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The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of inactivated viral vaccines

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ABSTRACT

Inactivated viral vaccines have long been used in humans for diseases of global health threat and are now among the vaccines for COVID-19 under development. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) has prepared a standardized template to describe the key considerations for the benefit-risk assessment of inactivated viral vaccines. This will help key stakeholders to assess potential safety issues and understand the benefit-risk of the vaccine platform. The standardized and structured assessment provided by the template would also help to contribute to improved communication and support public acceptance of licensed inactivated viral vaccines.

1. Introduction

The Brighton Collaboration (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 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/ sponsors, 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

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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. See Supplementary Material for definitions and additional guidance for completing this template.

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 [11].

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 [12]. 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 (see Table 1).

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.

2. 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. Finally, please provide references in the 'Reference' column. More than one reference can be used per question. You can simply write the first author's last name, first name initials, and year of publication (e.g., Lewis MH, 2003) in the "Reference" column here, but please provide the full citation for the reference at the end of the form. Unpublished data are acceptable, though we do wish for you to include the source and contact information.
- 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 [13].
- 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".

3. Disclaimer

The findings, opinions, conclusions, and assertions contained in this consensus document are those of the individual members of the Working Group. They do not necessarily represent the official positions of any participant's organization (e.g., government, university, or corporations) and should not be construed to represent any Agency determination or policy.

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Table 1

Brighton collaboration concatenated version of standardized template for collection of key information for benefit -risk assessment of inactivated viral vaccines. For regular version, see https://brightoncollaboration.us/v3swg/.

1. Authorship and affiliation	2. Basic vaccine information	3. Target pathogen and population	4. Characteristics of antigen	5. Inactivation method(s)	6. Adjuvant (optional, if applicable)	7. Delivery and administration	8. Toxicology and nonclinical	9. Human efficacy and other important information	10. Adverse Event (AE) assessment of the vaccine platform ([14] see instructions):	11. Overall risk assessment
1.1 Author(s) and affiliation(s)	**2.1** Vaccine name	**3.1** What is the target pathogen?	**4.1** Virus strains, sequence (including homology among strains), source, propagation, disruption, whole virus or subunit/subvirion (if applicable)?	**5.1** Method/s (e.g., thermal, beta propiolactone, UV, formaldehyde, ionizing radiation) and potential impact on safety	**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	**7.1** Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral, or combination thereof)	**8.1** What is the possible risk of autoimmunity or a harmful immune response?	**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)?	**10.1** Approximately how many humans have received this vaccine to date? If variants of the vaccine, please list separately.	**11.1** Please summarize key safety issues of concern identified to date, if any:
1.2. Date completed/ updated	**2.2** Virus name, genus, family, strains/ serotypes, origin (e.g., geography, patient, asymptomatic), and any other specific characteristics such as genetic modifications	**3.2** What are the disease manifestations caused by the target pathogen in humans, for the following categories:	**4.2** Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? What is the evidence?	**5.2** At what stage of the downstream process is inactivation/s performed and why?	**6.2** What is the evidence that an adjuvant improves/boosts/ enhances the immune response?	**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	**8.2** Summarize the preclinical safety data that supports the use of this product in humans including any related information from similar products	**9.2** Describe other key information that may impact benefit-risk	**10.2** Method(s) used for safety monitoring:	●how should they be addressed going forward
	2.3 Substrate for vaccine virus growth (e.g., cell substrate, eggs, animal, etc.)	●In healthy people	**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.)?	**5.3** QC/confirmation method/log reduction in viability	**6.3** What is the mechanism of action of the adjuvant (if known)?		**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		●Spontaneous reports/passive surveillance	**11.2** What is the potential for causing serious unwanted effects and toxicities in:
	2.4 Inactivation method	●In immunocompromised people		**5.4** Could the inactivation method/s compromise the antigenic structure of the vaccine (e.g., conformation of the protein antigens)	**6.4** How is the adjuvant formulated with the antigen?		**8.4** What is the evidence of disease enhancement or absence thereof *in vitro* or in animal models? [14]		●Diary	● healthy humans?

Table 1 (*continued*)

Brighton collaboration concatenated version of standardized template for collection of key information for benefit -risk assessment of inactivated viral vaccines. For regular version, see https://brightoncollaboration.us/v3swg/.										
1. Authorship and affiliation	**2. Basic vaccine information**	**3. Target pathogen and population**	**4. Characteristics of antigen**	**5. Inactivation method(s)**	**6. Adjuvant (optional, if applicable)**	**7. Delivery and administration**	**8. Toxicology and nonclinical**	**9. Human efficacy and other important information**	**10. Adverse Event (AE) assessment of the vaccine platform ([14] see instructions):**	**11. Overall risk assessment**
	2.5 Adjuvant (if applicable)	●In neonates, infants, children			**6.5** How might the adjuvant impact the safety profile of the vaccine?		**8.5** Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?		●Other active surveillance	●immunocompromised humans?
	2.6 Final vaccine formulation components	●During pregnancy and in the fetus			**6.6** Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen				**10.3** What criteria were used for grading the AEs?	●human neonates, infants, children?
	2.7 Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal, other mucosal)	●In elderly							●2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials	●pregnancy and in the fetus in humans?
		●In any other special populations							●If no criteria were used for grading, or if other metrics were employed, please describe:	●elderly
		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 (R_0), and spontaneous mutation)?							**10.4** List and provide frequency of any related or possibly related serious[14] AEs and well as any severe expected or unexpected AEs observed: ([14]see Instructions):	●in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?

(*continued on next page*)

Table 1 (*continued*)

Brighton collaboration concatenated version of standardized template for collection of key information for benefit -risk assessment of inactivated viral vaccines. For regular version, see https://brightoncollaboration.us/v3swg/.										
1. Authorship and affiliation	**2. Basic vaccine information**	**3. Target pathogen and population**	**4. Characteristics of antigen**	**5. Inactivation method(s)**	**6. Adjuvant (optional, if applicable)**	**7. Delivery and administration**	**8. Toxicology and nonclinical**	**9. Human efficacy and other important information**	**10. Adverse Event (AE) assessment of the vaccine platform ([14] see instructions):**	**11. Overall risk assessment**
		3.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast-feeding), adult, elderly)?							**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:	
		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							**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? ●Did it identify any safety issue of concern? ●If so describe:	

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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