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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.

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) 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.

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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://brighton-collaboration.us/bravato/). The V3WSG 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 BAVATO template

- Please read these instructions before you complete the thirteen sections. Send questions to: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 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 competing 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

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Table 1

Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO) Working Group Standardized Template v3.0 for Collection of Key Information for Risk Assessment of Viral Vaccine Vector Candidates. For the regular version, see https://brightoncollaboration.us/v3swg/.

	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 the 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 the Vaccine**	**13. Any other information concerning either the viral vector or the vaccine**
1.1. Author(s) and affiliation	2.1 Vector name	3.1 Name of wild type virus (common name; Family/Genus/ Species/subtype)	4.1 Describe the source of the vector (e.g. isolation, synthesis)	5.1. What is known about the replication,	6.1. Approximately how many humans have received any vaccine using this viral vector to date? If variants of the vector, please list separately.	7.1. Please summarize key safety issues of concern identified to date, if any:	8.1 What is the target pathogen for the vaccine?	9.1 Vaccine name	10.1. What is known about the replication,transmission and pathogenicity of the vaccine in and between animals?	11.1. Approximately how many humans have received this viral vector vaccine to date? If variants of the vector, please list separately	12.1. Please summarize key safety issues of concern identified to date, if any:	
1.2. Date completed/ updated	2.2. Vector origin Family/ Genus/ Species / subtype	3.2 What is the natural host for the wild type virus?	4.2. What is the basis of attenuation/ inactivation of the wild type virus to create the vector?	transmission and pathogenicity of the vector in and between animals?	6.2. Method(s) used for safety monitoring:	● how should they be addressed going forward:	8.2 What are the disease manifestations caused by the target pathogen in humans, for the following categories:	9.2. What is the identity and source of the transgene?	10.2. For replicating vectors, has a comparative virulence and viral kinetic study been conducted in permissive and susceptible species? (yes/no) If not, what species would be used for such a study? Is it feasible to conduct such a study?	11.2. Method(s) used for safety monitoring:	● how should they be addressed going forward:	
	2.3. Vector replication in humans (replicating or non-replicating)	3.3. How is the wild type virus normally transmitted?	4.3. What is known about the replication, transmission and pathogenicity of the vector in humans in the following categories:	5.2. For replicating vectors, has a comparative virulence and viral kinetic study been conducted in permissive and susceptible species? (yes/no) If not, what species would be used for such a study? Is it feasible to conduct such a study?	● Spontaneous reports/passive surveillance	7.2. What is the potential for causing serious unwanted effects and toxicities in:	● In healthy people	9.3. Is the transgene likely to induce immunity to all strains/genotypes of the target pathogen?	10.3. Does an animal model relevant to assess attenuation exist?	● Spontaneous reports/passive surveillance	12.2. What is the potential for causing serious unwanted effects and toxicities in:	
		3.4. Does the wild type virus establish a latent or persistent infection?	● In healthy people	5.3. Does an animal model relevant to assess attenuation exist?	● Diary	●healthy humans?	● In immunocompromised people	9.4. Where in the vector genome is the transgene inserted?	10.4. Does an animal model for safety including immuno-compromised animals exist?	●Diary	● healthy humans?	
		3.5. Does the wild type virus replicate in the nucleus?	● In immunocompromised people	5.4. Does an animal model for safety including immuno-compromised animals exist?	● Other active surveillance	●immunocompromised humans?	● In neonates, infants, children	9.5. Does the insertion of the transgene involve deletion or other rearrangement of any vector genome sequences?	10.5. Does an animal model for reproductive toxicity exist?	●Other active surveillance	● immunocompromised humans?	
		3.6. What is the risk of integration into the human genome?	● In breast milk, neonates, infants, children	5.5. Does an animal model for reproductive toxicity exist?	6.3. What criteria were used for grading the AE's?	● Breast milk, human neonates, infants, children?	● During pregnancy and in the fetus	9.6. How is the transgene expression controlled (transcriptional promoters, etc.)?	10.6. Does an animal model for immunogenicity and efficacy exists?	11.3. What criteria were used for grading the AE's?	● Breast milk, human neonates, infants, children?	
		3.7. List any disease manifestations caused by the wild type virus, the strength of evidence, severity, and duration of disease for	● during pregnancy and in the fetus	5.6. Does an animal model for immunogenicity and efficacy exists?	● 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy	● pregnancy and in the fetus in humans?	● In elderly	9.7. Does insertion or expression of the transgene affect the pathogenicity or phenotype of the vector?	10.7 Does an animal model for antibody enhanced disease (including antibody dependent enhancement (ADE), vaccine associated	● 2007 US FDA Guidance for Industry Toxicity Grading Scale for Healthy	● pregnancy and in the fetus in humans?	

(*continued on next page*)

Table 1 (*continued*)

1. Authorship and Affiliation	Part I: Viral Vector (Sections 2-7)						Part II: Vaccine (Sections 8-12)					
	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 the 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 the Vaccine**	**13. Any other information concerning either the viral vector or the vaccine**
		the following categories:			Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials				enhanced respiratory disease (VAERD)) or immune complex disease exist?	Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials		
		● in the healthy natural host	● in gene therapy experiments	5.7 Does an animal model for antibody enhanced disease (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) or immune complex disease exist?	● If no criteria were used for grading, or if other metrics were employed, please describe:	● elderly	●In any other special populations	9.8. Is the vaccine replication-competent in humans or other species?	10.8. What is known about biodistribution in animal models or in humans, including neurovirulence and/or neuroinvasion?	●If no criteria were used for grading, or if other metrics were employed, please describe:	● elderly	
		● In laboratory hosts (specify species)	● in any other special populations	5.8. What is known about biodistribution in animal models or in humans, including neurovirulence and/or neuroinvasion?	6.4. List and provide frequency of any related or possibly related serious* AE's as well as any severe, expected or unexpected AE observed: (*see Instructions):	● in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?	8.3 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 intrinsic mutation)?	9.9. What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?	10.9 What is the evidence that vector derived vaccines will generate a beneficial immune response in:	11.4. List and provide frequency of any related or possibly related serious* AE's as well as any severe, expected or unexpected AE observed: (*see Instructions)	● in any other special populations (e.g., institutionalized population, individuals with associated chronic comorbidity)?	
		●In healthy human host	4.4. Is the vector replication-competent in non-human species?	5.9 What is the evidence that vector derived vaccines will generate a beneficial immune response in:	6.5. List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control group:	7.3. What is the potential for shedding and transmission in risk groups?	8.4 What sections of the population are most affected by the target pathogen (e.g. pediatric, pregnant, lactating women (breast feeding), adult, elderly)	9.10. Is the vaccine genetically stable in vitro and/or in vivo?	● Small animal models?	11.5. List and provide frequency of any serious, unexpected significantly increased AE or lab abnormality in vaccinee vs. control group:	12.3. What is the potential for shedding and transmission in risk groups?	
		● In immunocompromised humans	4.5. What is the risk of reversion to virulence, recombination or reassortment with wild type virus or other agents?	●Small animal models?	●Describe the control group:	●Nonhuman primates (NHP)?	8.5 What is known about the immune responses, duration, and potential correlates of protective immunity to the target pathogen or to the disease?	9.11. What is the potential for shedding and transmission to humans or other species?	● Nonhuman primates (NHP)?	● Describe the control group		
		● In breast milk, human neonates, infants, children	4.6 Is the vector genetically stable in vitro and/or in vivo?	● Nonhuman primates (NHP)?	6.6. List and provide frequency of Adverse Events of Special Interest		8.6 Please describe any other key information about the target pathogen or population that may inform benefit-risk	9.12. Does the vaccine establish a latent or persistent infection?	● Human?	11.6. List and provide frequency of Adverse Events of Special Interest		
		●During pregnancy and in the unborn in humans	4.7. What is the potential for shedding and transmission,	●Human?	6.7. Did a Data Safety Monitoring			9.13. Does the vaccine replicate in the nucleus?	10.10. Have challenge or efficacy studies been conducted in subjects	11.7. Did a Data Safety Monitoring		

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 the 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 the Vaccine**	**13. Any other information concerning either the viral vector or the vaccine**
			including arthropod borne transmission, to humans or other species?		Board (DSMB) or its equivalent oversee the study?				with:	Board (DSMB) or its equivalent oversee the study?		
		● In any other special populations?	4.8. Does the vector establish a latent or persistent infection?	5.10. Have challenge or efficacy studies been conducted in subjects with:	● Did it identify any safety issue of concern?			9.14. What is the risk of integration into the human genome?	● Immunocompromised conditions including HIV?	● Did it identify any safety issue of concern?		
		3.8. What cell types are infected and what receptors are used in the natural host and in humans?	4.9. Does the vector replicate in the nucleus?	● Immunocompromised conditions including HIV?	● If so describe:			9.15. List any disease manifestations caused by the vaccine in humans, the strength of evidence, severity, and duration of disease for the following categories:	●Other diseases?	● If so describe:		
		3.9. What is known about the mechanisms of immunity to the wild type virus?	4.10. What is the risk of integration into the human genome?	●Other diseases?				● In healthy people	10.11 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes? Is there evidence for interaction/ interference?			
		3.10 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the wild type virus:	4.11. Is there any previous human experience with this or a similar vector (safety and immunogenicity records)?	5.11 Have studies been done simultaneously or sequentially administering more than one vector with different transgenes? Is there evidence for interaction/ interference?				●In immunocompromised people				
		● in vitro?	4.12. What cell types are infected and what receptors are used in humans?					●In breast milk, neonates, infants, children				
		● in animal models?	4.13. What is known about the mechanisms of immunity to the vector?					● During pregnancy and in the fetus				
		● in human hosts?	4.14 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vector?					●In any other special populations				
		3.11 Is disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory	● in vitro?					9.16. What cell types are infected and what receptors are used in humans?				

(*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 (Pharmacology) of the Vector**	**6. Adverse Event (AE) Assessment of the Vector (*see Instructions):**	**7. Overall Risk Assessment of the 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 the Vaccine**	**13. Any other information concerning either the viral vector or the vaccine**
		disease (VAERD)) a possible vaccine-induced contributor to the pathogenesis of wild type disease										
		3.12 What is the background prevalence of natural immunity to the virus?	● in animal models?					9.17. What is known about the mechanisms of immunity to the vaccine?				
		3.13 Is there any vaccine available for the wild-type virus? If yes,	● in human hosts?					9.18 Has disease enhancement (including antibody dependent enhancement (ADE), vaccine associated enhanced respiratory disease (VAERD)) been demonstrated with the vaccine?				
		● What populations are immunized?	4.15. Is there antiviral treatment available for disease manifestations caused by the vector?					● in vitro?				
		● What is the background prevalence of artificial immunity?	4.16. Can the vector accommodate multigenic inserts or will several vectors be required for multigenic vaccines?					● in animal models?				
		3.14 Is there treatment available for the disease caused by the wild type virus						● in human hosts?				
								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?				
								9.20. Is the vaccine transmissible in humans or other species (including arthropods) and/or stable in the environment?				
								9.21. Are there antiviral or other treatments available for disease manifestations caused by the vaccine?				
								9.22. Vaccine formulation				

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 the 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 the Vaccine**	**13. Any other information concerning either the viral vector or the vaccine**
								9.23. Proposed route 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.)				

'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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