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## Review

## The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of protein vaccines

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## ABSTRACT

Several protein vaccine candidates are among the COVID-19 vaccines in 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 protein vaccines. This will help key stakeholders to assess potential safety issues and understand the benefit-risk of such a vaccine platform. The structured and standardized assessment provided by the template would also help contribute to improved public acceptance and communication of licensed protein vaccines.

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## Contents

1. Introduction .....	00
2. Specific instructions for completing the V3SWG template .....	00
3. Disclaimer .....	00
Funding .....	00
Declaration of Competing Interest .....	00

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Acknowledgment .....	00
References .....	00

## 1. Introduction

The Brighton Collaboration ([www.brightoncollaboration.org](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 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 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. Several protein vaccine candidates (e.g., recombinant protein or synthetic peptide vaccines) are among the COVID-19 vaccines in development. The Brighton Collaboration V3SWG has therefore developed a specific template for protein 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.

Protein vaccines generally comprise the viral surface antigen responsible for the stimulation of neutralizing antibodies (spike protein in the case of COVID-19) [8]. They are typically recombinant-derived and highly purified. Peptides are also included in this category of vaccines and most of these are likely to be synthetic in nature. Examples of licensed protein vaccines include an influenza vaccine comprising highly purified recombinant hemagglutinin [9], and a herpes zoster vaccine with highly purified varicella zoster surface glycoprotein E antigen [10]. Many other protein vaccines have undergone clinical testing for example HIV gp120 and gp140 vaccines, but are not yet licensed. Recombinant proteins have often been used in vector or DNA prime, and protein boost regimens, in particular for HIV vaccines [11]. Some recombinant viral antigens spontaneously assemble into virus-like particles (VLPs). These may be single or multi protein structures that are stable and more immunogenic compared to purified protein antigens. Examples of licensed vaccines containing recombinant VLPs include hepatitis B and human papillomavirus vaccines [12]. It should be highlighted that, in contrast to inactivated, live attenuated, and viral vectored vaccines, the manufacture of protein vaccines does not involve the cultivation of any live viruses and they do not contain any viral genomes, their production and quality control is simpler, they are generally considered safer in cases where viruses can establish a persistent infection or are oncogenic, and they are feasible to manufacture even if the virus

cannot be cultivated. Commercialized recombinant protein vaccines have been shown to be safe and efficacious and their manufacture can be scaled-up with relative ease [13–15]. However, due to the limited immunogenicity of some protein-based vaccines in humans, their development has also focused on methods to enhance the immune response, for example through the use of adjuvants, optimizing the route or method of administration, and the use of a heterologous prime-boost strategies.

In particular, protein vaccines are likely to require a potent adjuvant that will direct the immune response to a predominantly Th1-type response. Adjuvants are not usually licensed *per se* and it is the adjuvanted vaccine that is granted marketing authorization. There are only a few different types of adjuvant used in commercial vaccines although many are under investigation and the availability of particular adjuvants may be limited. Whilst enhancing the immune response, adjuvants impart additional safety considerations to a vaccine that have to be carefully assessed [16].

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.

## 2. Specific instructions for completing the V3SWG template:

- Please read these instructions before you complete the ten sections. Send questions to: [brightoncollaborationv3swg@gmail.com](mailto: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), adjuvant (Section 5), delivery and administration (Section 6), toxicology and nonclinical (Section 7), and human efficacy and other important information (Section 8). 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 refer-

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 See for regular <https://brightoncollaboration.us/v3swg> version.

1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Antigen	5. Adjuvant	6. Delivery and Administration	7. Toxicology and Nonclinical	8. Human Efficacy and Other Important Information	9. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	10. Overall Risk Assessment
1.1. Author(s)	2.1 Vaccine name	3.1 What is the target pathogen?	4.1 Is the vaccine likely to induce immunity to all strains/genotypes of the target pathogen? Was there evidence generated?	5.1 If applicable, 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	6.1 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?	7.1 What is known about biodistribution of the antigen in its final formulation and mode of administration in animal models?	8.1 What is the evidence that the vaccine would generate a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?	9.1 Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately	10.1 Please summarize key safety issues of concern identified to date, if any:
1.2. Date completed/ updated	2.2 Protein type (e.g., molecular clamp, virus-like particle, peptide) and any special characteristics	3.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:	4.2 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.)?	5.2 What is the rationale for using the adjuvant?	6.2 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	7.2 How long does the vaccine antigen persist in vivo (may specify in tissue/serum; proximal/distal to site of administration)?	8.2 Describe other key information that may impact benefit-risk	9.2 Method(s) used for safety monitoring:	● how should they be addressed going forward
	2.3 Type of heterologous expression system used for antigen production (e.g., bacteria, yeast, plants, mammalian or insect cells, chemical synthesis)	● In healthy people	4.3 Is there homology in the sequence of the vaccine antigen and human proteins?	5.3 What is the mechanism of action of the adjuvant (if known)?	6.3 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	7.3 What is the possible risk of autoimmunity or a harmful immune response?		● Spontaneous reports/passive surveillance	10.2 What is the potential for causing serious unwanted effects and toxicities in:
	2.4 Adjuvant (if applicable)	● In immunocompromised people		5.4 How is the adjuvant formulated with the antigen?	6.4 Describe how the mode of vaccine delivery may impact safety (e.g., intramuscular by needle injection, microneedles, intranasal, oral)	7.4 Do animal models for toxicity exist? Summarize results		● Diary	● healthy humans?
	2.5 Final vaccine formulation components that may impact delivery into cells, stability, and safety (e.g., preservatives (e.g.,	● In neonates, infants, children		5.5 How might the adjuvant impact the safety profile of the vaccine?		7.5 Do animal models for immunogenicity and/or efficacy exist? Summarize results		● Other active surveillance	● immunocompromised humans?

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1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Antigen	5. Adjuvant	6. Delivery and Administration	7. Toxicology and Nonclinical	8. Human Efficacy and Other Important Information	9. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	10. Overall Risk Assessment
	<p>thimerosal, phenol, benzethonium chloride, 2-phenoxyethanol), complexing with polymers, encapsulation within microparticles, liposomes, depot formulations)</p> <p><b>2.6</b> Route and method of delivery (e.g., intramuscular injection, microneedles, skin patch, intranasal)</p>	<ul style="list-style-type: none"> <li>• During pregnancy and in the fetus</li> <li>• In elderly</li> <li>• In any other special populations</li> </ul> <p><b>3.3</b> 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 (<math>R_0</math>))?</p>		<p><b>5.6</b> Summarize the safety findings (preclinical and clinical) with the adjuvant, formulated with any antigen</p>		<p><b>7.6</b> What is the evidence of disease enhancement (if any) in animal models?*</p> <p><b>7.7</b> Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit-risk?</p> <p><b>7.8</b> What is the evidence that the vaccine has generated a beneficial immune response in:</p> <ul style="list-style-type: none"> <li>• Small animal models?</li> </ul>		<p><b>9.3</b> What criteria were used for grading the AEs?</p> <ul style="list-style-type: none"> <li>• 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials</li> <li>• If no criteria were used for grading, or if other metrics were employed, please describe:</li> </ul> <p><b>9.4</b> List and provide frequency of any related or possibly related serious* AEs observed (*see Instructions)</p>	<ul style="list-style-type: none"> <li>• human neonates, infants, children?</li> <li>• pregnancy and in the fetus in humans?</li> <li>• elderly</li> <li>• in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?</li> </ul>

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1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Antigen	5. Adjuvant	6. Delivery and Administration	7. Toxicology and Nonclinical	8. Human Efficacy and Other Important Information	9. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	10. Overall Risk Assessment
		<p><b>3.4</b> What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast-feeding), adult, elderly)?</p> <p><b>3.5</b> What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?</p> <p><b>3.6</b> Please describe any other key information about the target pathogen or population that may inform benefit-risk</p>				<ul style="list-style-type: none"> <li>● Nonhuman primates (NHP)?</li> </ul>	<p><b>9.5</b> List and provide frequency of any serious, unexpected statistically significantly increased AE or lab abnormality in vaccinee vs. control groups:</p> <ul style="list-style-type: none"> <li>● Describe the control group: _____</li> </ul> <p><b>9.6</b> List and provide frequency of Adverse Events of Special Interest</p> <p><b>9.7.</b> Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study?</p> <ul style="list-style-type: none"> <li>● Did it identify any safety issue of concern?</li> <li>● If so describe</li> </ul>		

\*Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed relevant for safety purpose.\*There are two different syndromes previously associated with vaccine-enhanced disease. One is antibody-dependent enhancement (ADE) and the other is vaccine-associated enhanced respiratory disease (VAERD) [8].

ences 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 9 and 10 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 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 [17].
- 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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### 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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