COMMISSION ON HUMAN MEDICINES (CHM)
COVID-19 VACCINES BENEFIT RISK EXPERT WORKING GROUP

Minutes of the meeting held on **Friday 10th September 2021** at **10:30** via videoconference

Participants Present

Members

Professor Sir M Pirmohamed (Chair)
Professor J Breuer
Mr VI G Fenton-May
Professor N French
Professor D Goldblatt[1]
Ms S Hunneyball
Professor K Hyrich
Sir M Jacobs
Dr S Misbah
Professor Y Perrie
Professor S Price
Dr A Riordan[2]
Professor C Robertson[1]
Professor T Solomon[3]
Professor K M G Taylor
Dr R Thorpe
Professor M Turner
Professor S Walsh
Mrs M Wang

Apologies

Professor G Dougan
Professor H J Lachmann
Professor P J Lehner
Mr R Lowe
Professor C Weir

Visiting Experts[4]

[redacted]

Observers

[redacted]

Secretariat

[redacted]

Professional Staff of MHRA Present

Principal Assessors

Dr J Bonnerjea - LD
[redacted] - VRMM

Presenters supporting specific items[5]

[redacted] - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - VRMM
[redacted] - LD

MHRA Observers

Dr S Branch - VRMM
[redacted] - VRMM
[redacted] – MHRA Policy
[redacted] - VRMM
[redacted] – VRMM
[redacted] – Comms
[redacted] – LD
[redacted] - LD
[redacted] - VRMM
Mr P Tregunno - VRMM
[redacted] - LD
[redacted] - VRMM
[redacted] - LD

Key
LD = Licensing Division
VRMM = Vigilance & Risk Management of Medicines
NIBSC = National Institute for Biological Standards & Control

[1] joined during item 2
[2] joined during item 4
[3] left after item 3
[4] particpated for item 2 only
[5] supported specific items

[redacted]

25th August 2022

1. Introduction and Announcement

1.1 The Chair reminded Members, invited Experts and observers that the content of papers and proceeding of the meeting are strictly confidential and should be treated as 'Official – sensitive commercial' and should not be disclosed. There is no consent for members / participants to record the meeting, take screenshots or photographs of presentations. The meeting was recorded by the MHRA Secretariat for minute taking purposes only. The Chair & Members including all participants gave full consent to the recording prior to the start of the meeting.

1.2 Conflict of Interest Policy (Annex I to the minutes)

The Chair reminded members and participants that, in accordance with the CHM Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members were also reminded to declare any other matter which could reasonably be perceived as affecting their impartiality.

1.3 Participants declared interests and other relevant interests for this meeting listed at **Annex II** to the minutes.

1.4 Apologies were received from Professors Dougan, Lachmann, Lehner, Weir and Mr Lowe for this meeting.

1.5 The Chair welcomed the following visiting experts:

[redacted] ONS

[redacted] Office for National Statistics

[redacted] Population Health

[redacted] ONS

1.6 The Chair welcomed the following observers:

[redacted] Public Health Wales

[redacted]
NHS England Medical [redacted]

[redacted]
Public Health England

[redacted]
NHS England and NHS Improvement (National)

2. Vaccine effective analysis – presentation from ONS

2.1 The EWG were presented with vaccine effectiveness (VE) and post-vaccination mortality data collated by the Office for National Statistics.

2.2 Question and Answer

The EWG mentioned that according to data from Israel (data not subject of ONS presentation) immunity in individuals vaccinated in January 2021 is beginning to wane, and noted the data presented by the ONS on vaccine effectiveness (VE) only covers 5 months. The EWG considered that this was perhaps too short a duration to detect considerable waning of vaccine induced immune responses. The invited expert confirmed that data collection and monitoring is continuing, and future analysis should help to determine the manner in which immunity wanes over time.

2.3 The EWG heard that from the data it is difficult to establish VE in those with prior COVID-19 infection in a strain specific manner due to limitations of the current data set.

2.4 The EWG heard that in collaboration with the ONS COVID-19 survey, a group from University of Manchester is analysing data on household transmission, but the data are reported on a monthly schedule, and this is a limitation when attempting to map household transmission. The EWG heard of studies that show, even, in hospitalised patients that the vaccinated reach viral clearance faster, than the unvaccinated.

2.5 The EWG noted waning immunity of the ChadOx1 nCoV-19 vaccine was the focus of a paper in the Lancet.

2.6 The EWG heard the separate models are currently being used to evaluate differential immunity to the vaccines and mentioned how these models are confounded by factors such as age group, co-morbidities, time of infection, and prior COVID-19 infection. The invited expert confirmed that the intention of their group is to generate a complex single model to improve confidence in their future analyses and to reduce confounding.

2.7 The EWG noted that the biological basis of COVID-19 protection waning is difficult to interpret. Data from Oxford were discussed as an example wherein homologous vaccination showed a Pfizer schedule to induce a 10-fold increase of antibodies compared to that induced by a homologous ChadOx1 nCoV-19 schedule. However, the consequence of this difference and how it correlates to protection against COVID-19 or COVID-19 hospitalisations is uncertain, partly due to the complexity of the humoral and cellular immune responses.

2.8 The EWG heard from the invited experts that the ONS are open to receive comments and suggestions on modes of analysis, statistical tests and so on, from members of the EWG. The invited experts also gave consent for their presentation to be shared with the MHRA.

2.9 In closing the item, the EWG heard from the perspective of the invited experts, that as data coverage increases, analyses by disease area, and analyses that consider concomitant medicine/s are expected to become feasible.

3. Deafness and Tinnitus with COVID-19 Vaccines

3.1 The EWG was presented with a review of the currently available evidence regarding deafness and tinnitus in association with the COVID-19 vaccines currently deployed in the UK (AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines). The EWG considered mechanistic, clinical trial and Yellow Card data (with a data lock point of 12 August 2021) as well as relevant published literature and data from the Yellow Card Vaccine Monitor.

3.2 The EWG noted that the EMA had recently updated the Janssen COVID-19 vaccine product information to add tinnitus & dizziness as suspected adverse reactions and that Janssen were planning to submit these changes for this vaccine (which is not yet deployed for use in the UK) to the MHRA via the reliance route. The EWG was informed that the Janssen submission to update the product information would be presented to the EWG when available and would include information on the basis for the updates to the product information.

3.3 The EWG agreed that the currently available data do not confirm an increased risk of hearing impairment following COVID-19 vaccination with the Pfizer, AstraZeneca and Moderna products deployed in the UK. The number of Yellow Card reports of tinnitus and deafness following administration of these COVID-19 vaccines was low in the context of the usage of these vaccines, and that the reporting rates following vaccination were lower than the background rates of these conditions.

3.4 The EWG supported the proposal that the companies should explore opportunities to investigate this potential signal in appropriately designed studies. The EWG noted that company reviews of hearing impairment were pending for AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines and that, once available, these reviews would be presented at a future EWG meeting. The EWG also noted that the MHRA was seeking input from UK ENT specialists to inform the future EWG consideration of this issue.

3.5 The EWG advised that no causal association between deafness and tinnitus and COVID-19 vaccination had been identified and no regulatory action was required at the present time. The EWG recommended that hearing impairment should be kept under review for AstraZeneca, Pfizer-BioNTech and Moderna COVID-19 vaccines.

4. Sixth update of myocarditis and pericarditis following administration of COVID-19 vaccines

4.1 The EWG were presented with an update on reports of myocarditis and pericarditis following administration of the Pfizer/BioNTech, Moderna and AstraZeneca COVID-19 vaccines, company data on the Janssen COVID-19 vaccine and all new international data.

4.2 The EWG were informed that for the Pfizer/BioNTech vaccine, the reporting rates were similar between the first and second doses in adults. For the under 18 years age group, the reporting rate is higher following the second dose, however this is based on limited exposure in this age group. For the Moderna vaccine, the reporting rates have remained highest in the 18-39-years age group, with higher rates following the second dose. The reporting rates for Moderna have remained higher than those for the Pfizer/BioNTech vaccine. For the AstraZeneca vaccine, the reporting rates have remained lower than for the mRNA vaccines.

4.3 The EWG were presented with company data for the Janssen COVID-19 vaccine. The company observed vs expected analysis showed disproportionality in males aged 18-29-years, however the analysis was based on a small number of reports and a low overall

reporting rate. The EWG considered the available data did not support a signal of myocarditis and pericarditis with the Janssen COVID-19 vaccine.

4.4 The EWG were presented an updated analysis from the US, with the vaccine adverse event reporting system (VAERS) showing a continued trend to more frequent reporting in males following the second dose with mRNA COVID-19 vaccines, with observed vs expected analysis showing a higher than expected number of cases in females aged 12-19-years and males aged 12-49-years. The EWG were informed that the US hospital data had shown the risk of myocarditis following COVID infection to be 6-34 times higher compared to mRNA vaccination.

4.5 The EWG were presented a pre-print paper[1] which conducted a harm-benefit assessment and showed an increased incidence of hospitalisation from myocarditis following administration of mRNA vaccines compared to COVID infection in adolescent age groups. The EWG considered that hospitalisation was not an appropriate measure for the harm-benefit analysis as healthcare professionals were likely to undertake further investigations as a precaution for myocarditis whereas hospitalisation for COVID only occurs for serious cases.

4.6 The EWG discussed the potential of myocarditis occurring again if patients went on to receive another dose of COVID-19 vaccine and concluded that further data should be collected on rechallenge. The EWG concluded that no further regulatory action was required at this time as the benefit:risk of COVID 19 vaccines remained unchanged; however the signal of myocarditis and pericarditis should continue to be closely monitored.

5. Update on amendments to the AstraZeneca EU SmPC to include GBS

5.1 The EWG were presented with an updated company review of re-assessed GBS cases using the Brighton collaboration criteria (BCC) 1-4. The EWG heard that the company had convened a panel to re-assess all cases of GBS, following which a number of reports were downgraded and no cases were considered probable or possible. Furthermore, no case reports from the literature were included in the company's report.

5.2 The EWG heard that the PRAC Rapporteur considered that the MAH was too stringent in its case assessment and that too many cases were categorised as unrelated due to confounders. Furthermore, a literature search by the EMA retrieved 27 cases where a causal association should be considered at least a reasonable possibility. The EWG endorsed the overall conclusions of the PRAC rapporteur.

5.3 The EWG was presented with a proposal to bring the GB product information (PI) in line with the EU PI with regards to GBS warnings. The proposed PI updates related to section 4.8 of the SmPC and section 2 and 4 of the PIL.

5.4 The EWG discussed concerns around potential recurrence of GBS where a patient experienced GBS after the first dose. The current advice is that individuals with a history of GBS should receive the vaccine and individuals who experienced GBS after the 1st dose

[1] published in the European Journal of Clinical Investigation. Krug A, Stevenson J, Høeg TB. BNT162b2 vaccine-associated Myo/pericarditis in adolescents: a stratified risk-benefit analysis. Eur J Clin Invest. 2022;52:e13759. doi:10.1111/eci.13759 https://onlinelibrary.wiley.com/doi/10.1111/eci.13759

(note original preprint link as title of paper changed between preprint and publication: https://www.medrxiv.org/content/10.1101/2021.08.30.21262866v2)

should receive a second dose as the risk of recurrence was low. The EWG supported the inclusion in the PIL of a recommendation for patients to speak to their doctor, pharmacist or nurse if they previously had GBS after being given AZ vaccine, in line with the EU PI.

5.5 The EWG endorsed all other proposed PI amendments.

6. A single-blind, randomised, Phase II multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules in adolescents (COMCOV-3)

6.1 COMCOV3 is a single-blind, randomised, phase II multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules in adolescents. All trial participants (12-16 years of age) will receive the Pfizer BioNTech COVID-19 vaccine as prime vaccine. The boost vaccine will be administered after eight weeks; participants will be randomised 1:1:1:1 to receive one of the following: Pfizer BioNTech COVID-19 vaccine full dose, Pfizer BioNTech COVID-19 vaccine half-dose, Novavax NVXCoV2373 vaccine full dose, Novavax NVXCoV2373 vaccine half-dose.

6.2 The trial has been designed to collect data that may inform JCVI decision regarding vaccination in the trial population. Since the main concern of using the Pfizer vaccine in younger subjects is the potential risk of myocarditis, reactogenicity has been chosen as a surrogate for the primary endpoint. The trial is a descriptive trial aimed at generating data with good accuracy in a timely manner.

6.3 The Clinical Trials and Biologicals and Vaccines Expert Advisory Group, Infectious Expert Advisory Group and the Paediatric Medicines Expert Advisory Group recommended approval of the trial following written comments. Upon review the Vaccine EWG also recommended that the trial was approved.

7. ACCESS Consortium: Alignment with ICMRA consensus on immunobridging for authorizing new COVID-19 vaccines

7.1 The EWG heard the ACCESS consortium is a coalition of medium-sized international regulatory authorities that work together to promote greater regulatory collaboration and alignment of regulatory requirements. The consortium was recently convened to discuss the data required to support applications for future novel COVID-19 vaccines. The Consortium (including those representing the Agency) supported use of immuno-bridging studies in place of placebo-controlled, or comparator-controlled efficacy trials, dependent on a number of provisos being fulfilled, as defined here. In short, the Consortium reached this position based on difficulties envisaged with recruitment to future trials, limitations that could prevent clinically meaningful interpretations of the results of such trials, and the suitability of cross-reference to other methods of data collection. And, of particular importance, the Access Consortium considered that the weight of evidence from studies with authorised COVID-19 vaccines is sufficient to support using neutralising antibody titres as a primary endpoint in cross-platform immunobridging trials.

7.2 The EWG was encouraged by the steps taken toward an aligned regulatory approach for authorising novel COVID-19 vaccines and backed the regulators intentions to allow use of cross vaccine platform immunobridging to support for a potential regulatory approval.

7.3 The EWG noted the ACCESS Consortium statement chiefly discusses neutralising antibodies and discussed the potential limitations of adopting such an approach. i) neutralising antibodies are difficult to measure, ii) cross-lab standardisation of assay methods is not yet commonplace, and iii) carries issues with the common frame of reference, the WHO standard

sera isolated from convalescent patients early in the pandemic, has strong neutralising activity against WT virus, but activity is somewhat diminished against alpha, beta, delta, and gamma (>10 fold decrease) and very low against lambda and mu SARS-CoV-2 variants. However, the EWG noted that pseudoviral assays are less affected, as they can be modified to evaluate the various variants of concern (VOC).

7.4 The EWG discussed that regulators should consider the value of binding antibodies in regulatory guidance. Research groups have evaluated the relationship between neutralising and binding antibodies and the differential activities on spike (S) protein, receptor binding domain RBD and other sites on the virus. One study showed that binding antibodies to S protein correlated more strongly with vaccine efficacy. The EWG mentioned pneumococcal conjugate vaccines, where since 2009 efficacy assessment has been guided by a threshold above a correlate of protection—one that considers both neutralising and binding antibodies.

7.5 The EWG noted that analysing geometric mean titers (GMT) of neutralising antibody is perhaps unlikely to produce a reliable comparison of COVID-19 vaccines efficacy. This may be improved by using a correlate of protection that is based on a threshold level of binding or neutralising antibodies.

7.6 An early manuscript by Plotkin et al[2] covers the topic of a threshold of binding antibody to WT spike. The EWG noted that further data and evaluation by other research groups or organisations will be required to see if other groups arrive at the same value, or if the threshold needs to be adjusted. Current data show that the threshold will need to be elevated to reflect VE against cases caused by variants of concern. Until such data is available, a threshold of 60 binding antibody units (BAU) per ml antibody, could be included in studies as an exploratory end-point.

7.7 The EWG noted that, aside from humoral immunity— as evidence mounts to suggest a significant role of T-cell activation and behaviour in curtailing disease progression—measuring cellular responses to the vaccine is becoming of increasing importance. The EWG noted to enable robust evaluation of cellular responses to the vaccine, further steps toward standardisation of assays are necessary.

7.8 The EWG heard that further discussions on the topics of assays, assay standardisation, and data requirements are on-going, and these include discussions with WHO and other competent authorities.

8. Any Other Business

8.1 Verbal update on the final booster PI updates and conditions following CHM

8.1.1 The EWG heard an update of the CHM meeting of 6h September 2021 where the Commissioners had considered homologous and heterologous boosters.

8.1.2 During this meeting Commissioners had discussed data from the COV-Boost study. Commissioners supported:

- homologous boosters for Pfizer and AZ vaccines.
- heterologous booster AZ followed by a third (booster dose) of Pfizer.
- Pfizer after Moderna primary immunisation – *extrapolation of the data was considered suitable due to the similarity of the vaccines.*

[2] Post-Meeting update: study was peer-reviewed and published: *Vaccine* doi: 10.1016/j.vaccine.2021.05.063

- concomitant administration of AZ or Pfizer vaccines with influenza (flu) vaccines from the 2020/21 flu season programme, as there is no notable consequence/s seen to immunogenicity, and reactogenicity was also shown to be similar. This decision was reached based on data from ComFluCOV study.

8.1.3 Commissioners also considered that:

- Due to concerns over inferior immune responses (primarily the antibody response), increased comparative reactogenicity, and the risk of TTS, the CHM could not approve the use of AZ vaccine following Pfizer primary immunisation.

- The COV-Boost data on use of a half dose of Pfizer was considered to be promising but did not convince Commissioners that a change to the dose stated in the Regulation 174 Authorisation was necessary.

8.1.4 For information relevant excerpts from Section 4.2 of the COVID-19 Reg 174 Information for HCPs:

Pfizer
One dose of COVID-19 mRNA Vaccine BNT162b2 may be administered as a third dose at least 8 weeks after the second dose of an mRNA or adenovirus-vectored COVID-19 vaccine when the potential benefits outweigh any potential risks.

AstraZeneca
A third dose of COVID 19 Vaccine AstraZeneca may be administered at least 8 weeks after the second dose of COVID 19 Vaccine AstraZeneca when the potential benefits outweigh any potential risks.

Moderna
There are no data available on the interchangeability of Spikevax with other COVID-19 vaccines to complete the vaccination course. Individuals who have received the first dose of Spikevax should receive the second dose of Spikevax to complete the vaccination course.

9. Date and time of next meeting

The next scheduled meeting is to take place on **Friday 17th September** at **14:30**.

The Meeting today started at 10:35 and ended at 13:14.

Members are reminded that the content of papers and proceeding of the meetings are to be treated as 'Official – sensitive commercial'. Members are also reminded that, in accordance with the Code of Practice, they should declare any financial interests (personal or non-personal, specific or non-specific) which they have, or which an immediate family member has, in any of the agenda items. Members must also declare any other matter which could reasonably be perceived as affecting their impartiality. Detailed guidance is set out in the Code of Practice

Annex I

Conflict of Interest Policy for CHM COVID-19 Vaccine Benefit Risk EWG

Chair and Members

- May not hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May not currently be or have previously been involved in the development of COVID-19 vaccines

Invited to all meetings, receives all papers and presentations and is permitted full participation in discussion, including drawing up conclusions and recommendations

Invited experts

- May hold current personal interests in one or more companies associated with the development of COVID-19 vaccines
- May currently be or have previously been involved in the development of COVID-19 vaccines

May be invited to all relevant meetings, receives all papers and presentations and is permitted to participate in discussions when invited by the Chair. Does not contribute to conclusions and recommendations

Observers

Are invited to attend all meetings. Will not participate in drawing up conclusions and recommendations.

Annex II

The following participants declared interests and other relevant interests at the meeting today:

Professor Sir Munir Pirmohamed - NPNS AstraZeneca - Research grant to UOL to support PhD in drug interactions.
Other relevant interests in Pfizer, Janssen, Sanofi – Sir Munir is part of an EU-funded IMI consortium on gene therapy, and these companies are partners in the project. The University of Liverpool will get funding from the EU (but not from the partners), this IMI project commences on 3rd November 2020.
AGILE – this is a Liverpool early phase trial platform (between University of Liverpool and Liverpool School of Tropical Medicine). It is funded by the Wellcome Trust and UKRI/DHSC/NIHR. It is NOT evaluating vaccines, but only drugs to treat COVID-19. Sir Munir is not on the trial management group, and he is not directly involved in choosing the compounds for the study. Sir Munir has no involvement with any of the developers of the compounds to be studied (academic or industrial).
Sir Munir is a member of the UK COVID Therapeutics Advisory Panel (UK-CTAP), which is advising the CMO on which compounds need to be prioritised for the RECOVERY+ trial (RECOVERY is funded via NIHR/DHSC).

Professor Breuer– NPNS – Professor Breuer is on the data safety monitoring committee, DSMB, a study looking at combining vaccines being run by Matthew Snape in Oxford. There does not appear to be any involvement of the vaccine manufacturers and is for already licensed vaccines. The study is funded by the NIHR (Dec 2020).

Professor French - Other relevant interest - Provides clinical care when in covering the acute medical wards where patients with COVID-19 are cared. NPNS in GSK - In September 2020 a sub-contract was signed with the Liverpool School of Tropical Medicine to undertake work evaluating the safety and effectiveness of GSK's RTS's malaria vaccine in Malawi. GSK are the primary funders to the LSTM.

Ms Hunneyball - Other relevant interest – writes articles published in the Chemist and Druggist magazine, a trade magazine for pharmacists, but receives no payment for these articles. The information referred to in the articles is in the public domain. Ms Hunneyball makes it clear that these are her personal views and reflections and references all sources of information used.

Professor Hyrich – NPNS - Professor Hyrich was co-I on an investigator-initiated research grant exploring predictors of outcome in rheumatoid arthritis. NPNS Pfizer- she is a Co-I on a grant exploring adherence to JAK inhibitors in rheumatoid arthritis. NPNS in Abbvie, Professor Hyrich gave some lectures at an education conference on effectiveness of treatment for rheumatoid arthritis.

Sir Michael Jacobs - Other relevant interest - As part of the academic role at the Liverpool School of Tropical Medicine, Sir Michael is a member of the Study Management Team and antiviral drug prioritisation group for the AGILE proof of concept (phase I/II) platform study. Sir Michael is also part of the team that submits new antiviral compounds against SARS-CoV2 for consideration by NIHR for testing on this platform. No commercial or financial interest in the trial or any of the compounds, or any pharmaceutical or biotechnology company.

Dr Misbah - NPNS - Holds honorary Senior Lectureship with University of Oxford & Oxford University Hospitals NHS Foundation Trust.

Professor Perrie - NPNS in Pfizer & AstraZeneca arising from a contract for a grant (March 2018), which includes contributions from these companies to the University of Strathclyde, Janssen in writing a grant for a PhD (now funded), GSK – arising from an EU grant to University of Strathclyde (Jan 2019-Dec 2019).

Professor Price - NPNS in GSK and AstraZeneca – which relates to donations provided by both companies to the British Toxicology Society (BTS) to support their Annual Congress and Education and Training of which Professor Price is currently President of the Society (2020-2022).

Dr Riordan - Other relevant interests - Participant in Oxford University's ChAdOx1 nCoV-19 clinical trial –received immunisation 27/8/2020. NPNS - Postgraduate External Examiner for Oxford University (Postgraduate Diploma in Paediatric Infectious Diseases). Member of the independent Data Safety Monitoring Board for COV-BOOST trial.

Professor Solomon - Other relevant interests – Professor Solomon provides clinical care for patients with Covid-19; chaired the MRC/NIHR committee which awarded funding for development of the Oxford Vaccine.

Mrs Wang – Other relevant interests arising from being highly sensitive to insect stings, and plant products such as Hyacinth bulbs, as recorded on Mrs Wang's medical records. The family of Mrs Wang lives with several rare diseases and conditions, some of which result in epileptic fits.

Observers

[redacted] - Other relevant interests in Pfizer & GSK- The Immunisation and Countermeasures Division has provided vaccine manufacturers (including Pfizer and GSK) with post-marketing surveillance reports on pneumococcal and meningococcal infection which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. A cost recovery charge is made for these reports.

Australian Government
Department of Health
Therapeutic Goods Administration

Access Consortium: Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines

14 September 2021

Placebo-controlled disease endpoint trial data are the gold standard for authorising vaccines. However, for COVID-19 vaccines, it is difficult to conduct efficacy trials in some countries, as few candidates are willing and available to participate. Without established humoral and/or cellular immune parameters that correlate to clinical protection against disease, other approaches are needed to provide sufficient evidence for authorising new COVID-19 vaccines.

The International Coalition of Medicines Regulatory Authorities (ICMRA) convened a workshop on 24 June 2021 to consider the development (http://www.icmra.info/drupal/en/covid-19/24june2021) of COVID-19 vaccines. The ICMRA focused on immunobridging, the design and use of controlled trials (placebo or other controls) and correlates of protection.

Access Consortium members agree that well-justified and appropriately designed immunobridging studies are an acceptable approach for authorising COVID-19 vaccines.

The Consortium provides additional considerations for cross-platform immunobridging. These include extending previous points of consideration for variant-based vaccines that was limited to currently authorised COVID-19 vaccines (//www.tga.gov.au/points-consider-strain-changes-authorised-covid-19-vaccines-ongoing-sars-cov-2-pandemic).

Consensus positions from the ICMRA meeting relevant to this statement include:

- study designs for pivotal trials to demonstrate the efficacy of COVID-19 vaccines must provide robust data for authorisation
- immunogenicity bridging studies can be used if clinical endpoint efficacy studies are no longer feasible
- study designs can be based on either:
    - non-inferiority immunogenicity if the comparator vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or
    - superiority if the comparator vaccine has demonstrated modest efficacy
- based on the specifics of the product under consideration, neutralising antibody titre may be justified as immune marker to predict vaccine effectiveness
- neutralising antibody titres should be determined using World Health Organization (WHO)-certified reference standards
- other parameters to be justified include:
    - choice of appropriate vaccine comparators considering the platform
    - statistical criteria

    - population comparator groups (for example, matched by age, gender, prior vaccination/infection status)
- applicant support for sharing information between regulators would help build global convergence.

The Access Consortium considers that the weight of evidence from studies with authorised COVID-19 vaccines is sufficient to support using neutralising antibody titres as a primary endpoint in cross-platform immunobridging trials.

Applicants are to provide a clear rationale regarding the:

- suitability of neutralising antibody as a primary endpoint in immunobridging studies, considering data that support the mechanism of action for the candidate vaccine
- proposed comparator and an appropriate design (for example, comparability margin).

The Consortium also recommends that applicants follow WHO standards in neutralisation assays and consult with the relevant authority early in the study process.

Applicants are also to provide the following:

Non-clinical data

As well as common non-clinical requirements for new vaccines (197kb) (https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonc63.pdf?ua=1) and adjuvants (519kb) (https://www.who.int/biologicals/areas/vaccines/ADJUVANTS_Post_ECBS_edited_clean_Guidelines_NCE non-clinical data should include:

- relevant animal challenge studies that support proof of concept for the candidate vaccine and demonstrate effectiveness against variants of concern (VOCs)
- characterisation of comparative immunogenicity profiles, including both antibody- and cell-mediated immunity

Clinical data

Along with a comparison of neutralising antibody titres, clinical data should include:

- characterisation of comparative immunogenicity profiles, including cell-mediated immunity
- characterisation of comparative in vitro neutralisation against VOCs
- safety database of at least 3,000 study participants vaccinated with the dosing regimen intended for authorisation (this is in line with the pre-authorisation safety data requirements for preventive vaccines for infectious diseases)
- commitment for safety and immunogenicity follow-up, for at least 12-months, of the subjects enrolled in safety/immunobridging trials, which would also record descriptive clinical efficacy data
- commitment for post-authorisation effectiveness studies supported with a study protocol considering current WHO guidance (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1)

Applicants are also advised to consult the following:

- Access Consortium Points to consider for strain changes in authorised COVID 19 vaccines in an ongoing SARS-CoV2 pandemic (//www.tga.gov.au/points-consider-strain-changes-authorised-covid-19-vaccines-ongoing-sars-cov-2-pandemic)

Tags: COVID-19 vaccines
URL http //www tga gov au/node/939809 (http //www tga gov au/node/939809)