Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Live-Attenuated Viral 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 Live-Attenuated Viral Vaccines		
1. Authorship	**Information**	
1.1 Author(s) and affiliation(s)		
1.2 Date completed/updated		
2. Basic Vaccine information	**Information**	**Comments/Concerns**
2.1 Vaccine name		
2.2 Virus name, genus, family strains/serotypes, origin (e.g., geography, patient, asymptomatic infection), and any other specific characteristics, such as genetic modifications		
2.3 Method of attenuation		
2.4 Substrate for vaccine virus growth and method of production (e.g., nature of substrate, cell line, eggs, bioreactor, microcarriers, etc.)		
2.5 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		
2.6 Route and method of delivery		
3. Target Pathogen and Population for the Vaccine	**Information**	**Comments/Concerns**
3.1 What is the target pathogen?		

3.2 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		
3.3 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		
3.4 Does the target pathogen establish a latent or persistent infection?		
3.5 Does the target pathogen virus replicate in the nucleus?		
3.6 What is the risk of integration into the human genome?		
3.7 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast feeding), adult, elderly)		

3.8 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		
3.9 Please describe any other key information about the target pathogen or population that may inform benefit-risk		
4. Characteristics of Attenuated Vaccine Virus	**Information**	**Comments/ Concerns**
4.1 Describe the source of the virus or virus strains (e.g. isolation, synthesis)		
4.2 How does attenuated virus differ from the pathogen?		
• Method of attenuation and validation		
4.3 Does the vaccine establish a latent or persistent infection?		
4.4 Does the vaccine virus replicate in the nucleus?		
4.5 What is the risk of integration into the human genome?		
4.6 What is known about the replication of vaccine virus in humans in the following categories:		
• Healthy people		
• Immunocompromised people		
• Neonates, infants, children		
• During pregnancy and in the fetus		
• Any other special populations		
4.7 What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?		
4.8 What is the potential for shedding and transmission to humans or other species?		
4.9 Is the vaccine virus genetically stable in vitro and/or in vivo?		

5. Delivery and Administration	Information	Comments/ Concerns
5.1 How might the vaccine formulation (antigen and diluent and/or any other co-administered component formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?		
5.2 If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety.		
5.3 Describe how components of the vaccine formulation that facilitate stability and delivery into cells (Section 2.5) may impact the safety profile of the vaccine		
5.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)		
* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed relevant for safety purpose.		
6. Toxicology and Non-Clinical of the Vaccine	**Information**	**Comments/ Concerns**
6.1 Will the vaccine virus express or replicate in non-human species?		
6.2 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products		
6.3 Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products		
6.4 What is the evidence of disease enhancement or absence thereof in vitro or in animal models?[13]		
6.5 Would the vaccine in its final formulation have any impact on innate immunity?		

• If so, what are the implications for benefit-risk in animal models and small non-human primates		
6.6 What is the evidence that the vaccine has generated a beneficial immune response in:		
• Animal models?		
• Nonhuman primates (NHP)?		
7. Human Efficacy and Other Important Information	**Information**	**Comments/ Concerns**
7.1 What is known about the replication of vaccine virus in humans in the following categories:		
• Healthy people		
• Immunocompromised people		
• Neonates, infants, children		
• During pregnancy and in the fetus		
• Dene therapy experiments		
• Any other special populations		
7.2 What is the evidence that the vaccine generates a protective immune response in humans (e.g. natural history, passive immunization, animal challenge studies)?		
7.3 If there are multiple strains of the pathogen, can the vaccine protect against multiple strains or serotypes?		
• Will separate strains be required for multigenic vaccines?		
• Was there evidence generated?		

• What is known about the immune response to the vaccine in animals and/or humans (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?		
7.4 Is there any previous human experience with this vaccine (safety and immunogenicity records)?		
• Any evidence for or against disease enhancement ?		
7.5 Describe other key information that may impact benefit-risk		
8. Adverse Event (AE) Assessment of the Vaccine (*see Instructions):	**Information**	**Comments/ Concerns**
8.1 Approximately how many humans have received this viral vector vaccine to date?		
• If variants of the vaccine platform, please list separately.		
8.2 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 (e.g., LTFU) and list the AEs solicited:
8.3 What criteria were used for grading the AEs?		
• If no criteria were used for grading, or if other metrics were employed, please describe:		
8.4 List and provide frequency of any related or possibly related serious* AEs, as well as any severe, expected or unexpected, AEs observed: (*see Instructions):		

8.5 List and provide frequency of any serious, unexpected statistically significantly increased AE or lab abnormality in vaccinee vs. control groups:		
• Describe the control group:		
8.6 List and provide frequency of Adverse Events of Special Interest		
8.7 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:		
9. Overall Risk Assessment	**Information**	**Comments/ Concerns**
9.1 Please summarize key safety issues of concern identified to date, and how should they be addressed going forward		
9.2 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)?		

References	Information
1.	
2.	
3.	
…	