



## Review

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



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## ABSTRACT

Many of the vaccines under development for COVID-19 involve the use of viral vectors. The Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO, formerly the Viral Vector Vaccine Safety Working Group, V3SWG) working group has prepared a standardized template to describe the key considerations for the benefit-risk assessment of viral vector vaccines. This will facilitate key stakeholders to anticipate potential safety issues and interpret or assess safety data. This would also help improve communication and public acceptance of licensed viral vector vaccines.

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<sup>1</sup> See Acknowledgement for other BRAVATO members.

## 1. Introduction

In 2020, the speed of vaccine development for COVID-19 is unprecedented [1]. Keeping in mind the volume and pace of vaccine development, a systematic and deliberate approach to vaccine safety that is understandable and accessible to diverse stakeholders is of considerable importance. Several viral vectored vaccines are among the COVID-19 vaccines in development. The Brighton Collaboration ([www.brightoncollaboration.us](http://www.brightoncollaboration.us)) was launched in 2000 to improve the science of vaccine safety [2]. The Brighton Collaboration formed the Viral Vector Vaccines Safety Working Group (V3SWG) in October 2008 to improve the ability to anticipate potential safety issues and meaningfully assess or interpret safety data, thereby facilitating greater public acceptance when a viral vector vaccine is licensed [3]. Pursuant to this goal, the V3SWG developed a standardized template that the Coalition for Epidemic Preparedness Innovations (CEPI) and other key stakeholders could use to evaluate and communicate key considerations for the benefit-risk assessment of viral vectors and viral vector vaccines. The information in the template will help in the communication of technical and complex data among key stakeholders, and increase the comprehension, transparency and comparability of essential information (see Table 1).

The viral vector vaccine template and the mission of the V3SWG has evolved over time. The first version of the template (v1.0) was used for the standardized benefit-risk assessment of several new viral vectors or viral vector vaccines [4–6], including a vaccine targeting Ebola. The WHO Global Advisory Committee on Vaccine Safety (GACVS) endorsed the use of the viral vector template for other new candidate Ebola vaccines “as it is a structured approach to vaccine safety” [7]. A second version of the template (v2.0) was used to describe viral vectors based on adenovirus 26 and Modified Vaccinia virus Ankara (in preparation). Experience with earlier versions of the viral vector template and with other vaccine platform templates under development by the V3SWG inspired improvements included with the template presented here. A detailed history of the development of the viral vector vaccine template is archived on the Brighton Collaboration website (<https://brightoncollaboration.us/bravato/>). The V3SWG 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 [8].

Viral vector vaccines are laboratory-generated, chimeric viruses that are based upon replicating or non-replicating virus vectors into which have been spliced genes encoding antigenic proteins for a target pathogen. Consideration of safety issues associated with viral vector vaccines requires a clear understanding of the agents used for construction of the vaccine. These include (1) the wild type virus from which the vector is derived, referred to in the template as “**wild type virus**”; (2) the vector itself before incorporation of the foreign antigen, referred to in the template as “**viral vector**”; and (3) the final recombinant viral vector vaccine, referred to in the template as “**vaccine**”. Wild type viruses used as vectors may originate from human or animal hosts and may have low or high pathogenic potential in humans regardless of species of origin. Understanding the characteristics of the wild type virus as directed in the template is critical in anticipating the potential behavior of any vector adapted from the wild type virus. Viral vectors can originate from attenuated viral vaccines used in humans (e.g. yellow fever, Modified Vaccinia virus Ankara); from attenuated human or animal viruses (e.g. human adenovirus, vesicular stomatitis virus); or from human or animal viruses with low pathogenic potential (e.g. adeno associated virus, chimp adenovirus). Viral vectors can be replicating (e.g. vesicular stomatitis virus) or

non-replicating (e.g. Modified Vaccinia virus Ankara). Viral vectors usually, but not always, have properties in a human host that differ from the wild type virus from which they were derived. Incorporation of a target antigen into a viral vector to create a vaccine may alter the properties of the vector such that the vaccine may have properties that differ from the vector.

This updated version of the Brighton Collaboration Vaccine Vector template is designed for dual use. It may be used to describe exclusively viral vectors into which transgenes may be incorporated to create vaccines, or it may be used to describe viral vector vaccines for specific pathogens. Thus, the template has two main parts. Part I is used to describe a viral vector and Part II is used additionally to describe a specific vaccine, where this is the intent. Pursuant to understanding completely the characteristics of a given vector, Part I considers the wild type virus from which the vector is derived (Section 3) in addition to characteristics of the vector itself (Sections 2 and 4). Pursuant to understanding completely the characteristics of a vaccine, Part II additionally considers the target pathogen (Section 8) and the potential impact of transgene insertion to create a vaccine (Section 9). Each part contains its own sections evaluating the toxicology, adverse effects and overall assessment of either the vector alone or a vaccine. When the template is being used to characterize a viral vector vaccine, it is understood that there may be limited information concerning the vector itself, especially concerning toxicology and potency of the vector (Section 5), and Section 6 on adverse events may not be relevant. Vaccine developers should nevertheless complete Section I to what extent this is feasible.

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

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

## 2. Specific instructions for completing the BRAVATO template

- Please read these instructions before you complete the thirteen sections. Send questions to: [brightoncollaborationv3swg@gmail.com](mailto:brightoncollaborationv3swg@gmail.com)
- The first section entitled “Authorship and Affiliation” should include your name, your affiliation and the latest date completing the form. If you are working with someone else to complete this form, their name and affiliation 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 BRAVATO and in subsequent Wiki updates on the BRAVATO website.
- Part I collects information regarding a viral vector alone, while Part II collects information regarding a vaccine based on the viral vector. If the template is being used to describe a vector only, then complete Part I only. If the template is being used







Table 1 (continued)

Part I: Viral Vector (Sections 2-7)			Part II: Vaccine (Sections 8-12)									
1. Authorship and Affiliation	2. Basic vector information	3. Characteristics of the wild type virus from which the vector is derived	4. Characteristics of the vector from which vaccine(s) may be derived	5. Toxicology and Potency (Pharmacology) of the Vector	6. Adverse Event (AE) Assessment of the Vector ("see Instructions):	7. Overall Risk Assessment of Vector	8. Target Pathogen and Population for the vaccine	9. Characteristics of the Vaccine	10. Toxicology and Potency (Pharmacology) of the Vaccine	11. Adverse Event (AE) Assessment of the Vaccine ("see Instructions):	12. Overall Risk Assessment of Vaccine	13. Any other information concerning either the viral vector or the vaccine
		<p>possible vaccine-induced contributor to the pathogenesis of wild type disease</p> <p>3.12 What is the background prevalence of natural immunity to the virus?</p> <p>3.13 Is there any vaccine available for the wild-type virus? If yes,</p>	<p>● in animal models?</p> <p>● in human hosts?</p>	<p>9.17. What is known about the mechanisms of immunity to the vaccine?</p> <p>9.18 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vaccine?</p> <p>● in vitro?</p> <p>● in animal models?</p> <p>● in human hosts?</p>	<p>9.19 What is known about the effect of pre-existing immunity, including both natural immunity and repeat administration of the vector or the vaccine, on 'take', safety or efficacy in any animal model or human studies using this vector?</p> <p>9.20. Is the vaccine transmissible in humans or other species (including arthropods) and/or stable in the environment?</p> <p>9.21. Are there antiviral or other treatments available for disease manifestations caused by the vaccine?</p> <p>9.22. Vaccine formulation</p> <p>9.23. Proposed route</p>							

(continued on next page)



Table 1 (continued)

Part I: Viral Vector (Sections 2-7)			Part II: Vaccine (Sections 8-12)									
1. Authorship and Affiliation	2. Basic vector information	3. Characteristics of the wild type virus from which the vector is derived	4. Characteristics of the vector from which vaccine(s) may be derived	5. Toxicology and Potency of the Vector	6. Adverse Event (AE) Assessment of the Vector (*see Instructions):	7. Overall Risk Assessment of Vector	8. Target Pathogen and Population for the vaccine	9. Characteristics of the Vaccine	10. Toxicology and Potency (Pharmacology) of the Vaccine	11. Adverse Event (AE) Assessment of the Vaccine (*see Instructions):	12. Overall Risk Assessment of Vaccine	13. Any other information concerning either the viral vector or the vaccine
								and method of vaccine delivery (e.g. oral, intramuscular injection microneedles, skin patch, intranasal, mucosal)				
								9.24. Target populations for the vaccine (e.g. pediatric, maternal, adult, elderly etc.)				

to describe a vector vaccine, then complete both Parts I and II. Within Part I, sections 2–7 collect information regarding the wild type virus (Section 3) and the vector (Sections 2 and 4–7). Within Part II, section 8 collects information regarding the target pathogen and population while sections 9–12 collect information regarding the vaccine based on the vector. Depending on the circumstances, some sections may be redundant, for example if a vector is in fact identical to the wild type virus. In cases of redundancies, an answer may simply refer to the answer in another section. Furthermore, some sections may not be applicable, for example if safety evaluations have been conducted only in the context of a vaccine and not with an empty viral vector alone. In such cases the answer should include “not applicable” or “not tested”, whichever is relevant. Whether completing only Part I or both Parts I and II, any supplementary information should be added in section 13.

- 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 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 6, 7, 11 and 12 have column titles that differ from preceding sections intended to provide a summary assessment of adverse effects and toxicity of the vector. 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 vector in humans to accurately make these assessments, please state so in response to the questions.
- When completing information on adverse effects in Sections 6 and 11, 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 [9].
- In the references, unpublished data 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 provide the following information in the Reference section: (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.

### 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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