**The Brighton Collaboration Standardized Template for Collection of Key Information for Benefit-Risk Assessment of Inactivated Viral Vaccines**

**Introduction:**

The Brighton Collaboration (www.brightoncollaboration.us) 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 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 One of the tools developed by the V3SWG is a standardized template describing the key considerations for benefit-risk assessment of viral vector vaccines. Completed by the vaccine developers, it will then be peer-reviewed by the V3SWG and published. The information in the template may facilitate communication of otherwise complex and highly technical data among key stakeholders 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

In 2020, the development of vaccines for COVID-19 is occurring with unprecedented speed.7 The pace and volume of vaccine development make a deliberate and systematic approach to safety that is accessible and understandable to a diversity of stakeholders of the utmost importance. Inactivated viral vaccine candidates are among the COVID-19 vaccines in development.8 The Brighton Collaboration V3SWG has therefore developed a specific template for inactivated vaccines that the Coalition for Epidemic Preparedness Innovations (CEPI) and other key stakeholders could use to evaluate and communicate the benefit-risk assessment of using this platform.

Inactivated viral vaccines have long been used in humans for diseases of global health threat, including poliomyelitis, pandemic and seasonal influenza, rabies, hepatitis A, Japanese encephalitis, tick borne encephalitis, and the technology of inactivation has more recently been used for emerging diseases such as West Nile, Chikungunya, Ross River and SARS.9,10 The vaccines can be whole inactivated virus or whole virus-derived subvirion vaccines.9 The potential advantages of inactivated vaccines are that they cannot replicate in the host or revert to pathogenicity, and are non-transmissible.9 Whole inactivated virus particles have the potential to induce a broad range of both humoral and cellular responses against all the different epitopes presented by the virus.

However, due to the limited immunogenicity of some inactivated viral vaccines in humans, their development has also focused on methods to enhance the immune response, for example through the use of adjuvants, and optimizing the route or method of administration. Adjuvants are not usually licensed per se and it is the adjuvanted vaccine that is granted marketing authorization. Only a few different types of adjuvants are used in commercial vaccines while several others are under investigation. Whilst enhancing the immune response, adjuvants impart additional safety considerations to a vaccine that have to be carefully assessed.

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. Although we recognize that other aspects of manufacturing, quality, and implementation can play an important role in the safety of a vaccine and vaccination, we have chosen to keep some of those issues out of scope in order to summarize the most useful information for stakeholders.

The latest version of 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.

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

●Please read these instructions before you complete the ten 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 2-8 collect information regarding the basic vaccine information (Section 2), the target pathogen and population (Section 3), characteristics of antigen (Section 4), inactivation method (Section 5), adjuvant (Section 6), delivery and administration (Section 7), toxicology and nonclinical (Section 8), and human efficacy and other important information (Section 9). Depending on the vaccine, some sections may be redundant or not applicable. 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 10 and 11 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 effect and toxicities as requested and rate the risk in 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 9, 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.12

● 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”.

**References**

1. Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, et al. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine. 2002; 21(3-4):298-302. doi.org/10.1016/S0264-410X(02)00449-8

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3. Monath TP, Seligman SJ, Robertson JS, Guy B, Hayes EB, Condit RC, et al. Live virus vaccines based on a yellow fever vaccine backbone: standardized template with key considerations for a risk/benefit assessment. Vaccine. 2015; 33(1):62–72. doi:10.1016/j.vaccine.2014.10.004

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5. Monath TP, Fast PE, Modjarrad K, Clarke DK, Martin BK, Fusco J, et al. rVSVΔG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment. Vaccine X. 2019; 1:100009. doi: 10.1016/j.jvacx.2019.100009

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12. Bonhoeffer J, Bentsi-Enchill A, Chen RT, Fisher MC, Gold MS, Hartman K, et al. Guidelines for collection, analysis and presentation of vaccine safety data in pre- and post-licensure clinical studies. Vaccine. 2009; 27(16):2282-8. doi.org/10.1016/j.vaccine.2008.11.036

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| **Brighton Collaboration**  **Standardized Template for Collection of Key Information for Benefit- Risk Assessment of Inactivated Viral Vaccines** | | |
| **1. Authorship and Affiliation** | **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), and any other specific characteristics such as genetic modifications |  |  |
| **2.3** Substrate for vaccine virus growth (e.g., cell substrate, eggs, animal, etc.) |  |  |
| **2.4** Inactivation method |  |  |
| **2.5** Adjuvant (if applicable) |  |  |
| **2.6** Final vaccineformulation components |  |  |
| **2.7** Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal) |  |  |
| **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 Antigen** | **Information** | **Comments/ Concerns** |
| **4.1** Virus strains, sequence (including homology among strains), source, propagation, disruption, whole virus or subunit/subvirion (if applicable)? |  |  |
| **4.2** Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence? |  |  |
| **4.3** What is known about the immune response to the vaccine in animals and/or humans (binding, neutralizing antibody, functional, and, B-cell, T-cell memory, etc.)? |  |  |
| **5. Inactivation Method(s)** | **Information** | **Comments/ Concerns** |
| **5.1** Method/s (e.g., thermal, beta propiolactone, UV, formaldehyde, ionizing radiation) and potential impact on safety |  |  |
| **5.2** At what stage of the downstream process is inactivation/s performed and why? |  |  |
| **5.3** QC/confirmation method/log reduction in viability |  |  |
| **5.4** Could the inactivation method/s compromise the antigenic structure of the vaccine (e.g., conformation of the protein antigens) |  |  |
| **6. Adjuvant (optional, if applicable)** | **Information** | **Comments/ Concerns** |
| **6.1** Describe the type of adjuvant, if it has been tested in humans, whether novel or commercialized, and if applicable, what other vaccines (preventive and therapeutic) are formulated with this adjuvant |  |  |
| **6.2** What is the evidence that an adjuvant improves/boosts/enhances the immune response? |  |  |
| **6.3** What is the mechanism of action of the adjuvant (if known)? |  |  |
| **6.4** How is the adjuvant formulated with the antigen? |  |  |
| **6.5** How might the adjuvant impact the safety profile of the vaccine? |  |  |
| **6.6** Summarize the safety findings (preclinical and clinical) with the adjuvant,formulated with any antigen |  |  |
| **7. Delivery and Administration** | **Information** | **Comments/ Concerns** |
| **7.1** Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral, or combination thereof) |  |  |
| **7.2** 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 |  |  |
| **8. Toxicology and Nonclinical** | **Information** | **Comments/ Concerns** |
| **8.1** What is the possible risk of autoimmunity or a harmful immune response? |  |  |
| **8.2** Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products |  |  |
| **8.3** Summarize the preclinical immunogenicity and efficacy data that supports the use of this product in humans including any related information from similar products |  |  |
| **8.4** What is the evidence of disease enhancement or absence thereof *in vitro* or in animal models?13 |  |  |
| **8.5** Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk? |  |  |
| **9. Human Efficacy and Other Important Information** | **Information** | **Comments/ Concerns** |
| **9.1** What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)? |  |  |
| **9.2** Describe other key information that may impact benefit-risk |  |  |
| **10. Adverse Event (AE) Assessment of the Vaccine Platform (\*see Instructions):** | **Information** | **Comments/ Concerns** |
| **10.1** Approximately how many humans have received this vaccine to date? If variants of the vaccine, please list separately. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |  |  |
| **10.2** 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: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| **10.3** 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: |  |  |
| **10.4** List and provide frequency of any related or possibly related serious\* AEs and well as any severe expected or unexpected AEs observed: (\*see Instructions): |  |  |
| **10.5** List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control groups: |  |  |
| * Describe the control group: \_\_\_\_\_\_\_\_\_\_. |  |  |
| **10.6** List and provide frequency of Adverse Events of Special Interest |  |  |
| **10.7** What is the evidence of disease enhancement (if any) in humans? |  |  |
| **10.8** 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: |  |  |
|  |  |  |
| **11. Overall Risk Assessment** | **Information** | **Comments/ Concerns** |
| **11.1** Please summarize key safety issues of concern identified to date, if any: |  |  |
| * how should they be addressed going forward |  |  |
| **11.2** 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 populations, individuals with associated chronic comorbidity)? |  |  |
| **References** | **Information** | |
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