Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) 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 Nucleic Acid (RNA and DNA) 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 Nucleic Acid Type: DNA, RNA, self-amplifying RNA		
2.3 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		
2.4 Route and method of delivery		

3. Target Pathogen and Population	Information	Comments/Concerns
3.1 What is the target pathogen for the vaccine?		
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 What sections of the population are most affected by the target pathogen?		
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		

3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk		
4. Characteristics of Vaccine Transgene and Expression	**Information**	**Comments/ Concerns**
4.1 Nature of the nucleic acid platform		
4.2 Gene(s) incorporated into the vaccine (antigen, T-cell epitopes, antibiotic resistance factors, cytokines, other)		
4.3 Factors enhancing/controlling gene expression		
4.4 Non-expressed features impacting vaccine efficacy (CpG sequences, other)		
4.5 Other sequence features that may impact safety (e.g. sequences in DNA that might facilitate insertion or recombination)		
4.6 Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?		
4.7 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.)?		
5. Delivery and Administration	**Information**	**Comments/ Concerns**
5.1 Describe how components of the vaccine formulation that facilitate stability* and delivery into cells (Section 2.5) impact the safety profile of the vaccine?		

* Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed important for safety purposes.		
5.2 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)		
5.3 How might the vaccine formulation (antigen and adjuvant already formulated in the same vial or combined prior to administration) impact the safety profile of the vaccine?		
5.4 If the vaccine is part of a heterologous prime-boost regimen, describe the regimen that this vaccine is a part of and the possible impact on safety		
6. Toxicology and Non-Clinical of the Vaccine	**Information**	**Comments/ Concerns**
6.1 What is known about biodistribution of the platform nucleic acid in its final formulation and mode of administration in animal models?		
6.2 How long does the RNA or DNA persist in vivo (may specify in tissue/serum, proximal/distal to site of administration)?		
6.3 What is the risk of integration into human genome?		
6.4 What is the possible risk of autoimmunity or a harmful immune response?		
6.5 Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products		

6.6 Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products		
6.7 What is the evidence of disease enhancement or absence thereof in vitro or in animal models?		
6.8 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		
7. Human Efficacy and Other Important Information	**Information**	**Comments/ Concerns**
7.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g. natural history, passive immunization, animal challenge studies)?		
7.2 Describe other key information that may impact benefit-risk		
7.3 If there are multiple strains of the pathogen, can the vaccine protect against multiple strains or serotypes?		
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 and well as any severe expected or unexpected AEs observed: (*see Instructions):		
8.5 List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccine 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		
8.8 What is the evidence of disease enhancement (if any) in humans?		
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 people, individuals with associated chronic comorbidity)?		

References	**Information**
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2.	
3.	
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