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| **Standardized Template Revision**  |
| The Brighton Collaboration (www.brightoncollaboration.us) 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 our 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 (2). Chief among the goals of the V3SWG has been the development of a standardized template describing the key characteristics of novel viral vaccine vectors, to facilitate the scientific discourse among key stakeholders and increase the transparency and comparability of information. In 2020, spurred by the SARS-C0V-2 pandemic, the mission of the V3SWG was expanded to include templates for other vaccine platforms including nucleic acid, protein, inactivated whole virus, and live attenuated viral vaccines. To reflect this expanded mission, V3SWG was renamed to the Benefit-Risk Assessment of VAccines by TechnolOgy (BRAVATO) Working Group (3).Development of a standardized template is an evolving process and has to date resulted in three distinct versions of the viral vector vaccine template. To distinguish template versions now and in the future, we use integers to indicate major version changes and decimals to indicate incremental updates, as in software nomenclature. Currently three versions of the template exist: v1.0, v2.0 and v3.0, detailed below. |
| **v1.0** |
| In 2015, the V3SWG published the v1.0 of the vector template, completed with a description of the yellow fever 17D vaccine vector (4-5), which has been used for construction of recombinant vaccines for Japanese encephalitis (6) and Dengue fever (7). v1.0 of the template was also used to describe a vesicular stomatitis virus (VSV) based vector (8) and a VSV-based Ebola vaccine, rVSVΔG-ZEBOV-GP (9), which was used successfully in a ring vaccination trial in Guinea (10).  |
| **v2.0** |
| Experience accumulated during completion of v1.0 of the template revealed that modifications to the template could improve its utility. Fundamental to the template revision was the recognition that a thorough understanding of safety issues associated with vectored vaccine requires a clear understanding of the characteristics of the wild type virus from which the vector is derived, the vector itself, and the vaccine(s) constructed using the vector platform. Depending on the vector or vaccine(s) under consideration, each of these components may exhibit different biological properties; therefore the generic template is constructed to embrace a broad spectrum of possibilities. v2.0 of the template thus contains separate sections devoted to each of the components: wild type virus, the vector, and vaccine(s) based on the vector. The revised template retains a focus on the vector. Because multiple vaccines with different properties may be constructed based on a single vector, the vaccine(s) section of the template may contain some generalities while the vector section (and the wild type virus section) are more specific. v2.0 of the template revision also deletes two sections from the original template, specifically “Manufacturing” and “Previous Human Use”. The rationale for these changes is that manufacturing is a post-licensing issue beyond the scope of the template, and relevant issues associated with previous human use are incorporated into other sections of the revised template. Lastly, the sections “Adverse Event Assessment of the Vector” and “Overall Risk Assessment of the Vector” have been updated to comprise a broad assessment of adverse events and overall risk consistent with existing tools for making these assessments.v2.0 of the template was used to describe an Adenovirus type 4 vector (submitted). v2.0 has also been used to describe an MVA vector (MVA-BN), an Adenovirus 26 vector, and a vaccine regimen combining both adenovirus and MVA vectored Ebola antigens (personal communication). |
| **V3.0** |
| v3.0 of the template specifically expands the purpose of the template from vector-centric to “dual use”, that is, it can be used to describe either a viral vector alone or a vectored vaccine. This expanded purpose is accomplished by dividing the template into separate “Parts”, “Part I: Viral Vector”, and “Part II: Vaccine”, which deal individually with the vector alone or a vaccine. Each part contains its own sections covering Toxicity and Potency, Adverse Effects, and Overall Assessment. In addition, Part 2, describing vaccines, now includes a section on the “Target Pathogen”. Numerous other incremental improvements were made to individual sections to harmonize the viral vector template with templates for other vaccine platforms being developed concurrently. |

**References:**

1) Bonhoeffer J, Kohl K, Chen R, Duclos P, Heijbel H, Heininger U, Jefferson T, Loupi E. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI). Vaccine. 2002 Dec 13;21(3-4):298-302. PubMed PMID: 12450705. Link: https://doi.org/10.1016/S0264-410X(02)00449-8

2) Chen RT, Carbery B, Mac L, Berns KI, Chapman L, Condit RC, Excler JL, Gurwith M, Hendry M, Khan AS, Khuri-Bulos N, Klug B, Robertson JS, Seligman SJ, Sheets R,Williamson AL; V3SWG. The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG). Vaccine. 2015 Jan 1;33(1):73-5. Link: <https://doi:10.1016/j.vaccine.2014.09.035>.

3) Chen RT, Kochhar S, Condit RC The Brighton Collaboration standardized templates for collection of key information for benefit-risk assessment of vaccines by technology (BRAVATO; formerly V3SWG). Vaccine. Submitted.

4) Monath TP, Seligman SJ, Robertson JS, Guy B, Hayes EB, Condit RC, Excler JL, Mac LM, Carbery B, Chen RT; Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG). Live virus Live virus vaccines based on a yellow fever vaccine backbone: standardized template with key considerations for a risk/benefit assessment. Vaccine. 2015;33:62-72.

5) Monath TP, McCarthy K, Bedford P, Johnson CT, Nichols R, Yoksan S, et al. Clinical proof of principle for ChimeriVax: recombinant live, attenuated vaccines against flavivirus infections. Vaccine 2002;20:1004–18

6) Appaiahgari MB, Vrati S. Clinical development of IMOJEV (R) – a recombinant Japanese encephalitis chimeric vaccine (JE-CV). Expert Opin Biol Ther 2012;12:1251–63

7) Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, Chua MN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet 2014.

8) Clarke DK, Hendry RM, Singh V, Rose JK, Seligman SJ, Klug B, Kochhar S, Mac LM, Carbery B, Chen RT; Brighton Collaboration Viral Vector Vaccines Safety Working Group. Live virus vaccines based on a vesicular stomatitis virus (VSV) backbone: Standardized template with key considerations for a risk/benefit assessment. Vaccine. 2016 Dec 12;34(51):6597-6609. doi: 10.1016/j.vaccine.2016.06.071. Epub 2016 Jul 6. Review.

9) Monath TP, Fast PE, Modjarrad K, Clarke DK, Martin BK, Fusco J, Nichols R, Heppner DG, Simon JK, Dubey S, Troth SP, Wolf J, Singh V, Coller BA, Robertson JS; Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG). rVSVΔG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment. Vaccine X. 2019 Jan 29;1:100009. doi: 10.1016/j.jvacx.2019.100009. eCollection 2019 Apr 11.

10) Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, Carroll MW, Dean NE, Diatta I, Doumbia M, Draguez B, Duraffour S, Enwere G, Grais R, Gunther S, Gsell PS, Hossmann S, Watle SV, Kondé MK, Kéïta S, Kone S, Kuisma E, Levine MM, Mandal S, Mauget T, Norheim G, Riveros X, Soumah A, Trelle S, Vicari AS, Røttingen JA, Kieny MP. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017 Feb 4;389(10068):505-518. doi: 10.1016/S0140-6736(16)32621-6. Epub 2016 Dec 23. Erratum in: Lancet. 2017 Feb 4;389(10068):504. Lancet. 2017 Feb 4;389(10068):504.