Drug Safety Research Unit

Post-authorisation active surveillance of the Safety of COVID-19 Vaccine AstraZeneca (AZD-1222) in the UK
A consortium study

[redacted]

Summary Information

Title	Post-authorisation active surveillance of the Safety of COVID-19 Vaccine AstraZeneca (AZD-1222) in the UK A consortium study
Protocol version identifier	1.1
Date of last version of protocol	1.0
Project number	
EU PAS register number	N/A
Active substance	
Medicinal product	
Research question and objectives	Overall aim: To monitor the safety and utilisation of the COVID-19 Vaccine AstraZeneca (AZD-1222) administered to vaccinees under real-world use in the UK Primary objective: • To examine the safety of COVID-19 vaccine AstraZeneca (AZD-1222) through active surveillance of all vaccinee reported adverse events and assessment of incidence. Secondary objectives: • (i) To describe and characterise serious adverse events following vaccination • (ii) To describe and characterise adverse events of special interest (AESI) including AESI relevant to vaccinations in general and AESI relevant to COVID-19 vaccine AstraZeneca (AZD-1222). • (iii) To describe and characterise the utilisation of COVID-19 vaccine AstraZeneca (AZD-1222) in the cohort, including vaccination site, demographics of vaccinee and brand/batch of vaccine administered. • (iv) To examine use and safety in populations with missing information including pregnant and breastfeeding women and individuals with

	immunodeficiency disorders, treatment with immunosuppressants, concurrent medical conditions, and administration of other vaccines within previous 30 days. Quality of Life sub-study objective • (i) To describe and characterise health-related quality of life among a sub-population (n=3500) vaccinated by COVID-19 vaccine AZD1222 and to describe the effect of the COVID-19 vaccine AstraZeneca (AZD-1222) on participant's lifestyle and productivity where affected by the COVID-19 pandemic.
Country of surveillance	UK
Contact author	[redacted] [redacted] DSRU Bursledon Hall Blundell Lane Southampton SO31 1AA UK

Marketing authorisation holder(s)

Marketing authorisation holder(s)	
MAH contact person	

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2 List of Abbreviations

Abbreviation	Term
AE	Adverse Event
AEFI	Adverse event following immunisation
AESI	Adverse event of special interest
A and E	Accident and emergency
BMA	British Medical Association
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organisations of Medical Sciences
DSRU	Drug Safety Research Unit
EMA	European Medicines Agency
ESS	Enhanced Safety Surveillance
EU	European Union
FDA	Food and Drug Administration
FFU	Fluorescent Focus Units
GMC	General Medical Council
GP	General Practitioner
HCP	Healthcare professional
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRAS	Integrated Research Application System
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
PASS	Post authorisation Safety Study
PHE	Public Health England
PIS	Participant Information Sheet
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
PS	Patient Safety
PSUR	Periodic Safety Update Report
sADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SDT	Signal Detection Team
SOC	System Organ Class
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
US	United States

3 Responsible Parties

Responsible party	Appointed person(s)
Chief investigator	[redacted] [redacted] DSRU Education and Research Ltd. Bursledon Hall Blundell Lane Southampton SO31 1AA UK
Co-investigators	[redacted]
Consortium members	[redacted]

4 Abstract

Title

Post-authorisation active surveillance of the Safety of COVID-19 Vaccine AstraZeneca (AZD-1222) in the UK - A consortium study

Rationale and background

COVID-19 vaccines have undergone rapid development and testing due to the current global pandemic. There is a requirement to monitor the safety and effectiveness post authorisation, to supplement evidence from the pre-authorisation phase and to identify new emerging issues in a timely manner. For a COVID-19 vaccine, given the public health need for comprehensive assessment of effectiveness and safety, an active surveillance method is considered superior to passive methods of surveillance.

Research question and objectives

Overall aim:

To monitor the safety and utilisation of the COVID-19 Vaccine AstraZeneca (AZD-1222) administered to vaccinees under real-world use in the UK

Primary objective:

- To examine the safety of COVID-19 vaccine AstraZeneca (AZD-1222) through active surveillance of all vaccinee reported adverse events and assessment of incidence.

Secondary objectives:

- (i) To describe and characterise serious adverse events following vaccination.

- (ii) To describe and characterise adverse events of special interest (AESI) including AESI relevant to vaccinations in general and AESI for the COVID-19 vaccine AstraZeneca (AZD-1222).

- (iii) To describe and characterise the utilisation of COVID-19 vaccine AstraZeneca (AZD-1222) in the cohort, including vaccination site, demographics of vaccinee and brand/batch of vaccine administered.

- (iv) To examine use and safety in populations with missing information including pregnant and breastfeeding women and individuals with immunodeficiency disorders, treatment with immunosuppressants, concurrent medical conditions, and administration of other vaccines within previous 30 days.

Quality of life sub-study objective

(i) To describe and characterise health-related quality of life among a sub-population (n=3500) vaccinated by COVID-19 vaccine AstraZeneca (AZD-1222) and to describe the effect of the COVID-19 vaccine AstraZeneca (AZD-1222) on participant's lifestyle and productivity where affected by the COVID-19 pandemic.

Design

This study is a non-interventional post-authorisation active surveillance study to monitor the utilisation and safety of COVID-19 vaccine AstraZeneca (AZD-1222) in the UK. Vaccinees will be recruited via the mass vaccination programme through various vaccination sites and other methods of recruitment will be used where appropriate (e.g. through social media, newspapers and local radio stations). Informed consent will be obtained. Baseline information and any symptom/condition following vaccination reported by the vaccinee will be collected. Further information related to serious and AESIs will be captured from General Practitioners (GPs) and/or healthcare professionals (HCPs) where appropriate. Vaccinees will be contacted at various time points through text message, email, or phone and asked whether they experienced an adverse event. If an adverse event has been reported by the vaccinee, they will be asked to provide further details via a questionnaire completed via an online portal. All data will be securely stored on the Drug Safety Research Unit (DSRU) database.

Population

Adults and children[1] vaccinated with COVID-19 vaccine AstraZeneca (AZD-1222) launched during the mass vaccination programme in the UK.

Data sources

Questionnaires at baseline (information from time of vaccination) and pre-defined follow up points thereafter (weeks 1, 4, and 14 then months 6,12, and 18 following first vaccination dose) will collect information from vaccinees. Where any pregnancies are reported, follow up will be conducted at 12 months post last menstrual period for ascertainment of pregnancy outcomes. Further follow up at 24 months post last menstrual period will be conducted to monitor for outcomes in babies. Follow up information may also be obtained from vaccinees and/or GPs/Healthcare Professionals (HCPs) if serious or selected adverse events are reported. In order to validate data obtained from vaccinees, questionnaires will also be sent to GPs for a random sample of vaccinees who have not reported adverse events in order to confirm that no events occurred.

[1] Although the current guidance does not include children below the age of 16 years, we will include this group if they have received the vaccine.

Sample size

A minimum sample size of 10,000 vaccinees.

Data analysis

Monthly summary reports will be produced.

Interim reports will be produced at months 1 (or at the first 1,000 vaccinees, whichever comes first), 3 (or at the first 5,000 vaccinees), 6 (or at the first 10,000 vaccinees) and 12. Findings will also be summarised in a final report. Summary descriptive statistics including age, gender and specific co-morbidities/conditions (e.g. sub-populations of interest) reported on questionnaires will be presented, alongside event frequencies.

Observed vs expected analysis will be performed for selected AESIs (where appropriate background rate information is available) at regular intervals (at least every 3 months) throughout the study. For the final report, cumulative incidence risk and rates will be calculated with 95% confidence intervals. Time to onset analyses will be performed for AESI and serious adverse events where a sufficient number of events are reported. Descriptive statistics will be used for other outcome measures.

5 Amendments and Updates

Number	Date	Section of document	Amendment or update	Reason
1	04/02/2021	9.7.1	Update	Paragraph updated to provide further clarity on the situations where additional analyses may be performed.
2	04/02/2021	10.3	Update	Additional text added following REC review

6 Milestones

Milestone	Planned date
Start of data collection	TBC
End of data collection /recruitment	TBC
Final report of results	TBC

7 Rationale and Background

Vaccine benefit and risk evaluation is a continuum throughout the lifecycle of the vaccine, starting from pre-marketing development to post-marketing use. Whilst pre-marketing activities provide important information on vaccine safety and efficacy, post-marketing data is essential in providing evidence on post-authorisation use, short, medium and long-term safety and effectiveness of the vaccine.

The normal process for developing a vaccine is broadly similar to drug development. It is lengthy and can take 10-15 years. Animal studies follow chemical and biological development; the vaccine is then tested in humans in phase I-III clinical trials. Assessing the efficacy of a vaccine in phase III studies takes longer than medicines because the outcomes are not simply the beneficial effects of a drug on a disease but a combination of examining effects on biomarkers, e.g. antibodies, T lymphocytes and other biomarkers such as mucosal IgA in blood and saliva, and most importantly the reduction in the incidence of developing the disease in a comparable susceptible population.

In cases of urgent public health needs, such as the COVID-19 pandemic, the process of developing a vaccine is dramatically shortened; for example, developing, testing and releasing a vaccine in 12-18 months or less. Advances in genetics and biotechnology and parallel rather than sequential clinical studies are contributing to this efficiency in the case of COVID-19. To protect populations urgently, the release of a COVID-19 vaccine likely will be based on favourable effects on biomarkers and pre-marketing clinical studies with shorter observational periods compared to pre-marketing development in less urgent circumstances. Therefore, post-marketing observational studies will be vital to better understand effectiveness and safety. First, from a public health perspective, effectiveness (protecting vaccinees from the disease in real-world vaccination programmes) is different to vaccine efficacy tested in a clinical trial setting on a selected sample with inclusion and exclusion criteria. Secondly, given the limited pre-authorisation data, it is crucial to obtain near real-time notification of the safety and effectiveness signals of the vaccine when used routinely in the population so that actions to protect public health are taken promptly.

A fundamental function of the post-authorisation study is the prompted reporting by vaccinees which facilitates early identification of safety signals. The aim is to facilitate public health decisions based on findings from the study.
Also given public concerns about the novelty of some COVID-19 vaccine platforms and rapid vaccines development, transparent active vaccine surveillance that reports and evaluates signals in near real time is important to gain public trust.

In terms of safety it is important to detect any increased local and systemic adverse events, including adverse immune responses that may arise during vaccination programmes. Safety signals can be rapidly detected in near real-time during the vaccination programme. Serious adverse events are defined by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in the ICH E2A guidelines. Seriousness is based on patient/event outcome or action criteria and defines regulatory reporting obligations (1). An adverse event following immunisation (AEFI) will be considered serious if it results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. The ICH E2A guidelines also state that other situations, such as other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes above, should also be considered serious after applying medical and scientific judgment. This study will comply with all these regulations.

In May 2020, the Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Collaboration, the largest global organisation of scientific experts on vaccine safety, launched the Safety Platform for Emergency vACcines (SPEAC). SPEAC has prepared a list of potential AESI relevant to specific vaccine platforms for COVID-19 vaccines, with associated case definitions. The most recent version of the AESI list (September 2020) has been included in Appendix 1 and will be reviewed on a quarterly basis and updated as necessary. SPEAC will also develop case definitions for those AESI without existing case definitions. The AESI that still lack a case definition include enhanced disease after immunisation, multisystem inflammatory syndrome in children and acute respiratory distress syndrome. SPEAC will also review published evidence to identify the background incidence rates in target populations and the causes, risk factors and differential diagnoses and map the AESI to the corresponding codes of the International Classification of Diseases (ICD) and the Medical Dictionary for Regulatory

Activities (MedDRA). We will use the case definitions and associated MedDRA codes to identify AESIs in this study, in addition to AESIs provided by AstraZeneca.

The more familiar safety evaluation methods involve comparing adverse event incidence between vaccinated and unvaccinated groups (cohort studies) or comparing rates of adverse events between infected cases and uninfected controls (case-control studies). For an active surveillance programme, in pandemics such as COVID-19 where vaccination coverage in a population is expected to be high and achieved quickly, traditional methods for evaluating vaccine safety may not be suitable due to the lack of availability of an unvaccinated comparator group for a sufficient length of time to conduct a comparative study and the associated ethical considerations. Furthermore, if an unvaccinated group is available as a result of gradual introduction of vaccination whereby prioritisation is made for certain groups (e.g. at-risk individuals, healthcare professionals) before reaching full vaccination coverage, comparison of these specific vaccinated groups to the remaining unvaccinated population may not be appropriate. This is due to the potential for significant biases, as an individual's baseline level of risk of infection and risk of developing severe disease will be different between patients in high and lower risk groups and the different demographic and biological characteristics, e.g. prevalence of underlying illnesses between the two groups. Lastly, timeliness of results from comparative studies may be longer than desired for pandemics such as COVID-19 which demand an urgent public health response.

In such scenarios, implementation of a faster and more responsive study design can provide timely information in the immediate post-marketing period with respect to safety of the vaccine in the 'real-world'. Nonetheless, single arm studies still possess methodological challenges (e.g. confounding) which require the same careful consideration in terms of statistical analyses as other study designs. Findings from post-marketing studies on vaccines can guide pharmacovigilance decisions by marketing authorisation holders and regulatory authorities.

However, it is possible to include intra-cohort comparisons within the cohort, such as nested case-control and self-controlled studies for people who develop specific adverse events such as events which have been associated with vaccines, e.g. narcolepsy, severe allergic reactions. Other analyses that can be considered include examination of secular trends, ecological and cross-sectional analyses.

The COVID-19 pandemic has potentially changed population perceptions of health, management of health by health-care professionals, lifestyle choices and behaviours (2,3). To address this emerging evidence and the impact of COVID-19 pandemics on daily lives of study participants and their response to being vaccinated against SARS-Cov-2, we aim to collect targeted information on the health-related quality of life (HRQoL) and the impact of the COVID-19 pandemic on their perception of health and productivity. A sub-study to examine quality of life outcomes will be conducted for a sample of the total cohort (Appendix 2).

For COVID-19, the urgent public health need for accelerated vaccine development has resulted in the evaluation of novel vaccine mechanisms, with animal studies and phase I human clinical trials occurring in parallel. Fast-tracking through phase II and III clinical trials has occurred and the authorisation in the UK is for emergency use. However, the COVID-19 vaccine will be given to entire populations of healthy people. Vaccination of a very large number of people (millions) over a short period of time poses challenges compared to a gradual introduction of a product. However, the latter is not an option for a vaccine for COVID-19 for obvious reasons. While the benefit of having a vaccine available for susceptible individuals will likely be considered to outweigh the uncertainties of expedited development of a vaccine(s) for COVID-19, such scenarios merit even more rigorous post-marketing observational studies on the newly licensed vaccine. Specifically, post-marketing studies should address concerns about the safety of different vectors and adjuvants used by different COVID-19 vaccines.

Another important objective of the study is that the regular interim reports will contribute to alleviating concerns which may arise about the safety of the vaccine with a negative effect on the vaccination programme. Medical conditions, including those that have been associated with vaccines previously will occur in the population during the vaccination programme regardless of relatedness of vaccination. Publicity of some of these events will likely adversely affect the vaccination programme with serious public health consequences. Therefore, it is important that the study investigates such events to assess causality and report the results promptly. In addition rapid and transparent communication of the findings of the study is expected to build public trust and facilitate decision making by members of the public; both those who decide to be vaccinated and people with an increasingly recognised vaccine hesitancy (4).

In the UK, a vaccination strategy has been developed by the Joint Committee on Vaccination and Immunisation which is being used by the National Health Service (NHS) for implementation of COVID-19 vaccines. Phase 1 of the vaccination programme outlines specific groups which should be vaccinated first in order to prevent mortality and support the NHS and social care system. These groups are:

1. residents in a care home for older adults and their carers
2. all those 80 years of age and over and frontline health and social care workers
3. all those 75 years of age and over
4. all those 70 years of age and over and clinically extremely vulnerable individuals
5. all those 65 years of age and over
6. all individuals aged 16 years to 64 years with underlying health conditions which put them at higher risk of serious disease and mortality
7. all those 60 years of age and over
8. all those 55 years of age and over
9. all those 50 years of age and over

This study will focus on studying those vaccinated in this first phase of the vaccination programme in the UK.

The study will build on the extensive experience of members of the consortium in conducting various types of observational studies on vaccines in the United Kingdom (UK), including both active and passive enhanced safety surveillance studies on seasonal influenza vaccines and the 2009 H1N1 (swine flu) vaccine. Study methods have included both vaccinated and unvaccinated cohorts or vaccinated individuals only. Active methods have involved organised data collection at specific time points on all individuals participating in the study, whereas passive methods relied on healthcare professionals or vaccinees completing questionnaires only if the vaccinee had experienced an adverse event. The H1N1 swine flu study monitored self-reported serious adverse events and pregnancy outcomes in patients offered swine flu vaccination (5). The seasonal influenza studies, conducted annually since 2014, have measured the incidence of suspected adverse drug reactions in children following vaccination with Fluenz Tetra (6), and compared patterns of adverse events observed with previous flu seasons. For a COVID-19 vaccine, given the public health need for comprehensive assessment of effectiveness and safety, an active surveillance method is considered necessary. However, specific characteristics of the COVID-19 pandemic require specific considerations in the study, e.g. frequency of monitoring.

This registry uses a large-scale active surveillance study, with many characteristics of a registry, to monitor the use and safety of the COVID-19 vaccination programme in near real-time in the UK. The nature of the National Health Service (NHS), Public Health England (PHE) and Public Health bodies in the devolved nations, along with the coverage of the National Institute for Health Research (NIHR) Clinical Research Networks, the accessibility of pharmacies and pharmacists nationwide will put the UK in an almost unique position to be able to lead a comprehensive, scientifically robust programme with effective capabilities to raise safety signals for rapid corrective actions.

8 Research Question and Objectives

Overall aim:

To monitor the safety and utilisation of the COVID-19 Vaccine AstraZeneca (AZD-1222) administered to vaccinees under real-world use in the UK

Primary objective:

- To examine the safety of COVID-19 vaccine AstraZeneca (AZD-1222) through active surveillance of all vaccinee reported adverse events and assessment of incidence.

Secondary objectives:

- (i) To describe and characterise serious adverse events following vaccination

To describe serious adverse events following vaccination, clinical data will be obtained and used to characterise the adverse event in detail. For example, if somebody reports weakness in a leg, characterisation includes obtaining more clinical information from the doctor and investigations such as MRI scan, nerve conduction studies etc. to enable a clinical diagnosis to decide whether this event was caused by myocitis, myopathy, transverse myelitis, a condition in the brain or any other cause. The information will then be used to help determine if the event may be linked to vaccination. An AEFI will be considered serious if it results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Other adverse events that may jeopardise the patient or may require intervention to prevent one of the outcomes above, may also be considered serious after applying medical and scientific judgment.

- (ii) To describe and characterise adverse events of special interest (AESI) including AESI relevant to vaccinations in general and AESI for the COVID-19 vaccine AstraZeneca (AZD-1222).

- (iii) To describe and characterise the utilisation of COVID-19 vaccine AstraZeneca (AZD-1222) in the cohort, including vaccination site, demographics of vaccinee and brand/batch of vaccine administered.

- (iv) To examine use and safety in populations with missing information including pregnant and breastfeeding women and individuals with immunodeficiency disorders, treatment with immunosuppressants, concurrent medical conditions, and administration of other vaccines within previous 30 days.

Quality of life sub-study objective

(i) To describe and characterise health-related quality of life among a sub-population (n=3500) vaccinated by COVID-19 vaccine AstraZeneca (AZD-1222) and to describe the effect of the COVID-19 vaccine AstraZeneca (AZD-1222) on participant's lifestyle and productivity where affected by the COVID-19 pandemic.

9 Research Methods

9.1 Design

This study design is a prospective evaluation of data collected through active surveillance to monitor the reporting of events related to safety in COVID-19 vaccinees in the UK. A minimum 18-month observation period will be used for each vaccinee. Vaccinees are eligible to consent to participate in the study up to a maximum of four weeks post first AstraZeneca vaccination dose.

Multiple recruitment strategies are anticipated for this study. Primary care (GP practices), pharmacies, and other vaccination sites within the UK (to be determined based on the nature of the vaccination programme) will all be invited to participate. Study information for sites will be made available through the online portal. Vaccinees that receive the vaccine at these sites will be provided with study information by immunisation staff after receiving the vaccine as part of the mass vaccination programme.

In addition, further recruitment of vaccinees through social media and other direct forms of advertisement, newspapers, radio and television stations will be used in order to maximise the sample size. Since we will not be collecting information directly from the vaccination site for these vaccinees, additional information will need to be collected directly from the vaccinee (place of vaccination, date of vaccination, brand of vaccination,

batch number (if known)). Recruitment could expand beyond advertisement of the study at time of vaccination to recruit vaccinees prior to their vaccination - they can be made aware of the study in advance (through advertisement and other collaborative efforts) and sign up, then they would be contacted for information once vaccination has taken place.

Study information will be provided electronically to vaccinees and sites where possible. All study information will be made available on the online portal and can be downloaded and printed by individual sites as required. Vaccinees will be directed by the study information provided to the portal's webpage. Vaccinees will be asked to provide informed consent to participate in the study, through the secure study online portal (this does not have to be completed at the exact time of vaccination and can be completed later). At time of consent, vaccinees will be asked to indicate their preferred method of contact for follow up; by text message or by email (linking to secure online portal). In the scenario where vaccinees do not have internet access or cannot use text messaging, a telephone follow up can be made available. Vaccinees would be contacted by telephone at the pre-defined contact points by trained study staff to complete the study. Telephone consent may also be possible for these vaccinees.

No remuneration will be offered to vaccinees. Figure 1 below gives an overview as to how vaccination sites and vaccinees will be involved in the surveillance project which will be implemented collaboratively as part of a consortium.

Figure 1. Example of study flow for a COVID-19 active surveillance post-marketing study in the UK

Consent to contact vaccinees for follow up, in addition to consent to contact their GPs and other HCPs will be required. Consented vaccinees will be asked to provide the email address and telephone number of an emergency contact (relative, family friend or carer) who can be contacted if the study team are unable to contact the vaccinee. This is important to ensure that the study does not miss events that cause vaccinees to be too ill to respond to communications from the study.

Following consent, vaccinees will be prompted to complete baseline information via the online portal (variables outlined in section 9.3.2). Vaccinees will then be contacted at weeks 1, 4, and 14 then months 6, 12, and 18 following first vaccination dose (variables outlined in section 9.3.2) via their chosen communication method. A questionnaire will only need to be completed where a vaccinee has experienced events during one of these periods of contact.

For a random sample of participants who did not report events, the GP will be contacted to obtain information on any events that the GP was aware the vaccinee had experienced during the observation period. This will be used to validate data obtained by the vaccinee. In addition, this process will also be used to confirm vaccination dates (for first and second dose) and batch numbers, validating the information provided by vaccinees. Randomisation will be conducted based on the cohort accrued at six months post study start and will performed using simple random sampling. A sample of 10% of those who had not reported events will be selected.

9.2 Setting

Adults and children[2] vaccinated with COVID-19 vaccine AZD-1222, at any vaccination site throughout the UK, will be eligible for inclusion in this surveillance.

GP sites:
GP practices in the UK will be invited to participate. Vaccinees and/or their representatives (parent/guardian) will be provided with study information explaining the surveillance by immunisation staff after vaccination. Sites will be provided with supporting information. Practices will be requested to provide information, on a weekly basis, about the brands and batch numbers used at their site.

[2] Although the current guidance does not include children below the age of 16 years, we will include this group if they have received the vaccine.

Other vaccination sites: To be determined based on other vaccination sites that will be used, which are unknown at this stage but likely to include workplaces, universities, health clinics etc.

Recruitment via social media/advertisement (newspapers, radio and television): To maximise participation, this method of recruitment will be used too. Those who have recently been vaccinated will be eligible to participate by signing up directly on the online portal, though these vaccinees would need to provide additional information as they will not have been recruited through their vaccination site. This could also be extended to recruit vaccinees prior to their vaccination. Participants would be contacted for information once vaccination has taken place.

Vaccination sites are invited to participate through early engagement with the UK Clinical Research Network (CRN) who provide operational support to assist with site recruitment and the NHS research approvals process. The Royal Pharmaceutical Society, the Pharmacy Forum in Northern Ireland, Pharmaceutical Services Negotiating Committee and pharmacists nationwide will also be engaged to participate in this study, along with other organisations including the NHS, Public Health bodies across the UK, research networks and any relevant organisations which may be involved in the vaccination programme e.g. care homes bodies and supermarket chains. No remuneration will be provided for participation.

9.3 Variables

9.3.1 Data from vaccination sites

Sites administering the vaccine will be required to carry out the following tasks, in addition to vaccination administration:

- Provide details of the site: vaccination administration centre and region (contact information).
- Provide details of batch numbers if possible[3]

9.3.2 Data from vaccinees or their representatives

Information requested from the participant at baseline (enrolment) will include:

- consent to contact vaccinee, contact details for vaccinee and relationship to vaccinee (if participant representative)

[3] We will aim to collect batch number for all vaccinees and where necessary this will be collected from the vaccinees' GP

- consent to contact GP and other HCPs for follow-up if necessary and contact details for GP
- emergency contact information for participant (e.g. next of kin)
- date of birth, gender, race/ethnicity, postcode
- pregnancy status including date of last menstrual period (LMP) if pregnant
- Breastfeeding status
- vaccination details (date and brand/batch number of vaccine)
- information on specific comorbidities/conditions
- COVID-19 disease prior to vaccination

Information requested from the vaccinee at weeks 1, 4, and 14 then months 6, 12 and 18 following first vaccination dose will include:

- Any symptom(s)/condition(s) experienced following vaccination
- If yes:
    - adverse events experienced
        - Including COVID diagnosis/symptoms
        - Including AESI for example diagnosis of Guillain-Barre syndrome, idiopathic thrombocytopenia or narcolepsy (full list in Appendix 1)
    - dates of onset and resolution of reported adverse events
    - contact with GP, attendance at A & E or hospital admission
    - vaccination details (date and brand/batch number of vaccine) of second dose
    - Anti-pyretic use following vaccination with first and second dose
    - pregnancy status including date of last menstrual period (LMP) if pregnant
    - Breastfeeding status

The vaccinee or their representative may be contacted to obtain supplementary information on any potentially serious adverse events or AESI reported, where further details are required to ascertain seriousness or for case assessment. Follow-up with vaccinees will be undertaken to clarify information on the adverse events reported or to obtain missing data if considered appropriate and necessary to assess the case. Any follow-up contact with vaccinees will be performed by study staff who are suitably trained and will utilise existing procedures for contact with vaccinees. Requests for follow-up information will be made by the chosen correspondence route. If no response is received from vaccinees after two contact attempts per follow up point, the emergency contact for the vaccinee will be contacted at the end of their observation period to determine if the vaccinee is still alive. If vaccinees report pregnancy during the study period, we will include further specific follow up with the vaccinee and with the GP at 12 months following last menstrual period (or first vaccination dose date where last menstrual period date unknown), and 24 months following delivery to examine outcomes in mother and baby.

The exposure period of interest is from 30 days prior to the last menstrual period date. Where breastfeeding is reported, this will also be followed up with the vaccinee with regards to the health of the baby.

9.3.3 Data from vaccinees' GPs or other HCPs (follow-up information about events)

Reported serious adverse events and AESI will be assessed by clinical staff at the DSRU. The GP or other HCP will be contacted to gather further information about the event. A standard follow-up questionnaire will be used to obtain further information and the GP or other HCP will complete this via the online portal.

Data collected from GPs/other HCPs will include the following:

- confirmation of date of onset (time when first sign/symptom indicative of the adverse event) and/or first observation if date of onset unknown.
- severity of event
- contact with GP, attendance at A & E or hospital admission
- clinical details, diagnosis and relevant investigations
- management and final outcome
- seriousness of the event
- relevant medical history (including pre-existing conditions or risk factors considered to be relevant to the event) and concomitant medication

In addition, the GP/HCP will be asked whether they feel the serious AE/AESI may be related to the vaccine or to an alternative cause. Other information may also be requested by DSRU clinical staff, based on clinical evaluation of event reports. The GP will also be contacted if pregnancy is reported to follow up on the health of the mother and baby.

In instances when no information has been received from the GP or other HCP following a request for further details, an initial reminder message will be sent to the GP/other HCP to prompt a response. If this is unsuccessful, this will be followed by a telephone call to the GP/other HCP practice for serious AESI only. Any telephone calls will be made by trained DSRU staff who will attempt to obtain further relevant details of the event from either the vaccinee's GP or another member of the practice staff, as applicable. For specific events of interest (as defined in the Risk Management Plan and for those previously associated with vaccines e.g. Guillain-Barre syndrome, idiopathic thrombocytopenia and narcolepsy), additional questionnaires will be used for follow-up.

9.4 Data Sources

See section 9.3.

9.5 Sample Size

A cohort of at least 10,000 vaccinees is required, to provide reassurance regarding safety for vaccine AZD-1222 that will be made available in the UK. Vaccinees from a variety of age groups will be recruited, with 25% of the sample from NHS staff, social care staff and vulnerable patients below 50 years. Ages 50 years and over will form the remaining 75% and be divided into 10 year age bands for recruitment, in line with the age distribution of the UK population where possible.

A minimum sample size of 10,000 vaccinees would allow 95% certainty that events not observed in the cohort occur less frequently than one in 3333 cases. (7)

A sample size of 10,000 should allow for the detection of at least three cases of an adverse event, with 85% power, if the event occurs at a rate of at least one in 2000 persons (assuming the background rate is zero). (8)

9.6 Data Management

Site agreements and site approvals will be held at the DSRU.

Data submitted by vaccinees and vaccination sites will be reviewed by DSRU research staff and entered into the secure DSRU database where access is restricted to authorised personnel only. Further privacy details of vaccinee can be read in the DSRU Privacy Notice on the DSRU's OSIRIS ResearchHub. Follow-up information received from GPs/other HCPs (as per Section 9.3.3) will also be reviewed and entered onto the database, along with denominator data.

Anonymised weekly line-listings will be produced to facilitate review, analysis and reporting.

All original documents, individual correspondence from HCPs and patients will be stored for at least 15 years after study completion, with considerable care taken to preserve patient confidentiality. Patient identifiable information will only be kept as long as needed (for the duration of the study and up to 12 months following completion of the study) and will subsequently be destroyed.

9.7 Data Analyses

Data analyses for the main study are described in this section. All data analyses for the QoL sub-study are described in Appendix 2.

9.7.1 To examine the safety of COVID-19 vaccine AstraZeneca (AZD-1222) through active surveillance of all vaccinee reported adverse events and assessment of incidence

The following section relates to the primary objective. Descriptive analysis of data will include summary tabulation of the number of vaccinee reported events and reporting proportion, in total and stratified by age group, and lot identifier (if appropriate). Stratifications will also be performed by populations of interest (pregnancy, children, elderly, severe co-morbidities). The crude reporting proportion will be used, whereby the denominator will be the total number of consented vaccinees.

All events reported, regardless of seriousness, will be tabulated. Serious adverse events will also be tabulated separately, in addition to AESI and non-serious adverse events. Information relating to whether the event resulted in the vaccinee contacting their GP, attending A & E or being admitted to hospital will also be collected and presented.

The ability to detect important differences between vaccine lots will depend on how many different lots are administered during the COVID-19 vaccination programme. Any comparison will be purely descriptive.

Cumulative incidence risk and rates per 12 months will be calculated in the final study report. The cumulative incidence risk of adverse events reported following vaccination will be explored by estimating the cumulative incidence of incident reports (plus 95% CI) and cumulative hazard rates (plus 95%CI) of incident events over time. The cumulative incidence risk will be calculated according to the formula:

$$\frac{\text{Total number of new cases during 18 month observation period}}{\text{Population initially at risk}} \times 100$$

Cumulative hazard rate methods account for truncation of observation time and censoring; for these analyses the observation time would be censored at the time of the first event. Vaccinee data will also be censored at death, loss to follow up or end of observation

period, as appropriate. Time to onset analyses will be performed for AESI and serious adverse events where a sufficient number of events are reported e.g. a minimum of 10 cases per event. Kaplan-Meier plots will be presented to describe time-to event as well as smoothed hazard plots to describe how the baseline risk of an event changes over time. Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time.

Observed vs expected analyses will be conducted for selected AESI[4] (where appropriate background rate information is available) at regular intervals (at least every 3 months) throughout the study. Any safety signals will be validated and assessed in the context of the benefit-risk of the vaccine.

A sensitivity analysis will be conducted to examine number of adverse events reported in relation to time of enrolment.

Further analyses using other methods may be considered to further investigate any specific safety signals or concerns. In addition to responding to regulatory requests within specified regulatory timeframes, further analyses of patient experience or pooling of study results with results from other studies, using scientifically appropriate methods, may be undertaken for the purposes of further increasing the power of the study and the significance, interpretation and impact of findings. Other additional analyses conducted for Public Health organisations, analysis/data requests that may be made by the Company to assist questions posed from regulatory authorities or for bona fide scientific reasons will also be conducted within appropriate timeframes.

9.7.2 To describe and characterise serious adverse events following vaccination.

The following section relates to secondary objective (i). Information about patient age, gender, race/ethnicity, specific current medications (e.g. that influence the adverse events from vaccines), specific comorbidities/conditions (e.g. sub-populations of interest), and time to onset of adverse events will be summarised descriptively for vaccinees reporting serious adverse events.

Individual case reports and case series will be produced for selected serious adverse events of interest. Causality assessments will be conducted for these serious adverse events (Appendix 3). Serious related and serious unrelated events will be presented separately.

[4] Further analyses will be considered for serious adverse events or emerging safety concerns which are considered to effect the ongoing benefit-risk assessment for the vaccine.

9.7.3 To describe and characterise adverse events of special interest (AESI) including AESI relevant to vaccinations in general and AESI for the COVID-19 vaccine AstraZeneca (AZD-1222).

The following section relates to secondary objective (ii). Information about patient age, gender, race/ethnicity, specific current medications, specific comorbidities/conditions, and time to onset of adverse events will be summarised descriptively for vaccinees reporting specific AESI.

Individual case reports and case series will be produced for all AESIs, regardless of causality and regardless of seriousness. Causality assessments will be conducted for these AESI (Appendix 3).

9.7.4 To describe and characterise the utilisation of COVID-19 vaccine AstraZeneca (AZD-1222) in the cohort, including vaccination site, demographics of vaccinee and brand/batch of vaccine administered

The following section relates to secondary objective (iii). Information relating to utilisation will be presented in a series of tables. Descriptive analysis of data will include summary tabulation of vaccination site type, vaccinee demographic information, specific comorbidities/conditions, and batch of vaccine administered. Information about patient age, gender, race/ethnicity, index of multiple deprivation (for socioeconomic status), and specific comorbidities/conditions (e.g. sub-populations of interest) will be summarised.

9.7.5 To examine use and safety in populations with missing information including pregnant and breastfeeding women and individuals with immunodeficiency disorders, treatment with immunosuppressants, concurrent medical conditions, and administration of other vaccines within previous 30 days.

The following section relates to secondary objective (iv). Information relating to use and safety in populations with missing information will be presented in a series of tables. Descriptive analysis of data will include summary tabulation of frequency of populations with missing information in the study and frequency of events within these populations.

9.8 Quality Control

Data quality is a high priority at the DSRU and is assured through a number of methods based on staff training, validated system, error-prevention, data monitoring, data cleaning and documentation. These include:

- Staff training on data processing standard operating procedures, data entry and coding conventions, MedDRA and authorised use of the DSRU Information System (OSIRIS);
- GxP validated system to conduct pharmacovigilance research studies;
- Data management plan for every research study outlining legal basis for data collection, data flows, data access rights, data retention periods, etc.;
- On screen validation during data entry by participants, for example, setting logical limits on date values, etc.;
- Adoption of and adherence to project-specific data coding conventions for free-text events;
- Code list and algorithms for free text events to facilitate specified outcome assessments;
- Retrospective quality review of adverse event data (a minimum 15% sample), error reporting and correction of discrepancies between the entries by data entry staff.
- Routine data cleaning to screen for errors, missing values and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by data manager or allocated staff;
- Relevant maintenance of reference tables, e.g., Event Dictionary;
- System process logs to document staff access, etc.;
- Pilot testing of documentation.

9.9 Limitations of the Research Method

9.9.1 Under-reporting

Under-reporting is a potential limitation where vaccinees may not report events experienced during the observation period. This is considered to be more likely to occur with mild/non-serious events, and reminders will be sent to vaccinees who do not respond to follow up requests during the observation period. In addition, we will obtain emergency contact details in the scenario where a vaccinee may have died during the observation period. However, given the perceived gravity of COVID-19 by people, it is expected that the response rate will be high among vaccinees and doctors. This will be augmented by a campaign of publicity for the study in social media and other platforms such as newspapers, radio and television.

9.9.2 Response rate

Response rate may vary by method and vaccination site. Response rates at different sites will be monitored throughout the study and steps will be taken to maximise response rate where required. In addition, we have provided multiple options for preferred methods of communication in the study to maximise response.

As with all longitudinal studies, there is the potential for loss to follow up. This will be minimised by maintaining contact with vaccinees at various time points throughout the observation period. In addition, we will obtain emergency contact information in the scenario where a vaccinee cannot be contacted due to death during the study observation period.

9.9.3 Selection bias

Selection bias is possible since those who participate may be different from those who do not take part. In addition, the participating vaccination sites are not selected at random. Rather, selection of sites is based on their willingness to participate in this surveillance, thus, the sample may not be fully representative of the general population of vaccinees in the UK. The multiple enrolment method which will mirror the vaccination programme as much as possible combined with enrolment by social media, newspapers, radio and television offer a reasonable expectation that vaccinees enrolled in the study will represent the UK vaccinees as much as possible. Adjustments of enrolment will be made if it is identified that some groups, e.g. residents in care homes, are under-represented in the study.

9.9.4 Missing data

Due to the nature of the study design (vaccinee reported information), there is the possibility that missing data will arise for specific variables. Missingness will be examined and an appropriate method will be used to handle missing data where appropriate. Such methods would not be used where missing values represent less than 20% of data for an individual variable.

10 Protection of Human Subjects

10.1 General

This surveillance will be conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical

Sciences (CIOMS) in collaboration with the World Health Organisation (2002). (13) The method also complies with the Guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians. (14)

10.2 Approvals

Ethics Committee and NHS approvals will be requested via the UK Health Research Authority (HRA).

10.3 Consent process

The decision to participate in this surveillance must be made voluntarily and should be based on a clear understanding of what is involved. The study information will emphasise that participation is voluntary. Contact details for the DSRU will be provided on the study information to ensure that vaccinees are given every opportunity to clarify any points they do not understand.

The study information will be provided to vaccinees or their representatives. Study information will also be made available on the online portal for those who learn about the study via social media and advertisements. Study information can also be printed and provided by vaccination sites or mailed out by call centre staff. Vaccinees will be given 2 to 7 days to consider participation before being contacted again. The study information will explain the purpose of the surveillance and who their information will be sent to and shared with for the purposes of analysis. All study information can be provided in languages commonly spoken in the UK. The vaccinee, or representative (as appropriate) is asked to complete the consent form via the online portal (using check boxes) to confirm that they wish to take part and to confirm that they have read and understood the information provided and how their information may be used and shared by DSRU for the purposes described in the study information. In addition, the study information will explain the possible need to contact the vaccinee or their representative for further details of any serious adverse events reported and the potential need to contact the vaccinee's GP so that their medical notes will be accessed during the study by the GP in order to validate any serious adverse events of interest. Participants will be asked to tick a check box in the on-line portal to give consent to contact the vaccinee and the GP and other HCPs for follow up information. Where providing consent over the phone, call centre staff will complete the consent form on behalf of the participant. Children aged 16 or 17 years can complete the consent form themselves. Although the current guidance does not include children below the age of 16 years, we will include this group if they have received the vaccine. For children under 16 years of age, consent must be completed by a parent or guardian.

10.4 Confidentiality

All DSRU staff sign confidentiality agreements and are registered with the Information Commissioner's Office (DSRU Registration No. Z5438861)

DSRU have information security policies in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provide suitable physical and environmental security, all equipment is secure and protected against malicious software, the network can only be accessed by authorised staff, telecommunication lines to the premises are protected from interception by being routed overhead or underground and personnel receive training regarding security awareness.

All original documents, and any individual correspondence from HCPs and vaccinees (or their representatives), will be stored at the DSRU for 15 years after study completion, with considerable care taken to preserve the confidentiality of data. Databases at the DSRU are well protected. Access to identifiable information is limited to those personnel whose job roles mean they have a legitimate need to see it and is governed by policies and procedures. Patient identifiable information will only be kept as long as needed (for the duration of the study and up to 12 months following completion of the study) and will subsequently be destroyed.

Any datasets that are shared with the vaccine manufacturer, for the purposes of this project or shared with the regulatory authorities for the purpose of routine pharmacovigilance activities are anonymised.

11 Management and Reporting of Suspected ADRs

All vaccinee reported events will be assessed for possible causality and any suspected ADRs will be classified as either serious or non-serious based on information available from the vaccinee. Reports will be submitted to the MHRA within regulatory reporting timelines (15 calendar days for serious suspected ADRs and 90 days for non-serious suspected ADRs) (Appendix 3). All serious suspected ADRs and any other events which meet the definition of an AESI will be adjudicated by a second DSRU study physician and followed up with the vaccinees' GP. Upon receipt of follow up data the case will be further assessed for seriousness and relatedness and submitted within regulatory timelines. Non-

serious suspected ADRs may also be followed up with the GP at the discretion of the reviewing physician.

External adjudication may be sought for certain events considered to have an important effect on the risk benefit of the vaccine, e.g., serious neurological conditions. For such events, additional information may be requested from the GP including correspondence such as hospital discharge summaries and test results.

Key clinical characteristics for both serious suspected ADRs and all AESIs will be presented in case series tables as per sections 9.7.2 and 9.7.3.

12 Plans for Disseminating and Communicating Results

Monthly summary reports will be produced. Interim reports will be produced at months 1 (or at the first 1,000 vaccinees, whichever comes first), 3 (or at the first 5,000 vaccinees), 6 (or at the first 10,000 vaccinees) and 12.

A final report, summarising the results of the surveillance, will be provided independently (in pdf format) by the DSRU upon study completion.

Results of the final study report will be published in a peer-reviewed journal.

13 References

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14 Annex 1. List of stand-alone documents

Appendix 1: AESI list (September 2020)

Appendix 2: Quality of Life (QOL) sub-study

Appendix 3: Management of adverse events

Safety Platform for Emergency vACcines

SO2-D2.1.1 Priority List of COVID-19 Adverse events of special interest: Quarterly update 1

Work Package: WP2 Standards and tools

V1.2 Date September 9, 2020

Authors: Barbara Law

Nature: Report | Diss. level: Confidential

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ANNEXES 16

ANNEX I. REVISED SEARCH STRATEGY 2.0 FOR LITERATURE RELEVANT TO UPDATES TO THE POTENTIAL AESI LIST FOR COVID-19 (USED TO RETRIEVE ARTICLES FROM MAY 16-JULY 20, 2020) 17

ANNEX II. REVISED SEARCH STRATEGY 2.1 FOR LITERATURE RELEVANT TO UPDATES TO THE POTENTIAL AESI LIST FOR COVID-19 (USED TO RETRIEVE ARTICLES FROM JULY 20 – AUGUST 7, 2020) 20

DOCUMENT INFORMATION

Master Service Agreement		Service order	SO2
Project acronym	SPEAC	Full project title	Safety Platform for Emergency Vaccines
CEPI Project Lead	Nadia Tornieporth / Jakob Cramer		
CEPI Project Manager	Brett Barnett		
CEPI Contract Manager	Nishat Miah		

Deliverable number	D2.1.1	Title	Priority List of COVID-19 Adverse events of special interest: Quarterly update 1
Work package number	WP2	Title	Standards and tools

Delivery date	10/09/2020	Changes on due date ☑	Actual date	9/09/2020
Status	Draft ☑ Final ☐	Past due date: 31/08/2020	Version 1.2	
Nature	Report ☐ Toolbox ☑ List ☐ Template ☐ Guidance ☐ Handbook ☐ Questionnaire ☐			
Dissemination Level	Public ☐ Confidential ☑			

SPEAC Project Lead	Robert Chen	E-mail: robert.chen@cepi.net
Scientific Coordinator	Miriam Sturkenboom	E-mail: miriam.sturkenboom@cepi.net

Author 1	Barbara Law	E-mail: barbara.law@cepi.net
Author 2	-	-
WP Leader	Barbara Law	E-mail: barbara.law@cepi.net

Reviewer 1	Robert Chen	E-mail: robert.chen@cepi.net

Description of the deliverable	This deliverable provides the methods and results of the quarterly update to the Priority List of potential Adverse events of special interest relevant to COVID-19 vaccine trials (SO1 deliverable 2.3 V2.0, May 25, 2020)
Key words	Toolbox, adverse events of special interest, guidance documents

DOCUMENT HISTORY

NAME OF DOCUMENT	DATE	VERSION	CONTRIBUTOR(S)	DESCRIPTION
SO2-D2.1.1 Priority List of COVID-19 Adverse events of special interest: Quarterly update 1 _ v0.1	12/06/2020	v0.1	Barbara Law, Matthew Dudley	Search strategy revised for retrieving articles to inform updates to COVID-19 AESI. 1st search using strategy run Jun 12, 2020 dating back to May 16, 2020 which was last search done for the SO1 D2.3 V2.0 deliverable
V1.0 COVID-19 update	01/09/2020	v.1.0	Barbara Law	Updated version
	07/09/2020	v1.1	Robert Chen	Revised version
SO2-D2.1.1 Priority List of COVID-19 Adverse events of special interest: Quarterly update 1 _ v1.1	09/09/2020	v1.1	Executive Board	Reviewed by Executive Board
SO2-D2.1.1 Priority List of COVID-19 Adverse events of special interest: Quarterly update 1 _ v1.2	10/09/2020	v1.2	Mark McKinley	TFGH Final Approval

1. Background

CEPI has contracted with the Brighton Collaboration, through the Task Force for Global Health, to harmonize the safety assessment of CEPI-funded vaccines via its Safety Platform for Emergency vACcines (SPEAC) Project.

A key aspect of this harmonization has been creation of lists of priority potential adverse events of special interest (AESI) that are relevant to vaccines targeting CEPI target diseases.

The initial AESI list for COVID-19 was approved March 5, 2020 based on the first published experiences from China. Subsequently PubMed searches were done on a daily basis and new articles screened for newly emerging COVID-19 clinical patterns and complications. A full description of the methodology and results including citations for the first two COVID-19 AESI lists is available on the Brighton website (https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf).

The COVID-19 list was presented to the WHO global Advisory Committee on Vaccine safety (GACVS) at a virtual meeting held May 27-28, 2020. The GACVS agreed to adopt the AESI list.[1] At the time it was clearly understood that new AESI could be added to the COVID-19 list as needed based on new knowledge learnt during the global pandemic. Accordingly, SPEAC continues to monitor the literature with quarterly updates to the AESI list planned (September 9 and December 9, 2020; March 10 and June 9, 2021. This deliverable presents the results of the 1st quarterly update and includes modifications to streamline the search strategy.

2. Objective of this deliverable

The primary objective is to present the first quarterly update for the COVID-19 AESI priority list. A detailed description of changes to the ongoing search strategy is included. This was necessitated by the huge volume of new publications on all aspects of COVID-19 spread, clinical presentation, complications, treatment and prevention.

3. Methods

To develop the May 25, 2020 list of potential COVID-19 AESI, a very broad search strategy was used capturing all COVID-19 publications from PubMed as well as pre-prints from bioRxiv and medRxiv. All citation titles were screened by one reviewer (Barb Law) from Feb 17, 2020 and those that addressed the clinical course and complications of COVID-19 were included in a further screen of abstract and/or full text. Duplicates were removed as were non-English articles. Letters to the editor were included as many of these contained relevant case report and case series data that informed the early development of the AESI list. Given the overwhelming volume of publications, the screening was not done in a systematic fashion following PRISMA guidelines. All articles included in the AESI list finalized May 25, 2020 were captured in the appendices of the D2.3 V2.0 deliverable document (available at Brighton website link in Background above).

Searches were discontinued May 16, 2020 in order to develop the final AESI list based on screened in citations and prepare a presentation to the WHO Global Advisory Committee on Vaccine Safety.

From May 16 through the end of May, over 5000 new citations were published. Ongoing review of such a large volume of literature using similar methods as those used to generate the first list was deemed impossible. Accordingly, the screened in articles for the May AESI list were reviewed and key words identified to inform a new search strategy. Also, the nature of the excluded articles which did not inform the AESI list (e.g. therapeutic/prevention strategies, infection control, transmission and other basic virology articles, changes in patterns of healthcare during the pandemic) was used to develop a list of exclusionary terms.

The first revised search strategy is shown in Appendix 1. To ensure that significant articles were not being excluded, all 5000 new citations released from May 16 to early June 2020, were screened in the same manner as used to develop the May 2020 AESI list. Separately, the revised search strategy was also run a) with and b) without exclusionary terms and a file generated with the citations included in (b) but not (a). None of the excluded citations would have contributed to the evolving AESI list. Essentially the revised strategy with exclusionary terms gained efficiency, cutting out 89% of articles captured by prior inclusive search strategies without loss of articles that informed identification of AESI.

The first strategy included 6 separate sub-searches by body system (Neurologic, Multisystem Inflammatory Syndrome, Dermatologic, Cardiac/Hematologic, Pregnancy/Pathology, and a broad category including kidney, gastrointestinal, musculoskeletal, ocular, respiratory and endocrine systems as well as the non-specific terms complications, dysfunction, case reports and case series). Ultimately this strategy decreased efficiency given retrieval of several duplicate publications in the sub-searches. Accordingly, the search strategy was condensed into a single search without changing any of the inclusion or exclusionary terms (Appendix 2).

Searches were conducted using the 1st revised strategy on June 12, July 8th and July 20th. The condensed 2nd revised strategy was used for searches run on July 31st and August 7th. The results from each search were loaded into an excel spreadsheet. A single expert (Barb Law) screened all citations. Several could be screened out based on title alone. Any that could not clearly be screened in or out were then retrieved for abstract and/or full text review.

The brief category name and descriptive rationale for exclusion included:

- 'Duplicate': duplicate of previously captured citation.
- 'Therapy/Testing/Prevention': as implied, articles with the main focus on COVID-19 therapy, testing or prevention of disease.
- 'Healthcare': focus on healthcare during the COVID-19 pandemic.
- 'Unrelated': article unrelated to COVID-19 infection in humans, such as animal model studies or other Coronavirus or related pathogens.
- 'Limited focus': clinical course information included but on a very small scale such as the first case report in a country.
- 'Noncontributory': articles that addressed entities already included on the AESI list with no new information such as an additional case report or limited series of cases.
- 'Non-English': articles in any language other than English.
- 'Comment/Response/Erratum': commentaries including editorials, letters to the editor, author responses to letters to the editor and errata. Of note, full text screening was required for most commentaries because several letters to the editor include case reports, case series and some studies relevant to the AESI list.

For all articles screened out, a distinction was made for whether it was done based on title alone or after abstract and/or full text review.

All screened in articles were categorized according to: 1. Primary topic (mainly by body system); 2. Subgroup 1 (mainly specific diagnosis or population subgroup); and 3. Subgroup 2 (type of article) using the following terms:

1. Primary topic:
    A. Categories from previous AESI list: Cardiac, Neurologic, Dermatologic, Gastrointestinal, Hematologic, Kidney, Liver, Multisystem inflammatory syndromes, Musculoskeletal, Ocular and Respiratory.
    B. Additional categories relevant to AESI list: Autoimmune, Co-infection, Endocrine, Enhanced disease, Pregnancy, Psychiatric, Mixed clinical (for reports, mainly reviews and meta-analyses, of extra-pulmonary manifestations of COVID19) and Other.
    C. Articles to keep for potential relevance to AESI Tools but not to the AESI list per se: Background rate, Risk factor, and Pathology were also categorized and kept but not all reviewed in depth for the AESI list. Within the pathology subgroup, any relating to autopsy findings were to be reviewed in full.
2. Subgroup 1: two groups of terms were used based on whether or not an AESI was already included in the list for COVID19 finalized in May 2020.
    A. Relevant to already identified AESI:
        - Cardiovascular: acute coronary syndrome, aneurysm, arrhythmia, endothelial dysfunction, heart failure, MI, myocarditis (including pericarditis), STEMI (For ST elevation myocardial infarction), sudden death, Takotsubo syndrome (stress cardiomyopathy);
        - Neurologic: acute disseminated encephalomyelitis (ADEM), CNS bleed, encephalitis, encephalopathy, Guillain Barré Syndrome (GBS), myelitis, seizure, Smell/Taste (for anosmia, ageusia, hyposmia, hypogeusia and dysgeusia); Cranial Nerve – other;
        - Dermatologic: angioedema, chilblain, erythema multiforme, urticaria, vasculitis, other rash;
        - Hematologic: coagulopathy, idiopathic thrombocytopenic purpura, ischemia, pulmonary embolus, stroke, thrombocytopenia, thromboembolism, thrombosis;
        - Kidney: injury;
        - Liver: injury;
        - Multisystem inflammatory syndromes: multisystem inflammatory syndrome in children (MISC);
        - Respiratory: ARDS
    B. Entities not on the May AESI list: several were known to have been reported but not in sufficient numbers to merit inclusion on the AESI list; others were added as search results were screened from May 16 to Aug 15. These included:
        - Clinical diagnoses: abscess, adrenal injury, alopecia, arthritis, autoimmune hemolytic anemia, cholecystitis, chronic complication, conjunctivitis, diarrhea, enteritis/colitis, hemophagocytic lymphohistiocytosis, hepatitis, hyperferritinemic syndrome, hyperglycemia, hyponatremia, Kawasaki syndrome, mania, myositis, pancreatitis, parotitis, peripheral neuropathy, pneumomediastinum, pneumothorax, psychosis, retinopathy, rhabdomyolysis, sudden death, thyroiditis, uveo-retinitis;

- Pregnancy/post-partum related: breast milk, ectopic pregnancy, foetal, HELLP syndrome, mortality, neonatal, outcomes, placenta, preeclampsia/eclampsia, transmission;
- Non-specific entities that could lead to identification of new AESI: autopsy, general, mixed clinical, other, outcomes, severity, virus in tissue
- Host-specific other than pregnancy-related: Adult, Geriatric, HIV, Pediatric

3. Subgroup 2: Case Reports (including case series), Commentary (mostly excluded but some kept because of reference to important publications to ensure captured in review), Guideline, Meta-analysis, Pathogenesis, Registry, Review, Study.

For events within the AESI categories identified in May 2020 (subgroup 2A) the number of new articles published for each entity by subgroup and article type were counted but the full article was not reviewed. A spreadsheet for each system group was created to capture all newly published citations.

Nine of the May 2020 COVID-19 AESI had no published case definition. These were prioritized for development of new case definitions. The status as of end of August is shown below. Ultimately up to 10 new case definitions are planned as part of the work for COVID-19.

1. Multisystem inflammatory syndrome in children: Working group established in July and submission for publication due by October 15th, 2020.
2. Acute respiratory distress syndrome: Working group established in July and submission for publication due by October 15th, 2020.
3. Acute cardiovascular injury: Working group established in August and submission for publication due by November 15th, 2020.
4. Coagulation disorder: Working group established in August and submission for publication due by November 15th, 2020.
5. Acute kidney injury: Call for Working group volunteers August 10th, with plans to start work by mid-September and submission for publication by November 30th, 2020.
6. Acute liver injury: Call for Working group volunteers August 10th, with plans to start work by mid-September and submission for publication by November 30th, 2020.
7. Anosmia / ageusia: Call for Working group volunteers August 10th, with plans to start work by mid-September and submission for publication by November 30th, 2020.
8. Chilblain like lesions: deferred start until 2021 and could be replaced by a new AESI of higher priority.
9. Erythema multiforme: deferred start until 2021 and could be replaced by a new AESI of higher priority.

Separate excel spreadsheets were created to capture all newly identified, screened in citations in each of the above categories, for sharing with the Brighton Working groups. These spreadsheets supplement the citations included in the appendices of the May 25th COVID-19 AESI deliverable document.

For events included in subgroup 2B, it is planned to review the articles in full and to prepare tabular summaries in the same way as done for the May 25, 2020 AESIs. These will then be used to prioritize newly emerging entities for addition to the potential COVID-19 AESI list.

4. Results

4.1. Summary of Excluded Publications

From May 16 through August 7, a total of 5 separate searches were run; yielding 4679 citations, of which 1980 (42.3%) were screened in and the other 2699 (57.7%) screened out. Among the articles screened out the decision was based on title alone for 87.3% (2355) and on review of abstract and/or full text article for 12.7% (344). Table 1 summarizes the reason articles were screened for all search dates, separated by whether it was based on title alone or review of abstract/full text. The table also shows variation in distribution of reason excluded for all separate search dates without distinguishing whether exclusion was by title alone or abstract / full text. The single largest reason for exclusion was duplicate publications as a result of the separate searches done by sub-category in the first 3 search dates and then likely overlap in the end date of one search and beginning of the next. Nearly half of the articles excluded by abstract/full text review (166 of 344) involved letters to the editor.

TABLE 1. REASONS FOR EXCLUDING ARTICLES OVERALL AND BY INDIVIDUAL SEARCH DATE

Reason for Exclusion	All Search Dates: Total (%) Excluded by:		Distribution of Reason for Exclusion by Search Date % all excluded (title & abstract/full text)				
	Title alone	Abstract / Full Text	June 12	July 8	July 21	July 31	August 7
Duplicate	979 (36.3%)	4 (0.1%)	25.9%	42.6%	35.8%	39.3%	48.0%
Therapy/Testing/Prevention	286 (10.6%)	29 (1.1%)	9.1%	13.2%	13.6%	13.7%	10.3%
Healthcare	309 (11.4%)	9 (0.3%)	13.9%	11.9%	8.4%	14.3%	9.6%
Unrelated	259 (9.6%)	7 (0.3%)	10.3%	8.8%	8.8%	8.3%	14.2%
Limited focus	76 (2.8%)	8 (0.2%)	4.8%	1.9%	2.7%	3.0%	1.3%
Non-contributory	104 (3.9%)	116 (4.3%)	12.2%	4.6%	10.0%	3.6%	6.3%
Non-English	3 (0.1%)	8 (0.3%)	0.5%	0.5%	0.6%	0.0%	0.0%
Comment/Response/Erratum	339 (12.6%)	166 (6.2%)	23.3%	16.5%	20.1%	17.9%	10.3%
Total excluded/all retrieved (% excluded)	2355/4679 (50.3%)	344/4679 (7.4%)	866/1550 (55.9%)	885/1517 (58.3%)	478/784 (61.0%)	168/357 (47.1%)	302/471 (64.1%)

4.2. Summary of Included Publications for the First Quarterly Update

Table 2 provides a summary by body system of the articles remaining after screening. These are ordered by Primary Topic as described in Methods.

AESI already on COVID-19 list: The vast majority of the recently published articles related to AESI already identified on the COVID-19 list.

- Neurologic: 258 (72%) of 350 new publications.
- Hematologic: 231 (83%) of 278 new publications.
- Cardiac: 178 (92%) of 193 new publications.
- Dermatologic: 63 (45.3%) of 139 new publications. An additional 41 (29.4%) related to entities that were well described but not considered a priority for the AESI list including urticaria, maculopapular, vesicular and livedoid rashes.
- Multisystem inflammatory syndrome: 59 (63%) of 94 articles focused on children.

- Gastrointestinal: 33 (44.6%) of 74 new publications were either for acute liver injury or intestinal thrombosis which is covered under the coagulation disorders.
- Kidney: 100% of the 37 new publications addressed acute kidney injury.

For each of the above, the new publications in the 'General Articles' column focused on the breadth of clinical complications already added to the COVID-19 AESI list. A spreadsheet has been prepared with all new publications listed separately by tab for the body system as noted in the table. This will be made available to the newly formed Brighton Collaboration working groups currently defining ARDS, Multisystem inflammatory disease in children, coagulation disorders, acute cardiovascular injury as well as the next 3 groups to be formed (anosmia/ageusia, acute kidney injury, acute liver injury).

4.3. Entities Not Yet included on the COVID-19 AESI List

While there have been a number of new system-specific complications reported, as shown in Table 2, most involve single or a few case reports. These are listed and will not be discussed further. However, 4 entities were reported in greater number and these are summarized below:

1. Musculoskeletal system- Rhabdomyolysis [2-13]
   - There was a total of 13 case reports from 6 countries (8 USA[2-8]; 1 each: France[9], Spain[10], China[11], Mexico[12], Turkey[13]). All were male, aged 16-88 years. Documented comorbidities were present in at least 9, including type 2 diabetes, obesity, hypertension. Rhabdomyolysis was the presenting complaint for 10 cases and developed during the course of hospitalization for COVID-19 in the other 3. Creatinine kinase elevation ranged from mild (1859 U/L) to massive (276,664 U/L). Six had associated acute kidney injury[2-5,8,9] with 4 needing hemodialysis[2,3,5,8]. All recovered. In the discussions most authors noted that viral infection can account for 5-10% of rhabdomyolysis with influenza virus causing the majority but other known causes including enteroviruses, mumps, adenovirus, orthomyxovirus, EBV, Hepatitis E, HIV, CMV, dengue and rubella. In the original descriptions of COVID-19 clinical disease from China, several reports noted myalgia and or elevated CK in about 10% of cases however the two were not linked. It was noted that acute kidney injury is a relatively common complication of rhabdomyolysis occurring in 7-10% of all cases. This is relevant since it is possible that it might be covered in the acute kidney injury case definition. This will be referred to the working group and is a reason not to add it to the AESI list at present. Additional reports will be found as the literature review continues and if not covered as part of acute kidney injury it could be considered for addition in the future.
2. Endocrine system - Pancreatitis 14[-28]
   - Prior to May 2020 there was a report from China that 17% of 52 COVID-19 patients had evidence of pancreatic injury, defined as any abnormality in amylase or lipase.[14] However, symptoms of pancreatitis were not reported. Since May 16, 2020, pancreatitis was the focus of 13 case reports plus for one report of MISC it was noted that pancreatitis was the presenting complaint.[18] Overall, there were 14 cases reported from 10 different countries. USA had 4 reports[15-18], Denmark 2 from the same family[19], and 1 from each of the remainder: France[20], Portugal[21], Romania[22], UK[23], Israel[24], Iran[25], UAE[26], Pakistan.[27] There were two pediatric cases (7[17] and 10[18] years) and the rest adults ranging from 24 to 68 (8 were aged <50yrs). There were 5 males, 9 females; Comorbidities were noted for 6 (obesity, hypertension most common). Pancreatitis was the presenting complaint for 5, concurrent with COVID19 infection in 2, onset after admission for COVID-19 and couldn't be determined for 1. All recovered. For most of the cases other factors such as alcohol, gallstones, trauma and recent invasive procedures were noted to be absent.
   - One report was an interesting study from the US that identified 339 patients with acute thyroiditis among whom 75 were tested for COVID.[28] They compared the 14 COVID + to the 61 negative; The two groups were similar for age, gender, race and pattern of pancreatitis (10-14% necrotizing and the rest interstitial).

Final diagnosis as to etiology of pancreatitis was significantly different between the two groups. Among the 61 COVID negative cases of acute pancreatitis 64% were alcohol related, 31% with gallstones, 3% other cause and 2% idiopathic. Among the 14 COVID positive 29% were alcohol related, 7% gallstones, 7% other and 57% idiopathic. The COVID positive cases also had higher mortality (21% versus 2%) and higher incidence of both multiorgan failure (14% vs 0) and persistent organ failure (57% vs 8%). Of interest an increased expression of SARS-CoV-1 in pancreatic islet cells was noted during the 2000-2004 SARS outbreak and that some survivors developed acute diabetes.[29 Yang 2010] Also noted by most authors was that up to 10% of acute pancreatitis is thought to have an infectious cause, most commonly viral (mumps, coxsackie, CMV). Also relevant to the setting of COVID-19 was the rarity of drug-related pancreatitis (<5%). That said it can follow use of acetaminophen, dexamethasone, ciprofloxacin, pantoprazole and tocilizumab and there have been two reports of acute pancreatitis with hypertriglyceridemia in COVID-19 patients treated with combination tocilizumab and lopinavir/ritonavir.[24]

3. Endocrine system – Thyroiditis [30-35]

- Thyroiditis is a newly reported entity since May 2020. There were 5 new case reports published, 1 from Singapore[30] and 4 from Italy.[31-34] The Singapore case was a 45-year-old previously healthy man who developed Hashimoto's autoimmune thyroiditis 1 week after a COVID-19 upper respiratory tract infection which had a mild course. In contrast the other case reports involved 4 women, aged 18, 41, 43 and 69 years, with subacute thyroiditis that onset 1-6 weeks following documented COVID-19 infection in 3 and was the sole presenting feature in one with no COVID symptoms but who was COVID PCR positive. All recovered on treatment.
- Muller et al[35] assessed the prevalence of subacute thyroiditis among patients admitted to ICU comparing 2020 during the COVID outbreak in Italy to 2019. They studied 93 consecutive COVID positive patients admitted to their high intensity ICU (HICU-20) as well as another 52 COVID positive admitted to the lower intensity ICU (LICU-20) and 101 patients admitted in 2019 to the high intensity ICU (HICU-19). Thyroid function was assessed on admission to ICU. They found evidence of thyrotoxicosis in 15% of the HICU-20 versus 1% of HICU-19. Of greatest interest was a follow-up study done in 8 HICU-20 patients. Patients were followed for a mean of 55 days post discharge and 2 (25% confirmed to have hypothyroidism and autoimmune thyroiditis features on thyroid scan. The rest had normal thyroid function and no thyroid auto-antibodies. They concluded that a substantial portion of critically ill COVID-19 patients present wtih thyrotoxicosis which is a mix of non-thyroidal illness syndrome related to severe illness and subacute thyroiditis.

4. Hematologic system - Autoimmune hemolytic anemia (AIHA) [36-42]

- By mid-May 2020 there were already 2 reports of AIHA. At the time these were considered insufficient to add this to the COVID-19 list. Lazarian et al described 7 patients (6 French, 1 Belgian hospital) who had their 1st episode of AIHA during acute COVID-19 infection.[36] At least 4 had known predisposing conditions (Chronic lymphocytic leukemia in 2, marginal zone lymphoma in 2). Lopez described a single case in an American 46-year-old female with congenital thrombocytopenia but not active and no other known associations.[37]
- Since May 16 there have been an additional 5 case reports of AIHA – 3 from the USA[38-40], 1 from Belgium[41] and 1 from Spain.[42] Age ranged from 13-62 years with 3 females and 2 males. 4 of the 5 had unusual medical history but not clear if it was associated: a 46 year old female had a history of ITP during pregnancy 27 years earlier; a 17 year old male had a history of refractory chronic ITP; a 51 year old female had a history of ductal breast carcinoma with mastectomy in early 2020; and a 62 year old male had orophyarngeal squamous cell cancer and was on day 3 after the first dose of cisplatin when he presented with COVID-19. The 5th case, a 13-year-old female was previously healthy.[42]

TABLE 2. AESI RELEVANT TO SPECIFIC VACCINE PLATFORMS FOR COVID-19 VACCINES

BODY SYSTEM	Total Articles	AESI (number articles) already on COVID-19 List	Entities (number articles) Not yet on the AESI list	General Articles
Neurologic	350	Anosmia/Ageusia (126), GBS (40), encephalitis (29) encephalopathy (23), brain hemorrhage (16), seizure (13), ADEM (7), myelitis (4)	Vasculitis(3), SIADH(2), Hearing loss(4), ophthalmoplegia(2), facial palsy(2), optic neuritis(1), transient cortical blindness(1), dysphagia(1), myoclonus(1), tremor+ataxia(1), mixed central/peripheral nervous system disorder(1), disrupted sleep quality(1), benign intracranial hypertension(1), hypothermia(1),fulminant cerebral edema(1), dysautonomia(1),	Reviews(32) Studies(12) Pathogenesis(11) Meta-analyses(4) Virus in tissue(5) Registry(3) Guideline(1)
Hematologic	278	Thrombosis(62), Stroke(59), Coagulopathy(42), Pulmonary embolus(39), other thromboembolism(20), Ischemia(7), endothelial dysfunction(2),	Autoimmune hemolytic anemia (5, all case reports)	Reviews(6) Pathogenesis(6)
Cardiac	193	Myocarditis(42), acute cardiac injury(41), STEMI(20), arrhythmia(18), heart failure(18), endothelial dysfunction(13), acute coronary syndrome(9), Takostsubo stress cardiomyopathy(7), MI(7), ruptured aneurysm(2), sudden cardiac death(1),	cardiac tamponade(2), micturition syncope(1),	Reviews(6) Studies(3) Meta-analysis(1) Pathogenesis(1) Virus in tissue(1)
Dermatologic	139	Chilblain(48), cutaneous vasculitis(9), erythema multiforme(4), alopecia(2)	Urticaria(11), maculopapular or vesicular rash(26), livedoid rash(4), necrotic/gangrene skin lesion(3), erythema nodosum(2), atypical Sweet's syndrome(1), lichenoid eruption(1), cutaneous hyperesthesia(1), pruritic papules(1), pityriasis rosea(1), non-genital warts(1), exfoliative toxic-shock like(1), eosinophilic granulomatosis mimicking COVID(1)	Reviews(13) Studies(6) Pathogenesis(1) Registry(1) Guideline(1)
Multisystem inflammatory syndrome(MIS)	94	MIS-Children(59)	MIS-Adult(7), Hemophagocytic lymphohistiocytosis(5), Hyperferritinemic syndrome(2), Macrophage activation syndrome(1),	Studies(4) Pathogenesis(15) Meta-analysis(1)

BODY SYSTEM	Total Articles	AESI (number articles) already on COVID-19 List	Entities (number articles) Not yet on the AESI list	General Articles
Gastrointestinal	74	Acute liver injury(24) GI ischemia/thrombosis(9)	Pancreatitis(13), enterocolitis(6), Acute hepatitis(3), presentation mimicking cute abdomen(2), appendicitis(2), oral mucosal lesions(2), bowel perforation(1), Acute cholecystitis(1)	Reviews(3) Studies(2) Meta-analyses(4) Pathogenesis(1)
Respiratory	38	ARDS(3-autopsy studies, 1 premature infant),	Pneumomediastinum(14) Pneumothorax(13) Lung abscess/cavitation(3), Pulmonary fibrosis(2)	Reviews (2)
Kidney	37	Acute kidney injury(37)		
Musculoskeletal	18		Rhabdomyolysis(11), arthritis(4), myositis(1)	Reviews(2)
Ocular	16		Conjunctivitis(2), retinopathy(2), uveo-retinitis as part of MIS(1), episcleritis(1), papillophlebitis(1), orbital emphysema(1), retro-orbital pain mimicking Dengue(1)	Reviews(2) Studies(5)
Endocrine	15		Thyroiditis(6), adrenal injury(4), hyperglycemia(3), parotitis(2)	
Miscellaneous other				
Co-infection	21	17 case reports (3 H. Zoster, 3 bacterial infection, 3 TB, 2 influenza, 1 respiratory pathogens, 1 RSV, 1 rhinovirus, 1 EBV, 1 parainfluenza, 1 HIV, 1 Dengue); 2 Meta-analyses; 2 Reviews.		
Enhanced disease	5	Case report (1-7 recurrent cases; no evidence for enhanced disease), Pathogenesis(2), Commentary(2);		
Psychiatric	3	Case reports(2; manic episode, psychotic episode); Meta-analysis (1)		
Autoimmune	1	Case report(1-concomitant onset of COVID-19 and new diagnosis of SLE)		
Mixed Clinical	59	Asymptomatic cases: 2 reviews, 1 metanalysis Neonatal/Pediatric cases: 6 case reports, 3 studies, 11 reviews, 2 meta-analyses Pregnancy focus: 7 studies, 1 review, 1 meta-analysis Adult clinical overviews (some include pregnancy): 2 case reports, 4 studies, 10 reviews, 8 meta-analyses, 1 commentary.		
Pregnancy	133	Case reports(50): fetal loss(2), fetal skin edema(1), fetal heart rate changes(1), breast milk non-transmission(1), breast milk antibody(1), placental involvement(4),premature birth(1), vertical transmission(14), neonatal infection(8), maternal mortality(4), maternal COVID complications(13), Meta-analyses/Reviews(40): Outcomes(25), Vertical transmission(12), Fetus(1), maternal mortality(1), thrombocytopenia(1). Studies(32): Outcomes(22), placental pathology(5), maternal mortality(3), vertical transmission(1), preeclampsia/eclampsia(1) Pathogenesis(7): vertical transmission(5), maternal mortality(1), placenta(1) Guidelines(2): Maternal mortality(1), Vertical transmission(1) Commentary(2): Outcomes(1), Neonatal(1)		

BODY SYSTEM	Total Articles	AESI (number articles) already on COVID-19 List	Entities (number articles) Not yet on the AESI list	General Articles
Articles screened in for potential relevance to AESI Tools but not to the AESI list per se				
Pathology	117	Autopsy studies(16; all consistent with AESI on COVID-19 list)	Mortality (99; most focus on case fatality rates by country or as part of systematic review or meta-analysis); Review(1) Pathogenesis(1)/	
Risk Factors	368	▪ For COVID Mortality (230); for COVID Severity(67); COVID mixed outcomes(27) ▪ By population: HIV(9), Children(4), by gender(2), Elderly(1), ▪ By co-morbidity: hematologic(6), autoimmune disease(4), cardiac(4), diabetes(3), kidney(2),myasthenia gravis(2), solid organ transplant(1), malignancy(1), obesity(1), immunocompromised(1), liver(1), multiple system(2).		
Background rate	22	Stroke(4), Acute coronary syndrome(6), Heart failure(3), STEMI(3), Takotsubo syndrome(2), ectopic pregnancy(1), Kawasaki disease(1), ectopic pregnancy(1), maternal/child mortality(1).		

**Review of nucleic acid platforms, and protein platforms has not been conducted since these are novel*

4.4. Pregnancy Outcomes: Maternal, Foetal, Neonatal

As per table 2 there have been 133 publications focused on various aspects of pregnancy outcomes since May 16th. The sheer volume of publications prohibited a detailed review that could be presented here. As noted in 5 below, this will be a priority in the coming month in order to determine whether or not any pregnancy-related AESI should be added to the COVID-19 list.

5. Recommendations & discussion

Based on the updated literature review, covering May 16 through August 7, 2020, SPEAC does not recommend adding any new AESI to the COVID-19 priority list at this time. Four conditions were notable for an increased number of reports including rhabdomyolysis, pancreatitis, subacute and possibly autoimmune thyroiditis and autoimmune hemolytic anemia. At this point in time it is not recommended that they be added to the AESI list. It is quite possible that rhabdomyolysis will be included in the case definition for acute kidney injury. Should there be an increase in new reports or a more definitive link to COVID-19 than currently exists over coming months, SPEAC may change this recommendation and add one or more to the AEIS list.

A priority over the next 1-2 months will be to review the many publications on pregnancy outcomes to determine which if any should be added to the AESI list. Should this happen SPEAC will notify CEPI and the COVID-19 vaccine developers using established communication channels.

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ANNEXES

Annex I

Revised Search Strategy 2.0 for literature relevant to updates to the potential AESI list for covid-19 (used to retrieve articles from May 16 - July 20, 2020)

Two different searches:

1. Go back to Jan 1, 2020; Update monthly – capture all systematic reviews and meta-analyses for COVID19 without any exclusions – so can capture scope of COVID with methodologic rigor covering more than just the clinical presentation/complications (e.g. compilations of clinical severity by region, risk scores, pathogenesis, immunity, vaccines)

(("Coronavirus"[Mesh] OR "coronavirus"[tiab] OR "nCoV"[tiab] OR "COVID"[tiab] OR "SARS-CoV-2"[tiab]) AND English[lang] AND ("2020/01/01"[PDat] : "2050/01/01"[PDat]) AND (systematic[sb] OR Meta-Analysis[ptyp]))

2. Subsearches – to be done first from May 16 up to Friday June 12 (when requested) and then every 2 weeks, thereafter each Friday
   - May 16 to Jun 12: ~ 11,544 citations in pubmed searches that would need manual screening
     - New strategy retrieved 1290 (11.2%) after removal of duplicates (212) (

Search Terms – looking in Title Only

Strategy
(((Main Terms) NOT (Exclusion Terms)) AND Sub Search X*)
*repeated iteratively for each sub search

Main Terms

(("Coronavirus"[Mesh] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) AND English[lang] AND "2020/05/15 15.00"[MHDA]:"2050/01/01 15.00"[MHDA])

Exclusion Terms

("inflammatory bowel disease"[ti] OR "inflammatory bowel diseases"[ti] OR "inflammatory bowel syndrome"[ti] OR "inflammatory bowel syndromes"[ti] OR "tocilizumab"[ti] OR "screen"[ti] OR "screening"[ti] OR "guidance"[ti] OR "guide"[ti] OR "therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "management"[ti] OR "manage"[ti] OR "managing"[ti] OR "pharmacologic"[ti] OR "pharmacological"[ti] OR "murine"[ti] OR "stroke care"[ti] OR "recommendation"[ti] OR "recommendations"[ti] OR "vaccine"[ti] OR "vaccines"[ti] OR "anti-viral"[ti] OR "anti-virals"[ti] OR "nutrition"[ti] OR "anxiety"[ti] OR "telemedicine"[ti] OR "rheumatic"[ti] OR "thromboprophylaxis"[ti] OR "methylprednisolone"[ti] OR "steroids"[ti] OR "corticosteroid"[ti] OR "corticosteroids"[ti] OR "chloroquine"[ti] OR "hydroxychloroquine"[ti] OR "azithromycin"[ti] OR "remdesivir"[ti] OR "ribavirin"[ti] OR "lopinavir"[ti] OR "ritonavir"[ti] OR "azithromycin"[ti] OR "favipiravir"[ti] OR "biomodulator"[ti] OR "biomodulators"[ti] OR "psychosis"[ti] OR "neuropsychiatric"[ti] OR "infection control"[ti] OR "precautions"[ti] OR "aspergillosis"[ti] OR "coccidioidomycosis"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti] OR "multiple sclerosis"[ti] OR "managed"[ti] OR "infusion"[ti] OR "IBD"[ti] OR "predict"[ti] OR "predictor"[ti] OR "predictors"[ti] OR "prediction"[ti] OR "predictions"[ti] OR "predicting"[ti] OR "gene"[ti] OR "genes"[ti] OR "transplant"[ti] OR "transplants"[ti] OR "transplantation"[ti] OR "racism"[ti] OR "ethnic"[ti] OR "racial"[ti] OR "ethnicity"[ti] OR "lifestyle"[ti] OR "chronic inflammation"[ti] OR "chronic inflammatory condition"[ti] OR

"chronic inflammatory conditions"[ti] OR "obesity"[ti] OR "chronic use"[ti] OR "chronic liver disease"[ti] OR "chronic hepatitis"[ti] OR "conference"[ti] OR "conferences"[ti] OR "infliximab"[ti] OR "colchicine"[ti] OR "anakinra"[ti] OR "famotidine"[ti] OR "ruxolitinib"[ti] OR "clozapine"[ti] OR "ocrelizumab"[ti] OR "Chron's"[ti] OR "cigarette"[ti] OR "smoker"[ti] OR "smoking"[ti] OR "vaping"[ti] OR "prognosis"[ti] OR "prognostic"[ti] OR "asthma"[ti])

Sub-Search 1: Neurologic Terms

("brain involvement"[ti] OR "neurological"[ti] OR "neurologic"[ti] OR "seizure"[ti] OR "seizures"[ti] OR "convulsion"[ti] OR "convulsions"[ti] OR "epilepsy"[ti] OR "status epilepticus"[ti] OR "leukoencephalopathy"[ti] OR "olfactory"[ti] OR "gustatory"[ti] OR "neuropathy"[ti] OR "paresthesia"[ti] OR "paraesthesia"[ti] OR "Miller Fisher"[ti] OR "smell"[ti] OR "taste"[ti] OR "nervous system"[ti] OR "stroke"[ti] OR "cerebrovascular"[ti] OR "myoclonus"[ti] OR Guillain*[ti] OR "encephalitis"[ti] OR "encephalopathy"[ti] OR "encephalitic"[ti] OR "encephalomyelitis"[ti] OR "rhomboencephalitis"[ti] OR "meningitis"[ti] OR "myelitis"[ti] OR "meningomyelitis"[ti] OR "meningoencephalitis"[ti] OR "anosmia"[ti] OR "hyposmia"[ti] OR "ageusia"[ti] OR "hypogeusia"[ti] OR "optic neuritis"[ti] OR "viral meningitis"[ti] OR "aseptic meningitis"[ti] OR "palsy"[ti] OR "cranial nerve"[ti] OR "dysphagia"[ti] OR "subarachnoid"[ti] OR "confusion"[ti] OR "confusional"[ti] OR "coma"[ti] OR "comatose"[ti] OR "unresponsive"[ti] OR "neuroinvasive"[ti] OR "neuroinvasion"[ti] OR "neurotropism"[ti] OR "neurotropic"[ti] OR "sensorineural hearing loss"[ti] OR "ataxia"[ti] OR "cerebellitis"[ti] OR "radiculitis"[ti] OR "neuritis"[ti] OR "polyneuritis"[ti] OR "polyneuropathy"[ti] OR "neuralgia"[ti] OR "weakness"[ti] OR "focal deficit"[ti])

Sub-Search2: Multisystem Inflammatory Syndromes Terms

("inflammatory"[ti] OR "hyperinflammatory"[ti] OR "hyper-inflammation"[ti] OR "hyper-inflammatory"[ti] OR "macrophage activation syndrome"[ti] OR "cytokine storm syndrome"[ti] OR "cytokine release syndrome"[ti] OR "kawasaki"[ti] OR "hemophagocytic lymphohistiocytosis"[ti] OR "haemophagocytic lymphohistiocytosis"[ti] OR "shock"[ti] OR "hyponatremia"[ti] OR "inflammation"[ti] OR "hyperferritinaemia"[ti] OR "hyperferritinemia"[ti] OR "hyperferritinaemic"[ti] OR "hyperferritinemic"[ti] OR "multisystem inflammatory syndrome"[ti] OR "inflammatory multisystem syndrome"[ti] OR "viral sepsis"[ti])

Sub-Search 3: Dermatologic Terms

("chilblain"[ti] OR "chilblains"[ti] OR "acral"[ti] OR "acro-ischemia"[ti] OR "urticaria"[ti] OR "urticarial"[ti] OR "rash"[ti] OR "rashes"[ti] OR "skin lesion"[ti] OR "skin lesions"[ti] OR "skin finding"[ti] OR "skin findings"[ti] OR "alopecia"[ti] OR "purpura"[ti] OR "purpuric"[ti] OR "vasculitis"[ti] OR "vasculitic"[ti] OR "angioedema"[ti] OR "Sweet's syndrome"[ti] OR "cutaneous"[ti] OR "Stevens-Johnson"[ti] OR "erythema multiforme"[ti] OR "pernio"[ti] OR "maculopapular"[ti] OR "varicella-like"[ti] OR "chickenpox-like"[ti] OR "papulovesicular"[ti] OR "exanthem"[ti] OR "exanthems"[ti] OR "exanthema"[ti] OR "exanthematous"[ti] OR "morbilliform"[ti] OR "erythema nodosum"[ti] OR "vesicular"[ti] OR "bullous"[ti] OR "bullae"[ti] OR "vesiculobullous"[ti] OR "livedoid"[ti] OR "livedo"[ti] OR "necrotic"[ti] OR "papule"[ti] OR "papules"[ti] OR "macule"[ti] OR "macules"[ti] OR "macular"[ti] or "papular"[ti] OR "petechial"[ti] OR "petechiae"[ti] OR "gangrene"[ti] OR "erythroderma"[ti] OR "pustulosis"[ti] OR "pustular"[ti] OR "pustule"[ti] OR "pustules"[ti] OR "angioedema"[ti] OR "vesicle"[ti] or "vesicles"[ti])

Sub-Search 4: Cardiac and Hematologic Terms

("myocarditis"[ti] OR "cardiomyopathy"[ti] OR "infarction"[ti] OR "infarct"[ti] OR "infarcts"[ti] OR "cardiac arrest"[ti] OR "microangiopathy"[ti] OR "micro-angiopathy"[ti] OR "microvascular inflammation"[ti] OR "vascular inflammation"[ti] OR "cardiogenic"[ti] OR "cardiogenic shock"[ti] OR "right ventricular failure"[ti] OR "cor pulmonale"[ti] OR "aneurysm"[ti] OR "aneurysmal"[ti] OR "mediastinum"[ti] OR "pneumomediastinum"[ti] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti] OR "myopericarditis"[ti] OR "pericarditis"[ti] OR "pericardial effusion"[ti] OR "endotheliitis"[ti] OR "heart failure"[ti] OR "vasculature"[ti] OR "acute coronary syndrome"[ti] OR "acute

coronary syndromes"[ti] OR "STEMI"[ti] OR "wide complex tachycardia"[ti] OR "vascular leak"[ti] OR "vascular leakage"[ti] OR "endothelial dysfunction"[ti] OR "microvascular dysfunction"[ti] OR "myocardial injury"[ti] OR "myocardial damage"[ti] OR "cardiac injury"[ti] OR "tachyarrhythmia"[ti] OR "tachyarrhythmias"[ti] OR "bradyarrhythmia"[ti] OR "bradyarrhythmias"[ti] OR "sudden cardiac death"[ti] OR "ischemia"[ti] OR "ischemic"[ti] OR "pericyte"[ti] OR "pericytes"[ti] OR "tachycardia"[ti] OR "bradycardia"[ti] OR "ventricular fibrillation"[ti] OR "atrial fibrillation"[ti] OR "atrial flutter"[ti] OR "cardiomegaly"[ti] OR "endomyocardial biopsy"[ti] OR "cardiac biopsy"[ti] OR "plaque rupture"[ti] OR "AV block"[ti] OR "bundle branch block"[ti] OR "asystole"[ti] OR "autoimmune hemolytic anemia"[ti] OR "disseminated intravascular coagulation"[ti] OR "lupus anticoagulant"[ti] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti] OR "microthrombus"[ti] OR "microthrombi"[ti] OR "embolism"[ti] OR "emboli"[ti] OR "embolic"[ti] OR "hemostasis disorder"[ti] OR "hemostasis disorders"[ti] OR "hemorrhage"[ti] OR "haemorrhage"[ti] OR "hemorrhagic"[ti] OR "haemorrhagic"[ti] OR "coagulopathy"[ti] OR "hypercoagulability"[ti] OR "microhemorrhage"[ti] OR "microhaemorrhage"[ti] OR "microhemorrhages"[ti] OR "microhaemorrhages"[ti] OR "microhemorrhagic"[ti] OR "microhaemorrhagic"[ti] OR "DIC"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti] OR "cardiac tamponade"[ti] OR "thrombocytopenia"[ti] OR "idiopathic thrombocytopenic purpura"[ti] OR "ITP"[ti] OR "antiphospholipid syndrome"[ti] OR "antiphospholipids"[ti] OR "complement-mediated"[ti] OR "complement activation"[ti])

Sub-Search 5: Combined kidney, gastrointestinal, musculoskeletal, ocular, respiratory, endocrine and general terms for complications including case report/case series

("acute kidney injury"[ti] OR "nephritis"[ti] OR "liver injury"[ti] OR "hepatitis"[ti] OR "pancreatitis"[ti] OR "hematochezia"[ti] OR "rhabdomyolysis"[ti] OR "musculoskeletal"[ti] OR "elevated creatinine kinase"[ti] OR "myositis"[ti] OR "follicular conjunctivitis"[ti] OR "keratoconjunctivitis"[ti] OR "retinitis"[ti] OR "uveitis"[ti] OR "pneumothorax"[ti] OR "atypical ARDS"[ti] OR "thyroiditis"[ti] OR "manifestation"[ti] OR "manifestations"[ti] OR "complication"[ti] OR "complications"[ti] OR "dysfunction"[ti] OR "case report"[ti] OR "case reports"[ti] OR "case-reports"[ti] OR "case-report"[ti] OR "first case"[ti] OR "case series"[ti])

Sub-Search 6: Pregnancy/Newborn/Fetus Terms plus pathology/pathogenesis/fatal outcomes

("pregnant"[ti] OR "pregnancy"[ti] OR "pregnancies"[ti] OR "maternal-fetal"[ti] OR "maternal"[ti] OR "maternal morbidity"[ti] OR "gestational diabetes"[ti] OR "antenatal bleeding"[ti] OR "spontaneous abortion"[ti] OR "missed abortion"[ti] OR "incomplete abortion"[ti] OR "chorioamnionitis"[ti] OR "endometritis"[ti] OR "preeclampsia"[ti] OR "HELLP"[ti] OR "congenital"[ti] OR "birth defect"[ti] OR "birth defects"[ti] OR "vertical transmission"[ti] OR "mother-to-newborn"[ti] OR "in utero"[ti] OR "intrauterine infection"[ti] OR "uterine infection"[ti] OR "amnionitis"[ti] OR "funisitis"[ti] OR "postpartum haemorrhage"[ti] OR "postpartum hemorrhage"[ti] OR "neonatal"[ti] OR "neonate"[ti] OR "neonates"[ti] OR "neurodevelopmental"[ti] OR "developmental delay"[ti] OR "disability"[ti] OR "small for gestational age"[ti] OR "growth retardation"[ti] OR "preterm"[ti] OR "premature"[ti] OR "prematurity"[ti] OR "failure to thrive"[ti] OR "fetal"[ti] OR "foetal"[ti] OR "fetus"[ti] OR "foetus"[ti] OR "fetuses"[ti] OR "fetuses"[ti] OR "placenta"[ti] OR "sepsis"[ti] OR "placentas"[ti] OR "placental"[ti] OR "miscarriage"[ti] OR "miscarriages"[ti] OR "stillbirth"[ti] OR "stillbirths"[ti] OR "stillborn"[ti] OR "autopsy"[ti] OR "autopsies"[ti] OR "postmortem"[ti] OR "mortem"[ti] OR "clinicopathological"[ti] OR "clinico-pathological"[ti] OR "clinical pathological"[ti] OR "immunopathology"[ti] OR "antibody-dependent"[ti] OR "mortality"[ti] OR "fatal"[ti] OR "fatality"[ti] OR "fatalities"[ti] OR "death"[ti] OR "deaths"[ti])

ANNEX II

Revised Search Strategy 2.1 for literature relevant to updates to the potential AESI list for covid-19 (used to retrieve articles from July 20 - August 7, 2020)

Updated to one big search on 7/20/20 (to be updated every Friday starting 7/31/20). Exclusionary terms shown in red Font. None of the inclusionary or exclusionary terms were changed from strategy 2.0. Main purpose of the change was to eliminate duplicates generated from multiple sub-searches.

((((("Coronavirus"[Mesh] OR "coronavirus"[ti] OR "nCoV"[ti] OR "COVID"[ti] OR "SARS-CoV-2"[ti]) AND English[lang] AND "2020/07/08 10.00"[MHDA]:"2050/01/01 15.00"[MHDA]) AND (("brain involvement"[ti] OR "neurological"[ti] OR "neurologic"[ti] OR "seizure"[ti] OR "seizures"[ti] OR "convulsion"[ti] OR "convulsions"[ti] OR "epilepsy"[ti] OR "status epilepticus"[ti] OR "leukoencephalopathy"[ti] OR "olfactory"[ti] OR "gustatory"[ti] OR "neuropathy"[ti] OR "paresthesia"[ti] OR "paraesthesia"[ti] OR "Miller Fisher"[ti] OR "smell"[ti] OR "taste"[ti] OR "nervous system"[ti] OR "stroke"[ti] OR "cerebrovascular"[ti] OR "myoclonus"[ti] OR Guillain*[ti] OR "encephalitis"[ti] OR "encephalopathy"[ti] OR "encephalitic"[ti] OR "encephalomyelitis"[ti] OR "rhomboencephalitis"[ti] OR "meningitis"[ti] OR "myelitis"[ti] OR "meningomyelitis"[ti] OR "meningoencephalitis"[ti] OR "anosmia"[ti] OR "hyposmia"[ti] OR "ageusia"[ti] OR "hypogeusia"[ti] OR "optic neuritis"[ti] OR "viral meningitis"[ti] OR "aseptic meningitis"[ti] OR "palsy"[ti] OR "cranial nerve"[ti] OR "dysphagia"[ti] OR "subarachnoid"[ti] OR "confusion"[ti] OR "confusional"[ti] OR "coma"[ti] OR "comatose"[ti] OR "unresponsive"[ti] OR "neuroinvasive"[ti] OR "neuroinvasion"[ti] OR "neurotropism"[ti] OR "neurotropic"[ti] OR "sensorineural hearing loss"[ti] OR "ataxia"[ti] OR "cerebellitis"[ti] OR "radiculitis"[ti] OR "neuritis"[ti] OR "polyneuritis"[ti] OR "polyneuropathy"[ti] OR "neuralgia"[ti] OR "weakness"[ti] OR "focal deficit"[ti]) OR ("inflammatory"[ti] OR "hyperinflammatory"[ti] OR "hyper-inflammation"[ti] OR "hyper-inflammatory"[ti] OR "macrophage activation syndrome"[ti] OR "cytokine storm syndrome"[ti] OR "cytokine release syndrome"[ti] OR "kawasaki"[ti] OR "hemophagocytic lymphohistiocytosis"[ti] OR "haemophagocytic lymphohistiocytosis"[ti] OR "shock"[ti] OR "hyponatremia"[ti] OR "inflammation"[ti] OR "hyperferritinaemia"[ti] OR "hyperferritinemia"[ti] OR "hyperferritinaemic"[ti] OR "hyperferritinemic"[ti] OR "multisystem inflammatory syndrome"[ti] OR "inflammatory multisystem syndrome"[ti] OR "viral sepsis"[ti]) OR ("chilblain"[ti] OR "chilblains"[ti] OR "acral"[ti] OR "acro-ischemia"[ti] OR "urticaria"[ti] OR "urticarial"[ti] OR "rash"[ti] OR "rashes"[ti] OR "skin lesion"[ti] OR "skin lesions"[ti] OR "skin finding"[ti] OR "skin findings"[ti] OR "alopecia"[ti] OR "purpura"[ti] OR "purpuric"[ti] OR "vasculitis"[ti] OR "vasculitic"[ti] OR "angioedema"[ti] OR "Sweet's syndrome"[ti] OR "cutaneous"[ti] OR "Stevens-Johnson"[ti] OR "erythema multiforme"[ti] OR "pernio"[ti] OR "maculopapular"[ti] OR "varicella-like"[ti] OR "chickenpox-like"[ti] OR "papulovesicular"[ti] OR "exanthem"[ti] OR "exanthems"[ti] OR "exanthema"[ti] OR "exanthematous"[ti] OR "morbilliform"[ti] OR "erythema nodosum"[ti] OR "vesicular"[ti] OR "bullous"[ti] OR "bullae"[ti] OR "vesiculobullous"[ti] OR "livedoid"[ti] OR "livedo"[ti] OR "necrotic"[ti] OR "papule"[ti] OR "papules"[ti] OR "macule"[ti] OR "macules"[ti] OR "macular"[ti] or "papular"[ti] OR "petechial"[ti] OR "petechiae"[ti] OR "gangrene"[ti] OR "erythroderma"[ti] OR "pustulosis"[ti] OR "pustular"[ti] OR "pustule"[ti] OR "pustules"[ti] OR "angioedema"[ti] OR "vesicle"[ti] or "vesicles"[ti]) OR ("myocarditis"[ti] OR "cardiomyopathy"[ti] OR "infarction"[ti] OR "infarct"[ti] OR "infarcts"[ti] OR "cardiac arrest"[ti] OR "microangiopathy"[ti] OR "micro-angiopathy"[ti] OR "microvascular inflammation"[ti] OR "vascular inflammation"[ti] OR "cardiogenic"[ti] OR "cardiogenic shock"[ti] OR "right ventricular failure"[ti] OR "cor pulmonale"[ti] OR "aneurysm"[ti] OR "aneurysmal"[ti] OR "mediastinum"[ti] OR "pneumomediastinum"[ti] OR "arrhythmia"[ti] OR "arrhythmias"[ti] OR "dysrhythmia"[ti] OR "dysrhythmias"[ti] OR "arrhythmic"[ti] OR "myopericarditis"[ti] OR "pericarditis"[ti] OR "pericardial effusion"[ti] OR "endotheliitis"[ti] OR "heart failure"[ti] OR "vasculature"[ti] OR "acute coronary syndrome"[ti] OR "acute coronary syndromes"[ti] OR "STEMI"[ti] OR "wide complex tachycardia"[ti] OR "vascular leak"[ti] OR "vascular leakage"[ti]

OR "endothelial dysfunction"[ti] OR "microvascular dysfunction"[ti] OR "myocardial injury"[ti] OR "myocardial damage"[ti] OR "cardiac injury"[ti] OR "tachyarrhythmia"[ti] OR "tachyarrhythmias"[ti] OR "bradyarrhythmia"[ti] OR "bradyarrhythmias"[ti] OR "sudden cardiac death"[ti] OR "ischemia"[ti] OR "ischemic"[ti] OR "pericyte"[ti] OR "pericytes"[ti] OR "tachycardia"[ti] OR "bradycardia"[ti] OR "ventricular fibrillation"[ti] OR "atrial fibrillation"[ti] OR "atrial flutter"[ti] OR "cardiomegaly"[ti] OR "endomyocardial biopsy"[ti] OR "cardiac biopsy"[ti] OR "plaque rupture"[ti] OR "AV block"[ti] OR "bundle branch block"[ti] OR "asystole"[ti] OR "autoimmune hemolytic anemia"[ti] OR "disseminated intravascular coagulation"[ti] OR "lupus anticoagulant"[ti] OR "thromboembolic"[ti] OR "thromboembolism"[ti] OR "thrombosis"[ti] OR "thromboses"[ti] OR "thrombotic"[ti] OR "microthrombus"[ti] OR "microthrombi"[ti] OR "embolism"[ti] OR "emboli"[ti] OR "embolic"[ti] OR "hemostasis disorder"[ti] OR "hemostasis disorders"[ti] OR "hemorrhage"[ti] OR "haemorrhage"[ti] OR "hemorrhagic"[ti] OR "haemorrhagic"[ti] OR "coagulopathy"[ti] OR "hypercoagulability"[ti] OR "microhemorrhage"[ti] OR "microhaemorrhage"[ti] OR "microhemorrhages"[ti] OR "microhaemorrhages"[ti] OR "microhemorrhagic"[ti] OR "microhaemorrhagic"[ti] OR "DIC"[ti] OR "Takotsubo"[ti] OR "Tako-Tsubo"[ti] OR "cardiac tamponade"[ti] OR "thrombocytopenia"[ti] OR "idiopathic thrombocytopenic purpura"[ti] OR "ITP"[ti] OR "antiphospholipid syndrome"[ti] OR "antiphospholipids"[ti] OR "complement-mediated"[ti] OR "complement activation"[ti]) OR ("acute kidney injury"[ti] OR "nephritis"[ti] OR "liver injury"[ti] OR "hepatitis"[ti] OR "pancreatitis"[ti] OR "hematochezia"[ti] OR "rhabdomyolysis"[ti] OR "musculoskeletal"[ti] OR "elevated creatinine kinase"[ti] OR "myositis"[ti] OR "follicular conjunctivitis"[ti] OR "keratoconjunctivitis"[ti] OR "retinitis"[ti] OR "uveitis"[ti] OR "pneumothorax"[ti] OR "atypical ARDS"[ti] OR "thyroiditis"[ti] OR "manifestation"[ti] OR "manifestations"[ti] OR "complication"[ti] OR "complications"[ti] OR "dysfunction"[ti] OR "case report"[ti] OR "case reports"[ti] OR "case-reports"[ti] OR "case-report"[ti] OR "first case"[ti] OR "case series"[ti]) OR ("pregnant"[ti] OR "pregnancy"[ti] OR "pregnancies"[ti] OR "maternal-fetal"[ti] OR "maternal"[ti] OR "maternal morbidity"[ti] OR "gestational diabetes"[ti] OR "antenatal bleeding"[ti] OR "spontaneous abortion"[ti] OR "missed abortion"[ti] OR "incomplete abortion"[ti] OR "chorioamnionitis"[ti] OR "endometritis"[ti] OR "preeclampsia"[ti] OR "HELLP"[ti] OR "congenital"[ti] OR "birth defect"[ti] OR "birth defects"[ti] OR "vertical transmission"[ti] OR "mother-to-newborn"[ti] OR "in utero"[ti] OR "intrauterine infection"[ti] OR "uterine infection"[ti] OR "amnionitis"[ti] OR "funisitis"[ti] OR "postpartum haemorrhage"[ti] OR "postpartum hemorrhage"[ti] OR "neonatal"[ti] OR "neonate"[ti] OR "neonates"[ti] OR "neurodevelopmental"[ti] OR "developmental delay"[ti] OR "disability"[ti] OR "small for gestational age"[ti] OR "growth retardation"[ti] OR "preterm"[ti] OR "premature"[ti] OR "prematurity"[ti] OR "failure to thrive"[ti] OR "fetal"[ti] OR "foetal"[ti] OR "fetus"[ti] OR "foetus"[ti] OR "fetuses"[ti] OR "fetuses"[ti] OR "placenta"[ti] OR "sepsis"[ti] OR "placentas"[ti] OR "placental"[ti] OR "miscarriage"[ti] OR "miscarriages"[ti] OR "stillbirth"[ti] OR "stillbirths"[ti] OR "stillborn"[ti] OR "autopsy"[ti] OR "autopsies"[ti] OR "postmortem"[ti] OR "mortem"[ti] OR "clinicopathological"[ti] OR "clinico-pathological"[ti] OR "clinical pathological"[ti] OR "immunopathology"[ti] OR "antibody-dependent"[ti] OR "mortality"[ti] OR "fatal"[ti] OR "fatality"[ti] OR "fatalities"[ti] OR "death"[ti] OR "deaths"[ti])))) NOT ("inflammatory bowel disease"[ti] OR "inflammatory bowel diseases"[ti] OR "inflammatory bowel syndrome"[ti] OR "inflammatory bowel syndromes"[ti] OR "tocilizumab"[ti] OR "screen"[ti] OR "screening"[ti] OR "guidance"[ti] OR "guide"[ti] OR "therapy"[ti] OR "therapies"[ti] OR "therapeutic"[ti] OR "treatment"[ti] OR "treatments"[ti] OR "drug"[ti] OR "drugs"[ti] OR "trial"[ti] OR "trials"[ti] OR "prevention"[ti] OR "prevent"[ti] OR "prevents"[ti] OR "management"[ti] OR "manage"[ti] OR "managing"[ti] OR "pharmacologic"[ti] OR "pharmacological"[ti] OR "murine"[ti] OR "stroke care"[ti] OR "recommendation"[ti] OR "recommendations"[ti] OR "vaccine"[ti] OR "vaccines"[ti] OR "anti-viral"[ti] OR "anti-virals"[ti] OR "nutrition"[ti] OR "anxiety"[ti] OR "telemedicine"[ti] OR "rheumatic"[ti] OR "thromboprophylaxis"[ti] OR "methylprednisolone"[ti] OR "steroids"[ti] OR "corticosteroid"[ti] OR "corticosteroids"[ti] OR "chloroquine"[ti] OR "hydroxychloroquine"[ti] OR "azithromycin"[ti] OR "remdesivir"[ti] OR "ribavirin"[ti] OR "lopinavir"[ti] OR "ritonavir"[ti] OR "azithromycin"[ti] OR "favipiravir"[ti] OR "biomodulator"[ti] OR "biomodulators"[ti] OR "psychosis"[ti] OR "neuropsychiatric"[ti] OR "infection control"[ti] OR "precautions"[ti] OR "aspergillosis"[ti] OR "coccidioidomycosis"[ti] OR "surgery"[ti] OR "procedure"[ti] OR "procedures"[ti] OR "multiple sclerosis"[ti] OR "managed"[ti] OR "infusion"[ti] OR "IBD"[ti] OR "predict"[ti] OR "predictor"[ti] OR "predictors"[ti] OR "prediction"[ti] OR "predictions"[ti] OR "predicting"[ti] OR "gene"[ti] OR "genes"[ti] OR "transplant"[ti]

OR "transplants"[ti] OR "transplantation"[ti] OR "racism"[ti] OR "ethnic"[ti] OR "racial"[ti] OR "ethnicity"[ti] OR "lifestyle"[ti] OR "chronic inflammation"[ti] OR "chronic inflammatory condition"[ti] OR "chronic inflammatory conditions"[ti] OR "obesity"[ti] OR "chronic use"[ti] OR "chronic liver disease"[ti] OR "chronic hepatitis"[ti] OR "conference"[ti] OR "conferences"[ti] OR "infliximab"[ti] OR "colchicine"[ti] OR "anakinra"[ti] OR "famotidine"[ti] OR "ruxolitinib"[ti] OR "clozapine"[ti] OR "ocrelizumab"[ti] OR "Chron's"[ti] OR "cigarette"[ti] OR "smoker"[ti] OR "smoking"[ti] OR "vaping"[ti] OR "prognosis"[ti] OR "prognostic"[ti] OR "asthma"[ti]))

Appendix 2 Quality of Life (QOL) sub-study

Introduction and aim

For a random sample of the total cohort, a sub-study will be conducted to assess quality of Life (QOL) outcomes in vaccinees.

COVID-19 has affected people's lives in many ways, not only for those who contract the virus but also for those who need to follow guidelines to restrict the spread of the virus. Restrictions throughout the UK have led to people spending more time at home, possibly in isolation, with the potential for loss of livelihoods, an inability to see family and friends and other restrictions on life. These changes have had an impact on quality of life both physically and emotionally. The aim of this sub-study is to estimate the effect of the COVID-19 vaccine on individual QOL in the UK.

Methods

A random sample of the total cohort will be selected in a prospective manner (during study recruitment) to participate in the sub-study. This sub-study sample size will consist of 3500 participants.

An additional questionnaire for the QOL sub-study will be administered at enrolment (baseline), 4.5 months and 12 months following first vaccination dose. This questionnaire will consist of the PROMIS Scale v1.2 – Global Health, which consists of 10 questions, plus some additional questions which will be asked on the 4.5 month and 12 month follow up points. The PROMIS Scale v1.2 – Global Health is a questionnaire which is widely used to assess health related QOL.

This sub-study is intended to be an exploratory analysis of changes in QOL outcomes between baseline, 4.5 months and 12 months following vaccination. Individual level change in outcomes will be calculated between the time periods and summary statistics will be used to display average change for the entire sub-study population. In addition, modelling may be used to assess potential associations between COVID-19 vaccination and individual QOL. Additional appropriate analyses using other suitable methods may be considered to further examine public health QOL related issues.

The PROMIS Scale v1.2 – Global Health questionnaire (sample provided below) is easy for vaccinees to complete (it takes less than 10 minutes to complete). Vaccinees who participate in the QOL sub-study will still receive all questionnaires administered in the main study. They will receive QOL questionnaires separately at the designated timepoints and will otherwise not be treated any differently from participants in the main study.

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Additional questions for 4.5 month and 12 month QOL study follow up

1. **Since being vaccinated, to what degree do you agree with the following statements.**

I am able to…..	**Strongly disagree**	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly agree**	**Not applicable**
…see my friends and family more in person						
….have more in person contact with my Health Care Professionals						
…contribute more to work-related activities or community service						

Appendix 3 Management of adverse events