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Review

The Brighton Collaboration standardized template for collection of key information for benefit-risk assessment of nucleic acid (RNA and DNA) vaccines

Denny Kim [a], James S. Robertson [b], Jean-Louis Excler [c], Richard C. Condit [d], Patricia E. Fast [e,f], Marc Gurwith [g], George Pavlakis [h], Thomas P. Monath [i], Jonathan Smith [j], David Wood [b], Emily R. Smith [g], Robert T. Chen [g], Sonali Kochhar [k,l], For the Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) [1]

[a] Janssen Pharmaceuticals, Titusville, NJ, USA
[b] Independent Adviser, United Kingdom
[c] International Vaccine Institute, Seoul, Republic of Korea
[d] Department of Molecular Genetics and Microbiology, University of Florida, Gainesville, FL 32610, USA
[e] International AIDS Vaccine Initiative, New York, NY 10004, USA
[f] Stanford School of Medicine, Palo Alto, CA 94305, USA
[g] Brighton Collaboration, A Program of the Task Force for Global Health, Decatur, GA, USA
[h] National Cancer Institute, National Institutes of Health, Frederick, MD 21702, USA
[i] Crozet BioPharma LLC, Devens, MA 01434, USA
[j] VLP Therapeutics, Gaithersburg, MD 20878, USA
[k] Global Healthcare Consulting, New Delhi, India
[l] University of Washington, Seattle, WA 98195, USA

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ABSTRACT

Nucleic acid (DNA and RNA) vaccines are among the most advanced 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 nucleic acid vaccines. This will facilitate the assessment by key stakeholders of potential safety issues and understanding of overall benefit-risk. The structured assessment provided by the template can also help improve communication and public acceptance of licensed nucleic acid vaccines.

Contents

[1] See Acknowledgement for other V3SWG members.

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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, to be completed by the vaccine developers/sponsors, ideally subsequently peer reviewed by the V3SWG and published. The information on the template can 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].

In 2020, the development of vaccines for COVID-19 is appropriately occurring with unprecedented speed [7]. The pace and volume of development make a deliberate and systematic approach that is accessible and understandable to a diversity of stakeholders all the more important. Several DNA and RNA vaccine candidates are among the most advanced COVID-19 vaccines in development. The Brighton Collaboration V3SWG has therefore developed a specific template for nucleic acid vaccines that the Coalition for Epidemic Preparedness Innovations (CEPI) and other key stakeholders will use to evaluate and communicate the benefit-risk of vaccines using these nucleic acid platforms. See Supplementary Material for definitions and additional guidance for completing this template.

DNA vaccines have been under development since the early 1990s. 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 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 (see Table 1).

2. 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,

Table 1
Brighton Collaboration.

Concatenated Version of Standardized Template for Collection of Key Information for Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines. For regular version, see https://brightoncollaboration.us/v3swg/.

1. Authorship	2. Basic Vaccine information	3. Target Pathogen and Population	4. Characteristics of Vaccine Transgene and Expression	5. Delivery and Administration	6. Toxicology and Nonclinical	7. Human Efficacy and Other Important Information	8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):	9. Overall Risk Assessment
1.1. Author(s)	**2.1** Vaccine name	**3.1** What is the target pathogen?	**4.1** Nature of the nucleic acid platform (**DNA** - synthetic, bacterial, plasmid, linear, >1 type/molecule, other; **RNA-** messenger, self-replicating, other)	**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?	**6.1** What is known about biodistribution of the platform nucleic acid in its final formulation and mode of administration in animal models?	**7.1** What is the evidence that the vaccine generates a protective immune response in humans (e.g., natural history, passive immunization, animal challenge studies)?	**8.1** Approximately how many humans have received this vaccine to date? If variants of the vaccine platform, please list separately _____	**9.1** Please summarize key safety issues of concern identified to date, if any:
1.2. Date completed/ updated	**2.2** Nucleic Acid Type: DNA, RNA, self-amplifying RNA	**3.2** What are the disease manifestations caused by the target pathogen in humans, for the following categories:	**4.2** Gene(s) incorporated into the vaccine (antigen, T-cell epitopes, antibiotic resistance factors, cytokines, other)	**5.2** Describe how the mode of vaccine delivery may impact safety?[1] (e.g., electroporation (please specify name of device), intradermal needle injection)	**6.2** How long does the RNA or DNA persist in vivo (may specify in tissue/ serum, proximal/ distal to site of administration)?	**7.2** Describe other key information that may impact benefit-risk	**8.2** Method(s) used for safety monitoring:	• How should they be addressed going forward
	2.3 Adjuvant (if applicable)	• In healthy people	**4.3** Factors enhancing/controlling gene expression	**5.3** How might any co-administered components (e.g., adjuvants, cytokines, immunomodulatory molecules) impact the safety profile?	**6.3** What is the risk of integration of sequences from the platform nucleic acid into the host genome?		• Spontaneous reports/passive surveillance	**9.2** What is the potential for causing serious unwanted effects and toxicities in:
	2.4 Final vaccine formulation components of formulation that may impact delivery into cells, stability, and safety (e.g., complexing with polymers, encapsulation within microparticles, liposomes)	• In immunocompromised people	**4.4** Non-expressed features impacting vaccine efficacy (CpG sequences, other)	**5.4** If applicable, describe the heterologous prime-boost regimen that this vaccine is a part of and the possible impact on safety	**6.4** What is the possible risk of autoimmunity or a harmful immune response?		• Diary	• Healthy humans?
	2.5 Route and method of Delivery (e.g., intramuscular injection, gene gun, electroporation)	• In neonates, infants, children	**4.5** Other sequence features that may impact safety (e.g., sequences in DNA that might facilitate insertion or recombination)		**6.5** Do animal models for toxicity exist? Summarize results		• Other active surveillance	• Immunocompromised humans?
		• During pregnancy and in the fetus	**4.6** Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?		**6.6** Do animal models for immunogenicity and/or efficacy exist? Summarize results		**8.3** What criteria were used for grading the AEs?	• Human neonates, infants, children?
			4.7 What is known		**6.7** What is the			

• In elderly	about the immune response to the vaccine (binding, functional, and neutralizing antibody, B-cell, T-cell memory, etc.)?	evidence of disease enhancement (if any) in vitro or in animal models?	• 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		**6.8** Would the vaccine in its final formulation have any impact on innate immunity? If so, what are the implications for benefit- risk?	• If no criteria were used for grading, or if other metrics were employed, please describe:	• In any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?	
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))?		**6.9** What is the evidence that the vaccine has generated a beneficial immune response in:	**8.4** List and provide frequency of any related or possibly related serious* AEs observed (*see Instructions)		
3.4 What sections of the population are most affected by the target pathogen (e.g., pediatric, pregnant, lactating women (breast-feeding), adult, elderly)?		• Small animal models?	**8.5** List and provide frequency of any serious, unexpected AE (may overlap with 8.4)		
3.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?		• Nonhuman primates (NHP)?	**8.6** List and provide frequency of any serious, unexpected statistically significantly increased AE or lab abnormality in vaccinee vs. control group		
3.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk			• Describe the control group: _____.		

(*continued on next page*)

Table 1 (*continued*)

Concatenated Version of Standardized Template for Collection of Key Information for Risk Assessment of Nucleic Acid (RNA and DNA) Vaccines. For regular version, see https://brightoncollaboration.us/v3swg/.								
1. Authorship	**2. Basic Vaccine information**	**3. Target Pathogen and Population**	**4. Characteristics of Vaccine Transgene and Expression**	**5. Delivery and Administration**	**6. Toxicology and Nonclinical**	**7. Human Efficacy and Other Important Information**	**8. Adverse Event (AE) Assessment of the Vaccine Platform (*see Instructions):**	**9. Overall Risk Assessment**
							8.7 List and provide frequency of Adverse Events of Special Interest **8.8** What is the evidence of disease enhancement (if any) in humans? **8.9** Did a Data Safety Monitoring Board (DSMB) or its equivalent oversee the study? • Did it identify any safety issue of concern? • If so describe	

[1] Also consider the safety impact of multi-dose delivery methods, the use of multi dose vaccine vials, and any special considerations for disposal.

[*] Stability is considered here in the context of any relevant intrinsic characteristic of the vaccine deemed relevant 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.

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. 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 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 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 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].
- 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.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.06.017.

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