PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

*In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)*

## A. General information

1. Details of notification

| | | |
|---|---|---|
| (a) | Member State of notification | **Ireland** |
| (b) | Notification number | B/../../…. |
| (c) | Date of acknowledgement of notification | ../../…. |
| ***(d)*** | Title of the project | A Phase I study to assess the safety and immunogenicity of prime-boost immunisations with vaccine candidates AdCh3NSmut1 and MVA-NSmut in HIV-1 seropositive HCV-uninfected adults on antiretroviral therapy (ART) |
| (e) | Proposed period of release | From 01/07/2014 until 31/12/2015 |

2. Notifier

Name of institution or company: **The GUIDE Department, St James's Hospital, Dublin 8**

3. GMO characterisation

(a) Indicate whether the GMO is a:

| | |
|---|---|
| viroid | (.) |
| RNA virus | (.) |
| DNA virus | (X) |
| bacterium | (.) |
| fungus | (.) |
| animal | |
| - mammals | (.) |
| - insect | (.) |
| - fish | (.) |
| - other animal | (.) |

specify phylum, class …

(b) Identity of the GMO (genus and species)
**1) Modified Vaccinia virus Anakara NSmut (MVA-NSmut)**
Family: Poxviridae, Subfamily: Chordapoxviridae, Genus: Orthopoxviruses, Species: Vaccinia, Strain: MVA (Modified Vaccinia virus Ankara)

(c) Genetic stability – according to Annex IIIa, II, A(10)

The MVA viral genome has been proven to be stable through a large series of passages in chicken embryo fibroblasts.

Previous batches of MVA used in Oxford University trials have undergone testing to demonstrate genetic stability of the virus. Polymerase Chain Reaction (PCR) analysis is used to demonstrate the presence of the antigen and the absence of wild type virus. Also the antigen in the virus is sequenced. The titre of the virus (originally calculated by Impfstoffwerk Dessau-Tornau (IDT)) is confirmed by the Sponsor. IDT will continue to re-titre the vaccine annually to check its viability. The same process will be followed for MVA-NSmut.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

   Yes (.) No (X)

   If yes, insert the country code(s) …

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

   Yes (.) No (X)

   If yes:

   - Member State of notification …
   - Notification number B/../../…

**Please use the following country codes:**
*Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE*

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

   Yes () No (X)

   If yes:

   - Member State of notification …
   - Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.

   MVA vaccines have been used many times without significant environmental impact. MVA is derived from Vaccinia virus which was used worldwide as a live vaccine to eliminate smallpox. MVA is a Vaccinia strain that has been highly attenuated and is unable to replicate effectively in mammalian cells and has been administered to numerous animal species with no major local or systemic side effects. Spread of the GMO in the environment could only occur due to leakage out of the injection site shortly after vaccination. Other persons might be exposed to the GMO, therefore infection of other persons cannot be absolutely excluded. The quantity of virus particles, however, will be much less than the quantity used during the vaccination of the participating patients. An ERA has been performed for MVA-NSmut and is included with this application.

## B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

| | |
|---|---|
| viroid | (.) |
| RNA virus | (.) |
| DNA virus | (X) |
| bacterium | (.) |
| fungus | (.) |
| animal | |
| - mammals | (.) |
| - insect | (.) |
| - fish | (.) |
| - other animal | (.) |
| (specify phylum, class) | … |

other, specify …

2. Name

| | | |
|---|---|---|
| (i) | order and/or higher taxon (for animals) | … |
| (ii) | genus | Orthopoxvirus |
| (iii) | species | Vaccinia Virus |
| (iv) | subspecies | not applicable |
| (v) | strain | Ankara (Modified Virus Ankara) |
| (vi) | pathovar (biotype, ecotype, race, etc.) | … |
| (vii) | common name | MVA |

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:

Yes (.) No (X) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:

(i) Yes (.)

If yes, indicate the type of ecosystem in which it is found:

| | |
|---|---|
| Atlantic | .. |
| Mediteranean | .. |
| Boreal | .. |
| Alpine | .. |
| Continental | .. |
| Macaronesian | .. |

(ii) No (X)

(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?

Yes (.) No (X)

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (X)

4. Natural habitat of the organism

(a) If the organism is a microorganism

| | |
|---|---|
| water | (.) |
| soil, free-living | (.) |
| soil in association with plant-root systems | (.) |
| in association with plant leaf/stem systems | (.) |
| other, specify | No natural host. Laboratory virus normally. |

(b) If the organism is an animal: natural habitat or usual agroecosystem:
Not applicable

5. (a) Detection techniques

Indirect – Neutralizing antibodies
Direct – Polymerase chain reaction (PCR)
Culture – Chicken embryo fibroblasts

(b) Identification techniques

Indirect – Neutralizing antibodies
Direct – Polymerase chain reaction (PCR)

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (X) No (.)
If yes, specify
In terms of classification of hazard, the human vaccinia virus is classified as a group 2 biological agent according to the European Economic Community (EEC) classification for the protection of workers with biological agents {Directive 2000/54/EC}.
The MVA strain has not been classified. However MVA is a highly attenuated vaccinia virus strain obtained after several passages on primary chicken embryo fibroblasts (CEF). It replicates within the cytoplasmic compartment of the cell and cannot propagate in humans.
Laboratory and other health-care personnel who work with highly attenuated strains of vaccinia virus (e.g., MVA) do not require routine vaccinia vaccination. Furthermore, no reports of transmission to health-care personnel from vaccine recipients have been published.

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)

Because of its inability to reproduce in mammalian cells

If yes:

(a) to which of the following organisms:

| | |
|---|---|
| humans | (.) |
| animals | (.) |
| plants | (.) |
| other | (.) |

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

…

8. Information concerning reproduction

(a) Generation time in natural ecosystems:

Does not generate in natural ecosystems

(b) Generation time in the ecosystem where the release will take place:

Will not generate effectively

(c) Way of reproduction: Sexual .. Asexual X

(c) Factors affecting reproduction:

It is highly attenuated due to loss of much of its genome through serial passages through chicken embryo fibroblasts resulting in its inability to replicate in the majority of mammalian cells.

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

| | | |
|---|---|---|
| (i) | endospores | (.) |
| (ii) | cysts | (.) |
| (iii) | sclerotia | (.) |
| (iv) | asexual spores (fungi) | (.) |
| (v) | sexual spores (funghi) | (.) |
| (vi) | eggs | (.) |
| (vii) | pupae | (.) |
| (viii) | larvae | (.) |
| (ix) | other, specify | None |

(b) relevant factors affecting survivability:

Temperature, Ultraviolet radiation, Chemical disinfection

10. (a) Ways of dissemination

Given the lack of ability of MVA to replicate in mammalian cells the only significant way of dissemination of MVA is purposeful inoculation by the research team. Theoretically there could be spread of the MVA from the inoculation site if the vaccine leaked out from this site post injection. Safety measures in the protocol will reduce the risk of this happening.

(b) Factors affecting dissemination

Safety measures and research protocols.
The attenuation of the MVA virus.

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)
…, B/../../…
Not applicable

C. **Information relating to the genetic modification**

1. Type of the genetic modification

| | | |
|---|---|---|
| (i) | insertion of genetic material | (X) |
| (ii) | deletion of genetic material | (.) |
| (iii) | base substitution | (.) |
| (iv) | cell fusion | (.) |
| (v) | others, specify … | |

2. Intended outcome of the genetic modification
Expression of the NSmut gene. The purpose of NSmut expressed by MVA is to induce T cell immune responses to Hepatitis C antigens, which may confer protection against chronic infection.

3. (a) Has a vector been used in the process of modification?
Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
Yes ( X) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

| | |
|---|---|
| plasmid | (X) |
| bacteriophage | (.) |
| virus | (.) |
| cosmid | (.) |
| transposable element | (.) |

other, specify …

(b) Identity of the vector
…Shuttle vector pMVA-GFP-TD-NSmut

(c) Host range of the vector
…E Coli

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (X) No (.)

antibiotic resistance (X)
other, specify GFP gene

Indication of which antibiotic resistance gene is inserted
Ampicillin resistance gene
…

(e) Constituent fragments of the vector

- E. Coli $Amp^r$ (Ampicillin Resistance gene)
- *ori* site derived from pMB1 vector
- TKL, thymidine kinase gene, left region
- TKR, thymidine kinase gene, right region
- GFP marker gene
- P7.5 promoter
- Kozac sequence
- NS mut transgene

(f) Method for introducing the vector into the recipient organism

(i) transformation (.)
(ii) electroporation (.)
(iii) macroinjection (.)
(iv) microinjection (.)
(v) infection (.)
(vi) other, specify … The recombinant vaccine MVA-NSmut virus was generated by in vivo recombination between the MVA- RFP vector genome and homologous sequences (TKL, thymidine kinase gene, left region and TKR, thymidine kinase gene, right region) within the transfer vector pMVA-GFP-TD-NSmut.

In detail, MVA expressing a red fluorescent protein (RFP) under the control of a viral promoter integrated at the TK locus was previously generated. In order to generate MVA-NSmut, the shuttle plasmid pMVA-GFP-TD-NSmut and MVA-RFP genome were allowed to recombine within CEF cells, resulting in the integration of the complete plasmid into MVA-RFP in some cases. These recombinant genomes were selected for by virtue of their double GFP and RFP expression. However, integration of the whole plasmid results in duplication of one of the TK flank sequences and the recombinant genome is therefore unstable. On further passaging of the virus, a second

recombination event occurs resulting in either loss of the whole plasmid (resulting in the regeneration of the original MVA-RFP), or loss of both the GFP and RFP marker genes and *E. coli* sequences leaving only the promoter and NSmut antigen integrated into the viral genome at the TK locus. In order to differentiate between the two possible outcomes of the second recombination event, these changes in fluorescent protein expression can be used. Thus the starting virus expresses RFP, the unstable intermediate expresses RFP and GFP, and after the second recombination event if the virus loses the entire plasmid it reverts to expressing RFP alone, or if it loses part of the plasmid but retains the antigen, it expresses no marker.

MVA forms opaque foci of infection (commonly referred to as plaques, although cell lysis does not generally occur) on monolayers of fresh CEF cells. Thus plaques may be identified by eye, marked, and checked for expression of fluorescent proteins using a UV microscope.

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i) transformation (.)
(ii) microinjection (.)
(iii) microencapsulation (.)
(iv) macroinjection (.)
(v) other, specify …

6. Composition of the insert

(a) Composition of the insert

NSmut – The insert NSmut encodes for the 1985 amino acid-long HCV non structural region (NS), with genetically inactivated RNA-dependent RNA polymerase activity (NS5B). The NS fragment of the Hepatitis C genome is translated into a single polyprotein which is then proteolytically cleaved into five mature products (NS3, NS4A, NS4B, NS5A and NS5B) by the encoded NS3 protease. The mutation in the active site of the HCV polymerase was introduced as a safety measure, to eliminate any potential replication capability of the vaccine.

(b) Source of each constituent part of the insert

NS region from HCV 1b genotype, BK strain isolate based on sequence accession number M58335

(c) Intended function of each constituent part of the insert in the GMO

The purpose of NSmut expressed by MVA is to induce T cell immune responses against Hepatitis C virus, which may confer protection against Hepatitis C chronic infection.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify

NSmut antigen integrated into the viral genome at the TK locus

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify …

## D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

| | |
|---|---|
| viroid | (.) |
| RNA virus | (X) |
| DNA virus | (.) |
| bacterium | (.) |
| fungus | (.) |
| animal | |
| - mammals | (.) |
| - insect | (.) |
| - fish | (.) |
| - other animal | (.) |
| (specify phylum, class) | … |
| other, specify | … |

2. Complete name

| | | |
|---|---|---|
| (i) | order and/or higher taxon (for animals) | … |
| (ii) | family name for plants | … |
| (iii) | genus | Hepacivirus (Family Flaviviridae) |
| (iv) | species | … |
| (v) | subspecies | … |
| (vi) | strain | Genotype 1, subtype B, BK strain isolate |
| (vii) | cultivar/breeding line | … |
| (viii) | pathovar | … |
| (ix) | common name | Hepatitis C virus |

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (X) No (.) Not known (.)
If yes, specify the following:

(b) to which of the following organisms:

| | |
|---|---|
| humans | (X) |
| animals | (X) |
| plants | (.) |
| other | .. |

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism

Yes (X) No () Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):

In the life cycle of Hepatitis C the non-structural (NS) proteins are involved in polyprotein processing and viral replication. The insert NSmut encodes for the 1985 amino acid-long HCV non structural region (NS), with genetically inactivated RNA-dependent RNA polymerase activity (NS5B). The NS fragment of the Hepatitis C genome is translated into a single polyprotein which is then proteolytically cleaved into five mature products (NS3, NS4A, NS4B, NS5A and NS5B) by the encoded NS3 protease. The mutation in the active site of the HCV polymerase was introduced as a safety measure, to eliminate any potential replication capability of the vaccine.

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?

Yes (X) No (.)

If yes, specify Classification 3*, Directive 93/88/EEC

5. Do the donor and recipient organism exchange genetic material naturally?

Yes (.) No (X) Not known (.)

**E. Information relating to the genetically modified organism**

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) is the GMO different from the recipient as far as survivability is concerned?

Yes (.) No (X) Not known (.)

Specify …Unable to replicate, therefore non pathogenic

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?

Yes (.) No (X) Unknown (.)

Specify …Unable to replicate, therefore non pathogenic

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?

Yes (.) No (X) Not known (.)

Specify …Unable to replicate, therefore dissemination not possible

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (X) Not known (.)

Specify …Unable to replicate, therefore non-pathogenic

2. Genetic stability of the genetically modified organism
The clinical batches of AdCh3NSmut1 have undergone testing to demonstrate genetic stability of the virus. Endonuclease restriction analysis is used to demonstrate that the genetic structure of the vector is identical to the original pre-Adenovirus plasmid and replication competent adenovirus (RCA) detection testing is performed to exclude the presence of replication competent virus. Also, the NSmut region in the vectors is sequenced, to check if it had undergone any mutations or deletions.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?
Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other …

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)
…

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment
Polymerase Chain Reaction (PCR testing)

(b) Techniques used to identify the GMO
Poymerase Chain Reaction (PCR testing)

## F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The vaccine has been developed as a candidate Hepatitis C vaccine. The release is necessary to conduct a clinical trial with the ultimate goal being to determine its suitability as a vaccine for Hepatitis C. More specifically the release is necessary to perform a phase 1 study to evaluate the safety of this vaccine candidate. If the safety is acceptable and immunogenicity encouraging, a phase 2 trial would be performed.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?
Yes (X) No (.)
If yes, specify

Normally the recipient organism is stored in laboratories. It is not found in the community at large. Vaccinia (un-attenuated) was used in the community at large until 1978, for the eradication of smallpox.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):
Release will occur at the Clinical Research Facility at St James's Hospital, Dublin 8

(b) Size of the site ($m^2$): … Approximately 30,000 $m^2$
(i) actual release site ($m^2$): …70 $m^2$
(ii) wider release site ($m^2$): … Dublin and surrounding areas 1 x $10^{10}$m2

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
Nil. There are many such areas, but affecting them is not thought possible

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
Nil. There are many flora and fauna but affecting them is not thought possible

4. Method and amount of release

(a) Quantities of GMOs to be released:
15 vials to be used in vaccination

(b) Duration of the operation:
Each vaccination takes only a few minutes. The vaccinations will be performed over a concentrated time period.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
Inoculation of the vaccine will only be performed at the Clinical Research Facility in St James's Hospital. The vaccination site will be covered with a bandage. Materials used in the vaccination such as needles, syringes and swabs will be incinerated.

5. Short description of average environmental conditions (weather, temperature, etc.)
The vaccination will be performed indoors at normal room temperature.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.
Detailed data regarding these issues is listed in the Environmental Risk Assessment. MVA vaccines have been used extensively in the past with no environmental concerns and are generally well tolerated with few safety concerns to human health.

## G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)

| | | |
|---|---|---|
| (i) | order and/or higher taxon (for animals) | … |
| (ii) | family name for plants | … |
| (iii) | genus | Homo |
| (iv) | species | sapiens |
| (v) | subspecies | … |
| (vi) | strain | … |
| (vii) | cultivar/breeding line | … |
| (viii) | pathovar | … |
| (ix) | common name | Human |

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

   The development of humoral and cellular immune response against the Hepatitis C immunogen.

3. Any other potentially significant interactions with other organisms in the environment

   No

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?

   Yes (.) No (X) Not known (.)

   Give details

   …

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

   MVA cannot maintain itself in an ecosystem due to the lack of replicative capacity in mammalian cells into which the inoculation occurs.

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

   None

| | | |
|---|---|---|
| (i) | order and/or higher taxon (for animals) | … |
| (ii) | family name for plants | … |
| (iii) | genus | … |
| (iv) | species | … |
| (v) | subspecies | … |
| (vi) | strain | … |
| (vii) | cultivar/breeding line | … |
| (viii) | pathovar | … |
| (ix) | common name | … |

7. Likelihood of genetic exchange in vivo

(a) from the GMO to other organisms in the release ecosystem:

Highly unlikely

(b) from other organisms to the GMO:

Highly unlikely

(c) likely consequences of gene transfer:

Nil

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):

Not available

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

Nil

## H. Information relating to monitoring

1. Methods for monitoring the GMOs

The GMO will not be specifically monitored but the patients who received the GMO will be followed up for clinical review and will have blood draws to assess safety.

2. Methods for monitoring ecosystem effects

Clinical evaluation of patients on a regular basis

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

Polymerase chain reaction (PCR) testing possible

4. Size of the monitoring area ($m^2$)
1 x 10^10 $m^2$

5. Duration of the monitoring

8 months

6. Frequency of the monitoring

Ongoing – patients will have 12 visits over 8 month period

## I. Information on post-release and waste treatment

1. Post-release treatment of the site

Injection site will be covered with a plaster. All materials will be disposed of and waste will be autoclaved. All surfaces that have been in contact with the GMO will be chemically disinfected with Virkon or equivalent.

2. Post-release treatment of the GMOs

Vials to be disposed of must be placed within a sharps box which will be autoclaved the same day.

All materials that have been in contact with the vaccine or vaccination site (e.g. dressings) must be punctiliously disposed of into an autoclave bag or suitable container for autoclaving. All sharps must be disposed of immediately after use into a sharps bin for autoclaving. Waste bags and sharps boxes must be placed in a robust container suitable for transport to the autoclave. The trial physician will be responsible for ensuring that this waste is autoclaved in a designated autoclave. A record of autoclaved waste will be kept local to the autoclave, by filing autoclave printouts in a designated log book with the date, time, name and signature of the person responsible for autoclaving the waste. The waste will then be disposed of with an approved waste contractor.

3. (a) Type and amount of waste generated

Vaccine vials, used needles, gloves and syringes.

3. (b) Treatment of waste

All materials that have been in contact with the vaccine or vaccination site (e.g. dressings) must be punctiliously disposed of into an autoclave bag or suitable container for autoclaving. All sharps must be disposed of immediately after use into a sharps bin for autoclaving. Waste bags and sharps boxes must be placed in a robust container suitable for transport to the autoclave. The trial physician will be responsible for ensuring that this waste is autoclaved in a designated autoclave. A record of autoclaved waste will be kept local to the autoclave, by filing autoclave printouts in a designated log book with the date, time, name and signature of the person responsible for autoclaving the waste

## J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

Standard national procedures for outbreak management. However this is an avirulent virus. If there is spillage of the GMO the affected area would be chemically disinfected. Standard Operating Procedures (SOPs) will be in place in the event of spillage or accidental exposure.

2. Methods for removal of the GMO(s) of the areas potentially affected

   Disinfection with alcohol or chlorine based solutions.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

   The study site will be an animal free area. Any affected materials will be autoclaved as per SOPs and disposed of with approved waste contractors.

4. Plans for protecting human health and the environment in the event of an undesirable effect

   Standard medical management for any unwell patients based on symptoms, signs and the results of medical investigations. Vaccinia immunoglobulin exists and could potentially be of use if there was a problem with a Vaccinia variant. Cidofovir has been used against poxviruses, although its treatment of vaccinia or vaccinia variants is unproven.