**Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG)**

**Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines**

**Introduction:**

The Brighton Collaboration ([www.brightoncollaboration.us](http://www.brightoncollaboration.org)) was launched in 2000 to improve the science of vaccine safety (1). The Brighton Collaboration formed the Viral Vector Vaccines Safety Working Group (V3SWG) in October 2008 to improve the to improve the ability of key stakeholders to anticipate potential safety issues and meaningfully assess or interpret safety data, thereby facilitating greater public acceptance when viral vector vaccines are licensed (2). The V3SWG has since published completed standardized templates describing the key considerations for a benefit-risk assessment of several new viral vectors or their vaccines. The information on the template will hopefully facilitate communication of otherwise complex and highly technical data among key stakeholders (some of whom may lack subspecialized training in biotechnology) and increase the transparency, comparability, and comprehension of essential information. The template has been used for the standardized risk-assessment of several new viral vector vaccines (3-5) including some targeting Ebola. The WHO Global Advisory Committee on Vaccine Safety (GACVS) endorsed the use of the template for other new candidate Ebola vaccines “as it is a structured approach to vaccine safety” (6).

The Brighton Collaboration V3SWG has therefore developed a specific template for nucleic acid vaccines that vaccine developers and other key stakeholders will use to evaluate and communicate the benefit-risk of vaccines using these nucleic acid platforms. Nucleic acid vaccines are being developed with speed (7). DNA vaccines have been under development since the early 1990’s. They comprise a bacterial plasmid DNA expressing an immunogen of interest under the control of a eukaryotic promoter. This results in the *de novo* synthesis of the immunogen in the vaccine recipient and the stimulation of both B- and T-cell immune responses. DNA vaccination was a highly promising approach to vaccination with relatively straightforward construction of the vaccine and ease of large-scale manufacture. Some are licensed for veterinary use and some have undergone clinical trials in humans, but to date none are licensed in humans. Due to the very low immune response in humans with simple naked plasmid DNA, research has focused on methods to enhance the response, including optimizing codon usage, optimizing the formulation for improved uptake of the DNA, optimizing the route or method of administration, or the co-administration of DNA encoding immune stimulatory molecules. The use of DNA to prime an individual followed by a heterologous vaccination with the same antigen in an alternate format, e.g., a viral vector, is producing promising results. Due to the uniqueness of DNA as a vaccine and the approaches being used to improve their immunogenic effect, vaccination with DNA presents a unique set of safety issues (8). The 2019 proposed revision of the WHO guidelines on DNA vaccines lists the approaches being employed to enhance the immunogenicity of a DNA vaccine (9).

RNA vaccines are a more novel approach. An RNA vaccine is typically a messenger RNA molecule that encodes the immunogen of interest; some RNA vaccines employ self-amplifying RNA that directs its own replication within the host cell thus expressing more of the immunogen. Self-amplifying RNA vaccines typically link the antigen-encoding RNA to an RNA replication cassette derived from an RNA virus. None have been licensed for use in either humans or animals, but several have shown promise in animal models and one is currently undergoing Phase I clinical trials (10). In contrast to a DNA vaccine, an RNA vaccine is translated directly within the cytoplasm of the cell without the need to be transported into the nucleus for transcription; thus there is no concern regarding insertional mutagenesis. Similar to a DNA vaccine though, the *de novo* intracellular synthesis of the immunogen of an RNA vaccine stimulates both B- and T-cell responses. Due to the greater lability of RNA compared with DNA, more care has to be given to their formulation. More data are required on RNA vaccines safety profile (11, 12).

RNA and DNA vaccines have, in theory, a distinct advantage of rapid development and deployment, especially in the context of an emerging pandemic, because the only requirement for construction of any particular vaccine is the nucleic acid sequence of the immunodominant antigen(s) of the target pathogen.

The V3SWG intends that this template focuses on key questions related to the essential safety and benefit-risk issues relevant for the intrinsic properties of the vaccine components. We recognize that there are many other aspects of manufacturing, quality, and implementation that can play an important role in the safety of a vaccine, but we have chosen to keep some of those issues out of scope for the template in order to summarize information that is the most useful to the most stakeholders.

The template can be accessed on <https://brightoncollaboration.us/v3swg/>. Vaccine developers are encouraged to complete the relevant templates for their vaccine candidate platform or vaccine candidate and collaborate with the V3SWG. The draft templates would be shared for review by the V3SWG and submitted for publication. Similarly, updates to the templates by the vaccine developers should be submitted to the Brighton Collaboration website for V3SWG review.

**Specific Instructions for Completing the V3SWG Template:**

● Please read these instructions before you complete the nine sections. Send questions

to: brightoncollaborationv3swg@gmail.com

● The first section entitled “Authorship” should include your name and the latest date completing the form. If you are working with someone else to complete this form, their name should be provided as well. If you are updating the form, please provide the updated date. These co-authors will be included in the final published template in Vaccine once reviewed and approved by the V3SWG and in subsequent Wiki updates on the V3SWG website.

● Sections 2-7 collect information regarding the basic vaccine information (Section 2), the target pathogen and population (Sections 3), characteristics of transgene and expression, (Section 4), delivery and administration (Section 5), toxicology and nonclinical (Section 6) and human efficacy and other important information (Section 7). Depending on the vaccine, some sections may be redundant or not applicable, for example if the section is for a DNA vaccine but the template is being completed for a RNA vaccine. In cases of redundancies, an answer may simply refer to the answer in a previous section.

● Answer questions by responding in the column entitled ‘Information.’ If you have any comments or concerns regarding the question or your answer to the question, note these in the ‘Comments/Concerns’ column. Please provide references wherever possible in both the “Information” and “Comments/Concerns” columns. Referencing should use the Vaccine journal format, with references numbered sequentially in the text and full citations listed in sequence at the end of the form. More than one reference can be used per question.

● Sections 8 and 9 have column titles that differ from preceding sections intended to provide a summary assessment of adverse effects and toxicity of the vaccine. Please summarize adverse effects and toxicities as requested and rate the riskin the following fashion: none, minimal, low, moderate, high, or unknown. If there is insufficient data for use of the platform in humans to accurately make these assessments, please state so in response to the questions.

● When completing information on adverse effects in Section 8, please provide as many details as possible based on the Brighton Collaboration Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies (13).

● In the references, unpublished and non-peer reviewed published data are acceptable, though we do wish that you include the source and contact information. If a literature search was conducted to complete any of the Sections (strongly encouraged), please add the following information in the Reference(s) column: 1) time period covered (e.g., month/year to month/year); 2) Medical Subject Headings (MeSH) terms used; 3) the number of references found; and 4) the actual references with relevant information used. For prior published templates, please [search PubMed for “Brighton Collaboration V3SWG”](https://www.ncbi.nlm.nih.gov/pubmed/?term=Brighton+Collaboration+V3SWG).

**References:**

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|  **Brighton Collaboration Standardized Template for Collection of Key Information for 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** Adjuvant (if applicable) |  |  |
| **2.4** Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g. complexing with polymers, encapsulation within microparticles, liposomes) |  |  |
| **2.5** Route and method of delivery (e.g. intramuscular injection, gene gun, electroporation) |  |  |
| **3. Target Pathogen and Population** | **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: |  |  |
| * In healthy people
 |  |  |
| * In immunocompromised people
 |  |  |
| * In neonates, infants, children
 |  |  |
| * During pregnancy and in the fetus
 |  |  |
| * In elderly
 |  |  |
| * In any other special populations
 |  |  |
| **3.3** Briefly, what are the key epidemiologic characteristics of the disease caused by the target pathogen (e.g. incubation period, communicable period*,* route/s of transmission,case fatality rate, transmissibility characteristics such as basic reproductive ratio *(*R0*),* and spontaneous mutation)? |  |  |
| **3.4** What sections of the population are most affected by the target pathogen (e.g. pediatric, pregnant, lactating women (breast-feeding), adult, elderly)? |  |  |
| **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 (**DNA** - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; **RNA-** messenger, self-replicating, other) |  |  |
| **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 2.4) 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. For example, among the risks that WHO, FDA, and EMA list for the use of DNA vaccines is the hazard of integration into recipient’s chromosomal DNA with the resulting risk of insertional mutagenesis or spreading of antibiotics resistance genes. The probability of chromosomal integration increases if the introduced pDNA has been linearized, and this is the reason that regulatory authorities require the plasmid preparation intended for vaccination or gene therapy to contain a high percentage of supercoiled material (usually >80%). The percentage of supercoiled material is also used as a criterion of DNA vaccine stability at different storage temperatures. |
| **5.2** Describe how the mode of vaccine delivery may impact safety \*(e.g., electroporation (please specify name of device), intradermal needle injection)  |  |  |
| \* Also consider the safety impact of multi-dose delivery methods, the use of multi dose vaccine vials, and any special considerations for disposal. |
| **5.3** How might any co-administered components (e.g. adjuvants, cytokines, immunomodulatory molecules) impact the safety profile? |  |  |
| **5.4** If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety |  |  |
| **6. Toxicology and Nonclinical**  | **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 of sequences from the platform nucleic acid into the host 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 (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD).) or absence thereof *in vitro* or in animal models?14 |  |  |
| **6.8** Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit- risk? |  |  |
| **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  |  |  |
| **8. Adverse Event (AE) Assessment of the Vaccine Platform (\*see Instructions):** | **Information** | **Comments/ Concerns** |
| **8.1** Approximately how many humans have received this 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? |  |  |
| * 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials
 |  Yes/No  |  |
| * 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** What is the evidence of disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) (if any) in humans?  |  |  |
| **8.8** 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, if any:  |  |  |
| * 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?
 |  |  |
| * human neonates, infants, children?
 |  |  |
| * pregnancy and in

 the fetus in humans? |  |  |
| * elderly?
 |  |  |
| * in any other special populations (e.g., institutionalized people, individuals with associated chronic comorbidity)?
 |  |  |
| **References** | **Information** |
| **1.** |  |
| **2.** |  |
| **3.** |  |
| **4.** |  |
| **5.** |  |
| **6.** |  |
| **7.**  |  |
| **8.** |  |
| **9.** |  |
| **10.** |  |