ChAdOx1 Template

Brighton Collaboration Reviewer's Comments

From BC Collated Spreadsheet:

Do you agree with all parts of Section 2. Basic Vaccine Information?

#1 You can add more information

Not sure what else is required or what exactly is missing.

Do you agree with all parts of Section 4. Characteristics of the vector from which vaccine(s) may be derived?

#1 Does not describe the risk with HIV patient. As there is a theoretical risk with them. Due to the reverse transcriptase enzyme.

The theoretical risks of host genome integration with mRNA vaccines and retrovirus recombination does not apply to Adenoviral vectored vaccines (DNA virus). Theoretical risks of HIV enhancement associated with Ad vectored vaccines are covered in section 3.10

Do you agree with all parts of Section 5. Characteristics of vector-based vaccine(s)?

#1 Does not describe the risk with HIV patient. As there is a theoretical risk with them. Due to the reverse transcriptase enzyme.

As above

Do you agree with all parts of Section 6. Toxicology and potency (Pharmacology) of the vector?

#1 Like to know more about reproductive toxicology

Added a comment on section 6.5 that reads: 'See reference for further details'

Do you agree with all parts of Section 7. Adverse Event (AE) Assessment of the Vector?

#1 It should cope more clinical entities.

What particular clinical entities do you find missing. Please clarify.

#2 Dose not describe the risk of GBS

GBS previously covered under demyelination disorder, but reworded now so it explicitly reads GBS

#3 The section lists ONLY the adverse events for ChAdOx-1. A more detailed summary for others would have been useful.

This is a ChAdOx1 template, and not a general adenoviral vector one.

Do you agree with all parts of Section 8. Overall Risk Assessment of the Vector?

#1 In Section 8.1 Comments - This sentence is misleading "Rates for thrombotic events following SARSCoV-2 infection are far higher than amongst those vaccinated." TTS and all thrombotic events are different types of events and this kind of comment seems defensive and also invites and implies conclusions that are not appropriate. The overarching issue is one of overall Benefit Risk - the harms

of TTS weighed against severe COVID and death prevented. Overwhelming evidence now points to TTS being a distinct vaccine induced phenomenon completely distinct from common thromboses or COVID related thromboses.

Statement replaced with a sentence on benefits of protection against severe COVID-19 and death outweighing risks of vaccine induced TTS.

Section 8.1 Summary of Safety Issues - Need to include Guillain Barre and Capillary Leak Syndrome as warnings in the EMA Label (CLS is actually mentioned later in Section 8 but is ommitted in the first part of Section 8.1). These are the conclusions from public health bodies and need to be included here. They are included in the introduction and this section needs to be consistent.

Added a statement now for clarity, although GBS was already covered under the previous statement on demyelination disorders.

In general we should be consistent with the major Labels (FDA and EMA) over the company core safety information if they disagree. In the template, we can say explicitly that Guillain Barre and TTS are Warnings in the EMA Label.

#2 Does not describe the risk of GBS

GBS previously covered under demyelination disorder, but reworded now so it explicitly reads GBS

#3 This is a very technical paper that most readers will not be able to "read thru" and understand appreciate, yet important . Perhaps a more simplified overview would be helpful for the many readers who need the information but not be able to appreciate the technologies/information as presented.

This is meant to be a technical paper.

<u>From emails:</u>

#1 I have carefully reviewed the article and the risk tables. I agree with Denny's comment. What I find missing after the tables is a Conclusion statement and verbal discussion on the current state for benefit risks and a statement that the benefit risk could be updated after the CADOX1 is fully approved.

Added a conclusion statement now after the template.

#2.1 I think the summaries of trials would be more useful if dose was indicated. The reactogenicity is very dose-dependent. For the Covid vaccine, the endpoint should be mentioned when an efficacy number is quoted.

Doses and endpoint added to preamble. Section 5.5 describes reactogenicity profile as dose-dependent.

#2.2 p. 8 the immunogenicity of ChAdY25 was shown to be equivalent to that of ChAd63 and AdC68 in both single dose and heterologous prime-boost vaccine regimens. -- does this mean immune responses against Ad or against inserted proteins of interest?

Against the antigen of interest. Minor edit to text included for clarity.

#2.3 In the table, there's a box that starts with 'furthermore'. What does this relate to?

This comment is from section 5.19 of the template. 'Furthermore' relates to the information in addition to what was already included in section 4.13. Deleted the term for clarity.

From the paper:

Age / gender specificity of TTS and GBS could be included - if available from ACIP - Bennett Levitan Aug 10th

Initial gender differences have been dismissed as relevant from most recent PRAC assessments. Here is the statement from the safety update published on EMA website dated from 8th Sep 2021: In September 2021, PRAC concluded to further update the product information by removing the current statement that reported TTS cases occurred mostly in women under 60 years of age, since the age and sex imbalance seemed smaller than previously observed.

The ACIP meetings had rates of TTS and GBS observed post approval. Seems appropriate to include those estimates in this template - Bennett Levitan Aug 10th

Estimates have significantly changed over time as we gather more data, moving from initial 1:100,000 to 8 cases per million vaccine doses. The latest PRAC assessment from 6th October reads: The frequency category (for TTS) will be 'unknown frequency' because it is generally difficult to robustly estimate side effect frequencies from cases of suspected side effects that have been reported spontaneously by healthcare professionals.

Need for anti-PF4 testing and avoiding heparin use should be included - this serves as a mitigation measure that reduces the frequency of TTS - Bennett Levitan Aug 10th

These are measures that would aid TTS diagnosis and management but won't reduce the frequency of TTS. Widespread anti-PF4 testing is impractical.

Would add mention of GBS here, especially since GBS was addressed at an ACIP meeting - Bennett Levitan Aug 10th

GBS previously covered under demyelination disorder, but reworded now so it explicitly reads GBS