Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Viral Vector Vaccines

Introduction:

The Brighton Collaboration formed the Viral Vector Vaccines Safety Working Group (V3SWG) in 2008 to enhance safety assessments for viral vector vaccines, enabling greater public trust. The Working Group developed a standardized template to evaluate benefit-risk considerations, facilitating clear communication among stakeholders. This template has evolved over time, informed by its use in assessing vaccines like those for Ebola, and is endorsed by the WHO. Additionally, the template approach has been modified to include other types vaccines such as live-attenuated, inactivated, and recombinant protein vaccines. The templates focus on the characteristics of wild-type viruses, viral vectors, and recombinant vaccines, with sections addressing toxicology, adverse effects, and overall safety. The V3WSG has recently been renamed to the Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group to reflect its expanded role in development of templates for additional vaccine platforms, namely nucleic acid based, live attenuated, inactivated, and protein based vaccines. The latest version of the template can be accessed on https://brightoncollaboration.us/bravato/, ensures transparency, comparability, and stakeholder collaboration for vaccine safety.

Note: This template is for viewing purposes only. Vaccine developers interested in completing the relevant templates for their vaccine platform or candidate and collaborating with BRAVATO should contact the coordinator at bc-coordinator@taskforce.org. The coordinator will provide an introduction and link to the digital tool for template completion.

Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group
Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Viral Vector Vaccines

1. Authorship and Affiliation	**Information**
1.1. Author(s) and affiliation	
1.2. Date completed/updated	

Part I: Viral Vector (Sections 2-7)

2. Basic vector information	**Information**	**Comments/Concerns**
2.1 Vector name		
2.2 Vector origin		
• Family		
• Genus		
• Species		
• Subtype		
2.3 Vector replication in humans		
3. Characteristics of the wild type virus from which the vector is derived	**Information**	**Comments/Concerns**
3.1 Name of wild type virus		
• Common name		
• Family		
• Genus		
• Species		
• Subtype		
3.2 What is the natural host for the wild type virus?		
3.3 How is the wild type virus normally transmitted?		
3.4 Does the wild type virus establish a latent or persistent infection?		
3.5 Does the wild type virus replicate in the nucleus?		

3.6 What is the risk of integration into the human genome?		
3.7 List any disease manifestations caused by the wild type virus, the strength of evidence, severity, and duration of disease for the following categories:		
• Healthy natural host		
• Laboratory hosts (specify species)		
• Healthy human host		
• Immunocompromised humans		
• Breast milk, human neonates, infants, children		
• During pregnancy and in the unborn in humans		
• Any other special populations?		
3.8 What cell types are infected and what receptors are used in the natural host and in humans?		
3.9 What is known about the mechanisms of immunity to the wild type virus?		
3.10 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the wild type virus:		
• In vitro?		
• In animal models?		
• In human hosts?		
3.11 Is disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) a possible vaccine-induced contributor to the pathogenesis of wild type disease		
3.12 What is the background prevalence of natural immunity to the virus?		
3.13 Is there any vaccine available for the wild-type virus? If yes,		
• What populations are immunized?		
• What is the background prevalence of artificial immunity?		
3.14 Is there treatment available for the disease caused by the wild type virus		
4. Characteristics of the vector from which vaccine(s) may be derived	**Information**	**Comments/ Concerns**
4.1 Describe the source of the vector (e.g. isolation, synthesis)		

4.2 What is the basis of attenuation/inactivation of the wild type virus to create the vector?		
4.3 What is known about the replication, transmission and pathogenicity of the vector in humans in the following categories:		
• Healthy people		
• Immunocompromised people		
• Breast milk, neonates, infants, children		
• During pregnancy and in the fetus		
• Gene therapy experiments		
• Any other special populations		
4.4 Is the vector replication-competent in non-human species?		
4.5 What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?		
4.6 Is the vector genetically stable:		
• In vitro		
• In vivo		
4.7 What is the potential for shedding and transmission, including arthropod borne transmission, to humans or other species?		
4.8 Does the vector establish a latent or persistent infection?		
4.9 Does the vector replicate in the nucleus?		
4.10 What is the risk of integration into the human genome?		
4.11 Is there any previous human experience with this or a similar vector (safety and immunogenicity records)?		
4.12 What cell types are infected and what receptors are used in humans?		
4.13 What is known about the mechanisms of immunity to the vector?		
4.14 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vector?		

• In vitro?		
• In animal models?		
• In human hosts?		
4.15 Is there antiviral treatment available for disease manifestations caused by the vector?		
4.16 Can the vector accommodate multigenic inserts or will several vectors be required for multigenic vaccines?		
5. Toxicology and non-clinical of the vector	**Information**	**Comments/ Concerns**
5.1 What is known about the replication, transmission and pathogenicity of the vector in and between animals?		
5.2 For replicating vectors, has a comparative virulence and viral kinetic study been conducted in permissive and susceptible species?		
• If not, what species would be used for such a study?		
• Is it feasible to conduct such a study?		
5.3 Does an animal model relevant to assess attenuation exist?		
5.4 Does an animal model for safety including immuno-compromised animals exist?		
5.5 Does an animal model for reproductive toxicity exist?		
5.6 Does an animal model for immunogenicity and efficacy exists?		
5.7 Does an animal model for antibody enhanced disease (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) or immune complex disease exist?		
5.8 What is known about biodistribution in animal models, including neurovirulence and/or neuroinvasion?		
5.9 What is known about biodistribution in humans, including neurovirulence and/or neuroinvasion?		
5.10 What is the evidence that vector derived vaccines will generate a beneficial immune response in:		
• Small animal models?		
• Nonhuman primates (NHP)?		

• Human?		
5.11 Have challenge or efficacy studies been conducted in subjects with:		
• Immunocompromised conditions including HIV?		
• Other diseases?		
5.12 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes?		
• Is there evidence for interaction/interference? Explain.		
6. Adverse Event (AE) Assessment of the Vector (*see Instructions):	**Information**	**Comments/ Concerns**
6.1 Approximately how many humans have received any vaccine using this viral vector to date?		
• If variants of the vector, please list separately.		
6.2 Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance	Yes/No	If yes, describe method:
• Diary	Yes/No	If yes, number of days:
• Other active surveillance	Yes/No	If yes, describe method and list the AE's solicited:
6.3 What criteria were used for grading the AE's?		
• If no criteria were used for grading, or if other metrics were employed, please describe:		
6.4 List and provide frequency of any related or possibly related serious* AE's as well as any severe, expected or unexpected AE observed: (*see Instructions):		
6.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control group:		
• Describe the control group:		
6.6 List and provide frequency of Adverse Events of Special Interest		
6.7 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes/No	
• Did it identify any safety issue of concern?	Yes/No	

• If so describe in the comments		
7. Overall Risk Assessment of the Vector	**Information**	**Comments/ Concerns**
7.1 Please summarize key safety issues of concern identified to date, if any:		
• How should they be addressed going forward:		
7.2 What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as: none, minimal, low, moderate, high, or unknown**
• Healthy humans?		
• Immunocompromised humans?		
• Breast milk, human neonates, infants, children?		
• Pregnancy and in the fetus in humans?		
• Elderly		
• Any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?		
7.3 What is the potential for shedding and transmission in risk groups?		
Part II: Vaccine (Sections 8-12)		
8. Target Pathogen and Population for the vaccine	**Information**	**Comments/Concerns**
8.1 What is the target pathogen for the vaccine?		
8.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:		
• Healthy people		
• Immunocompromised people		
• Neonates, infants, children		

• During pregnancy and in the fetus		
• Elderly		
• Any other special populations		
8.3 Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen:		
• Incubation period		
• Communicable period		
• Route/s of transmission		
• Case fatality rate		
• Reproductive Number (R0)		
• Stability of the Virus		
• Other Information		
8.4 What sections of the population are most affected by the target pathogen (e.g. pediatric, pregnant, lactating women (breast feeding), adult, elderly)		
8.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		
8.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk		
9. Characteristics of the Vaccine	**Information**	**Comments/ Concerns**
9.1 Vaccine name		
9.2. What is the identity and source of the transgene?		
9.3 Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?		
9.4 Where in the vector genome is the transgene inserted?		
9.5 Does the insertion of the transgene involve deletion or other rearrangement of any vector genome sequences?		
9.6 How is the transgene expression controlled (transcriptional promoters, etc.)?		
9.7 Does insertion or expression of the transgene affect the pathogenicity or phenotype of the vector?		

9.8 Is the vaccine replication-competent in humans or other species?		
9.9 What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?		
9.10 Is the vaccine genetically stable in vitro and/or in vivo?		
9.11 What is the potential for shedding and transmission to humans or other species?		
9.12 Does the vaccine establish a latent or persistent infection?		
9.13 Does the vaccine replicate in the nucleus?		
9.14 What is the risk of integration into the human genome?		
9.15 List any disease manifestations caused by the vaccine in humans, the strength of evidence, severity, and duration of disease for the following categories:		
• Healthy people		
• Immunocompromised people		
• Breast milk, neonates, infants, children		
• During pregnancy and in the fetus		
• Any other special populations		
9.16 What cell types are infected and what receptors are used in humans?		
9.17 What is known about the mechanisms of immunity to the vaccine?		
9.18 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vaccine?		
• In vitro?		
• In animal models?		
• In human hosts?		
6.19 What is known about the effect of pre-existing immunity, including both natural immunity and repeat administration of the vector or the vaccine, on 'take', safety or efficacy in any animal model or human studies using this vector?		
• If not, what species would be used for such a study?		
• Is it feasible to conduct such a study?		

9.20 Is the vaccine transmissible in humans or other species (including arthropods) and/or stable in the environment?		
9.21 Are there antiviral or other treatments available for disease manifestations caused by the vaccine?		
9.22 Final vaccine formulation components that may impact delivery into cells, stability, and safety		
• Antigen(s)		
• Adjuvants		
• Stabilizers		
• Preservatives		
• Surfactants		
• Diluents		
• Buffers		
• Lipids (in lipid nanoparticles)		
• Emulsifying agents		
• Other Excipients		
9.23 Route and method of delivery		
9.24 Target populations for the vaccine (e.g. pediatric, maternal, adult, elderly etc.)		
10. Toxicology and Potency (Pharmacology) of the Vaccine	**Information**	**Comments/ Concerns**
10.1 What is known about the replication, transmission and pathogenicity of the vaccine in and between animals?		
10.2 For replicating vectors, has a comparative virulence and viral kinetic study been conducted in permissive and susceptible species? (yes/no) If not, what species would be used for such a study? Is it feasible to conduct such a study?		
10.3 Does an animal model relevant to assess attenuation exist?		
10.4 Does an animal model for safety including immuno-compromised animals exist?		
10.5 Does an animal model for reproductive toxicity exist?		
10.6 Does an animal model for immunogenicity and efficacy exists?		

10.7 Does an animal model for antibody enhanced disease (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) or immune complex disease exist?		
10.8 What is known about biodistribution in animal models or in humans, including neurovirulence and/or neuroinvasion?		
10.9 What is the evidence that vector derived vaccines will generate a beneficial immune response in:		
• Small animal models?		
• Nonhuman primates (NHP)?		
• Human?		
10.10 Have challenge or efficacy studies been conducted in subjects with:		
• Immunocompromised conditions including HIV?		
• Other diseases?		
10.11 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes?		
10.12 Other sequence features that may impact safety (e.g. sequences in DNA that might facilitate insertion or recombination)		
• Is there evidence for interaction/interference?		
11. Adverse Event (AE) Assessment of the Vaccine (*see Instructions):	**Information**	**Comments/ Concerns**
11.1 Approximately how many humans have received this viral vector vaccine to date?		
• If variants of the vaccine platform, please list separately.		
11.2 Method(s) used for safety monitoring:		
• Spontaneous reports/passive surveillance	Yes/No	If yes, describe method:
• Diary	Yes/No	If yes, number of days
• Other active surveillance	Yes/No	If yes, describe method and list the AE's solicited:
11.3 What criteria were used for grading the AE's?		

• If no criteria were used for grading, or if other metrics were employed, please describe:		
11.4 List and provide frequency of any related or possibly related serious* AE's as well as any severe, expected or unexpected AE observed: (*see Instructions):		
11.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control group:		
• Describe the control group		
11.6 List and provide frequency of Adverse Events of Special Interest		
11.7 Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?	Yes/No	
• Did it identify any safety issue of concern?	Yes/No	
• If so describe:		
12. Overall Risk Assessment of the Vaccine	**Information**	**Comments/ Concerns**
12.1 Please summarize key safety issues of concern identified to date, and how should they be addressed going forward:		
12.2. What is the potential for causing serious unwanted effects and toxicities in:	**Describe the toxicities**	**Please rate risk as: none, minimal, low, moderate, high, or unknown**
• Healthy humans?		
• Immunocompromised humans?		
• Breast milk, human neonates, infants, children?		
• Pregnancy and in the fetus in humans?		
• Elderly		
• Any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?		
12.3 What is the potential for shedding and transmission in risk groups?		

13. Any other information concerning either the viral vector or the vaccine	Information	Comments/ Concerns

References	Information
1.	
2.	
3.	
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