicity testing of DNA and recombinant modified vaccinia Ankara vaccines expressing HIV-1 virus-like particles.* J Infect Dis, 2011. **203**(5): p. 610-9.
14. Howles, S., et al., *Vaccination with a modified vaccinia virus Ankara (MVA)-vectored HIV-1 immunogen induces modest vector-specific T cell responses in human subjects.* Vaccine, 2010. **28**(45): p. 7306-12.
15. Scriba, T.J., et al., *Modified vaccinia Ankara-expressing Ag85A, a novel tuberculosis vaccine, is safe in adolescents and children, and induces polyfunctional CD4+ T cells.* Eur J Immunol, 2010. **40**(1): p. 279-90.

16. Swadling, L., et al., *A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory.* Sci Transl Med, 2014. **6**(261): p. 261ra153.

17. Dangoor, A., et al., *Clinical and immunological responses in metastatic melanoma patients vaccinated with a high-dose poly-epitope vaccine.* Cancer Immunol Immunother, 2010. **59**(6): p. 863-73.

18. O'Hara, G.A., et al., *Clinical assessment of a recombinant simian adenovirus ChAd63: a potent new vaccine vector.* J Infect Dis, 2012. **205**(5): p. 772-81.

19. Antrobus, R.D., et al., *A T cell-inducing influenza vaccine for the elderly: safety and immunogenicity of MVA-NP+M1 in adults aged over 50 years.* PLoS One, 2012. **7**(10): p. e48322.

20. Antrobus, R.D., et al., *Coadministration of seasonal influenza vaccine and MVA-NP+M1 simultaneously achieves potent humoral and cell-mediated responses.* Mol Ther, 2014. **22**(1): p. 233-8.

21. Coughlan, L., et al., *Heterologous Two-Dose Vaccination with Simian Adenovirus and Poxvirus Vectors Elicits Long-Lasting Cellular Immunity to Influenza Virus A in Healthy Adults.* EBioMedicine, 2018. **29**: p. 146-154.

22. Lillie, P.J., et al., *Preliminary assessment of the efficacy of a T-cell-based influenza vaccine, MVA-NP+M1, in humans.* Clin Infect Dis, 2012. **55**(1): p. 19-25.

APPENDICES

Appendix 1 Detailed Description of Study Visits

Written informed consent must be obtained before any screening procedures are performed.

The following will be performed:

Screening Visit(s): Day 0 for the main cohort, may be up to -120 days for participants in the immunology cohort recruited through general advertising

1. Verify eligibility criteria
2. Review of medical history
3. Physical examination

Vaccination: Day 0

1. Verify eligibility criteria (if screening done prior to Day 0)
2. Urine pregnancy test pre-vaccination (women of childbearing potential)
3. Randomisation to study vaccine (MVA-NP+M1 or placebo)
4. Take pre-vaccination safety laboratory blood sample (immunology cohort only)
5. Take pre-vaccination immunology blood sample (immunology cohort only)
6. Vaccinate participant with study vaccine
7. Cover the vaccination site with a sterile dressing for 30 minutes, then remove and dispose as GMO waste.
8. Observe participant for at least 30 minutes; record any immediate adverse events
9. Provide eDiary, tape measure and thermometer
10. Instruct participant to:
    - Take their oral temperature (for the next 7 days)
    - Assess other solicited adverse events (for the next 7 days)
    - Assess unsolicited adverse events (for the next 28 days)
    - Assess influenza symptoms over the duration of the influenza season between 01 May and 15 October. Assessments should be made weekly unless symptoms are experienced then the severity of symptoms should be recorded daily plus any medications to treat symptoms
    - Arrange to attend the clinic in the event of any influenza symptom(s)

- Inform the study site of any hospitalisations, other SAEs or AESI over the duration of the influenza season

11. Discharge participant

Follow-up: Day 1 until the end of the influenza season into which the participant is recruited

In the event of any influenza symptom(s), participants should attend the clinic on two occasions, the first within 72 hours of the onset of symptoms for deep nasal/mid-turbinate swabs to be taken. Both swabs must be taken within 96 hours of symptom onset.

Days 1-28

1. Weekly reminders through the IBM system or through site appointment systems, to complete eDiary[2]
2. Day 1 (+2 days): Telephone participant to assess adverse events
3. Day 7 (+3 days):
   - Main cohort: Telephone participant to assess adverse events
   - Immunology cohort: In clinic visit
     - Perform physical examination (if considered necessary)
     - Assessment of solicited adverse events
     - Assessment of unsolicited adverse events
     - Take safety laboratory blood sample
4. Day 28 (±7 days):
   - Immunology cohort: In clinic visit
     - Assessment of unsolicited adverse events
     - Take safety laboratory blood sample
     - Take immunogenicity blood sample

Follow-up Day 29-End of Influenza Season

1. 4 weekly (±1 week) telephone call to:

[2] For participants vaccinated early in the influenza season and having Day 28 assessments before the start of the ILI reporting period on 15 May, these reminders will not be required after Day 28 and before 15 May

- Remind participant to assess influenza symptom weekly and record any symptoms daily in the eDiary (between 01 May and 15 October)
- Review whether there have been any hospitalisations, other SAEs or AESI and record these in the eCRF

2. Week 26 (±1 week):
   - Immunology cohort: In-clinic visit
     - Take immunogenicity blood sample
   - Notify participant of end of follow-up and perform final review.

Appendix 2 Adverse Events of Special Interest

Adverse events of special interest represent a subset of adverse events that include autoimmune diseases and other systemic disorders of interest which could potentially have an autoimmune aetiology. Adverse events of special interest are listed below. The Principal Investigator should use clinical and scientific judgment in deciding whether other adverse events (i.e., events not listed here) could have an autoimmune origin and should therefore be reported as adverse events of special interest.

- Bell's Palsy
- Guillain Barré Syndrome
- Myocarditis
- Stevens-Johnson Syndrome

Appendix 3 Toxicity Table for Clinical and Laboratory Abnormalities

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007

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Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

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to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature, no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

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Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

5

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B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	–
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

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Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Contains Nonbinding Recommendations

IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.