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

Short Title: Comparing COVID-19 Vaccine Schedule Combinations in adolescents (Com-COV3)

Ethics Ref: 21/SC/0310

IRAS Project ID: 304450

ISRCTN Number: 12348322

EudraCT Number: 2021-004267-27

OVG Study Number: OVG 2021/04

Date and Version No: V6.0 18- Jan-2022

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Sponsor:	University of Oxford
Funder:	UK Vaccine Task Force (VTF) National Institute Health Research (NIHR) Novavax (Vaccine supply)
Chief Investigator Signature:	Matthew Snape
Statistician Signature:	Xinxue Liu, Oxford Nick Andrews, PHE

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Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator	Signature	Site name or ID number	Date

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0. KEY TRIAL CONTACTS

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1. CONFLICT OF INTEREST DECLARATION

One of the COVID-19 vaccines approved for use in the current pandemic, ChAdOx1 nCOV-19, was developed as a partnership between the University of Oxford, who are sponsoring and coordinating this study, and AstraZeneca. The University of Oxford and AstraZeneca have committed to making the vaccine available on a 'not for profit' basis for the duration of the current pandemic. Both parties could potentially profit from this vaccine in the future. ChAdOx1 nCOV-19 is not included in this study, but this potential conflict is specified here for the sake of completeness.

M. Snape is an investigator on the Cov001, Cov002 and COV006 studies evaluating ChAdOx1 nCOV19. These studies are funded by NIHR and receive logistical support from AstraZeneca. M Snape is an investigator on Com-COV, funded by the NIHR. M Snape is currently, or has recently been, an investigator on studies funded +/- sponsored by vaccine manufacturers including Pfizer, GlaxoSmithKline, Janssen, MCM vaccines, Novavax and Medimmune. He receives no personal financial benefit for this work.

2. LAY SUMMARY

The successful roll-out of COVID vaccines such as 'COVID-19 mRNA Vaccine BNT162b2' and the Oxford/AstraZeneca ChAdOx1 nCOV-19 vaccine has saved approximately 60 000 lives in the UK alone up to July 2021.(1) Both of these vaccines are administered as a two-dose regimen, as is the adjuvanted protein COVID-19 vaccine from Novavax, NVXCoV2373, which is under rolling review of the MHRA at the time of writing.

The use of heterologous prime/boost (mix and match) schedules of COVID-19 vaccines has already been studied in COMCOV and COMCOV2, and a schedule with ChAdOx1 nCOV-19 as the first dose, followed by BNT162b2 as the second dose has been shown to be highly immunogenic and is now deployed routinely in non-elderly populations in Canada and many northern European countries.

Use of heterologous prime/boost schedules could also potentially be of benefit in an adolescent immunisation campaign. The potential benefits (and costs) of extending the UK COVID-19 vaccine immunisation to adolescents in the UK is under active review by the JCVI, and on 13th September 2021 it was announced that a first dose of BNT162b2 was recommended for all 12 to 17 –year-olds in the UK.(2) On 15th November 2021, a second dose of BNT162b2, to be given at least 12 weeks after the first, was recommended for all 16-to-17 year olds in the UK.(3) followed by a

recommendation for a second dose of BNT162b2, to be given at least 12 weeks after the first, for all 12 to 15 year-olds on 29th November 2021,.(4)

One concern regarding adolescent immunisation is a rare side effect of inflammation of the heart muscle (myocarditis) or membrane surrounding the heart (pericarditis) that has been observed after receipt of the second dose of BNT162b2, especially in young men.(5) Mixed schedules with alternative vaccines used for the second dose, or using fractional doses of COVID-19 vaccines, could be an alternative that allows protection against COVID-19 while avoiding a second full dose of BNT162b2, and could also help deploy existing stocks of vaccine as effectively as possible.

Accordingly, this study will determine the side effect profile, and the immune responses of heterologous and/or fractional COVID-19 vaccination schedules in adolescents, using BNT162b2 as a first dose, and a second dose administered from 8 weeks later of either BNT162b2 (full or one third dose) or NVXCoV2373 (full dose). Following the JCVI recommendation on 29th November 2021 that all 12 to 15 year-olds should be offered a second dose of BNT162b2 vaccine, the study design was amended to focus on immune response to BNT162b2. After this date, participants will be randomised 1:1 to either full or one-third dose BNT162b2 for their second vaccination. Participants will no longer be randomised to the Novavax arm of the study to prioritise the arms of the study that are likely to be more policy relevant. This does not reflect any concern regarding the safety or immunogenicity of the Novavax vaccine. A further review of the study design will be undertaken following an interim analysis in late 2021, and with input from the study Trial Steering Committee.

3. SYNOPSIS

Trial Title	A single-blind, randomised, phase II multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules in adolescents (COMCOV-3)
Internal ref. no. (or short title)	Comparing COVID-19 Vaccine Schedule Combinations in adolescents (Com-COV3)
Trial registration	EudraCT: 2021-004267-27 ISRCTN: 12348322
Sponsor	University of Oxford, Clinical Trials and Research Governance, Joint Research Office, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB, United Kingdom

Funder	UK Vaccine Task Force (VTF) National Institute Health Research (NIHR) Novavax (Vaccine supply)		
Clinical Phase	Phase II		
Trial Design	Single-blind, randomised homologous/heterologous-boost vaccine administration study using standard and/or fractional doses		
Trial Participants	Adolescents aged 12 to 16 years (inclusive)		
Sample Size	A total of up to 270 (+ up to an additional 10%) participants will be enrolled. A participant is considered enrolled at the time they receive a vaccine in this study		
Planned Trial Period	Approximately 26 or 34 weeks per participant Total trial period approximately 10 months		
	Objectives	**Outcome Measures**	**Timepoint(s)**
Primary	To evaluate the reactogenicity of heterologous boost at least 8 weeks following BNT162B2 prime vaccine administered to adolescents.	Solicited systemic reactions	7 days after booster immunisation
Secondary	To assess safety of heterologous boost COVID-19 vaccines	Serious adverse events Adverse events of special interest	Throughout the study
	To characterise immunogenicity of heterologous & homologous boost schedules	Anti-spike immunoglobulins	D0*, 56 post prime D 14, 28, 132, 236 post boost
		Anti-nucleocapsid immunoglobulins	D0*, 56 post prime D132, 236 post boost
		Cellular immune responses by ELISpot	D0*, 56 post prime D 14, 132, 236 post boost
	To assess reactogenicity and safety of heterologous and	Solicited local reactions	7 days after prime* and boost immunisation

	homologous boost schedules of COVID-19 vaccines	Unsolicited reactions	28 days after prime* and boost immunisation
	To evaluate immunogenicity, safety and reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment, compared with seronegative	Immunogenicity, safety & reactogenicity endpoints as outlined above	Timepoints as outlined above
Exploratory	To assess incidence of SARS-CoV-2 infection in participants receiving heterologous & homologous prime/boost schedules	Self-reported SARS-CoV-2 infection, from community testing	Throughout the study
	To further characterise the blood antibody response	Neutralizing and Functional antibody assays	D0*, 56 post prime D 14, 28, 132, 236 post boost
	To characterise and compare the mucosal immune response to immunisation with homologous and heterologous COVID-19 vaccines using nasal fluid (collected using SAM-strips) and saliva samples	IgA & IgG ELISA and exploratory immunological assays in participants at selected sites	D0*, 56 post prime D14 post boost
	To determine normal ranges of markers of cardiac muscle damage in adolescents, and to assess change post-immunisation	High sensitivity troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP)	D0*, 56 post prime D14, 28 post boost

Intervention(s)
- IMP(s)

*Only for participants receiving their first dose of COVID-19 vaccine in the study

Vaccine	Dose	Route of administration
Pfizer BioNTech (BNT162b2)	30 µg (0.3ml) and 10 µg (0.10ml)	Intramuscular
Novavax, NVXCoV2373	5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)	Intramuscular

4. ABBREVIATIONS

ADE	Antibody Dependant Enhancement
AE	Adverse event
AESI	Adverse Event of Special Interest
Anti-N IgG	Anti-nucleocapsid protein Immunoglobulin G
Anti-S IgG	Anti-spike protein Immunoglobulin G
AR	Adverse reaction
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine, Oxford
CEPI	Collaboration for Epidemic Preparedness Innovations
ChAdOx1	Chimpanzee adenovirus 1
ChAdOx1-nCoV-19	Oxford/AstraZeneca COVID-19 vaccine
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EDC	Electronic Data Capture
ELISPOT	Enzyme-linked Immunospot
FBC	Full blood count
GCP	Good Clinical Practice
GMT	Geometric Mean Titre
GP	General Practitioner
HIV	Human Immunodeficiency virus
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form

IM	Intramuscular
IMP	Investigational Medicinal Product
IV	Intravenous
JCVI	Joint Committee on Vaccines and Immunisation
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribo-nucleic-acid
NHS	National Health Service
NIHR	National Institute for Health Research
NISEC	National Immunisation Schedule Evaluation Consortium
Novavax, NVXCoV2373	Novavax COVID-19 vaccine
NT-proBNP	N-terminal pro B-type natriuretic peptide
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PIMS-TS	Paediatric multisystem inflammatory syndrome temporally associated with COVID-19
Pfizer BNT162b2	Pfizer COVID-19 vaccine
qPCR	Quantitative polymerase chain reaction
RES	Research Ethics Service
PB	Post-boost
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAM-strips	Synthetic absorbable matrix strips
SAR	Serious Adverse Reaction
SARS-CoV2	Severe acute respiratory syndrome – coronavirus 2

SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Trials Safety Group
µg	Microgram
VAED	Vaccine antibody enhanced disease
Vp	Viral particle
VTF	Vaccine Task Force
WHO	World Health Organisation

5. BACKGROUND AND RATIONALE

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV.(6) The virus was subsequently renamed to SARS-CoV-2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a lineage B betacoronavirus. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of the lineage C betacoronavirus.(7) COVID-19 is the infectious disease caused by SARS-CoV-2. By January 2020 there was increasing evidence of human-to-human transmission as the number of cases rapidly began to increase in China. Despite unprecedented containment measures adopted by the Chinese government, SARS-CoV-2 rapidly spread across the world. The WHO declared the COVID-19 outbreak a public health emergency of international concern on 30th January 2020. Globally, as of 13th August 2021, there have been 205,338,159 confirmed cases of COVID-19, including 4,333,094 deaths, reported to the WHO.(8)

Coronaviruses (CoVs) are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors.(9) SARS-CoV-2 belongs to the phylogenetic lineage B of the genus Betacoronavirus and it recognises the angiotensin-converting enzyme 2 (ACE2) as the entry receptor.(10) It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

Many social measures have been undertaken in countries across the world in order to limit the spread of the virus.(11) These have included social distancing, lockdown and mask-wearing. Currently there is no definitive treatment for COVID-19. Dexamethasone has been shown to improve mortality in those with confirmed disease and an Oxygen requirement.(12) Remdesivir, a direct anti-viral, has also been shown to reduce duration of symptoms in those who have only mild disease.(13)

Many countries have already experienced ‘second’ and ‘third’ waves of infection. On the 2nd December 2020 the MHRA granted emergency authorisation for a vaccine against COVID-19, ‘COVID-19 mRNA Vaccine BNT162b2’ the European Medicines Agency then granted conditional authorisation on 21st December 2020, which is now approved for use down to the age of 12

years. This was followed by emergency authorisation of the Oxford/AstraZeneca ChAdOx1 nCOV-19 vaccine on the 29th December 2020 by the UK MHRA. The adjuvanted protein COVID-19 vaccine from Novavax, NVXCoV2373, is under rolling review of the MHRA at the time of writing. All of these vaccines were developed for use as homologous two-dose regimens. Further vaccines using different platforms are expected to be approved for use, the majority of which are expected to be approved as two dose, homologous prime/boost schedules.

While older age groups and others at most risk of disease have been prioritised in COVID-19 immunisation campaigns, recommendations for immunisation are now being extended to adolescents in many countries including the USA, Israel and Ireland, given the high rates of infection in this age group. In the USA, as of 9th August 2021 more than 3.9 million 16 to 17 year-olds and 6.4 million 12 to 15 year-olds, have received at least one dose of COVID-19 vaccine, and 3.1 and 4.6 million (respectively) have received both doses.(14) These have almost all been with the mRNA vaccines, predominantly BNT162b2. The potential benefits (and costs) of extending the UK COVID-19 vaccine immunisation to adolescents in the UK is under active review by the JCVI, and on 13th September 2021 it was announced that a first dose of BNT162b2 was recommended for all 12 to 17 year-olds in the UK. A second dose of BNT162b2 was recommended for all 16-to-17 year olds in the UK on 15th November 2021, and for all 12 to 15 year olds on 29th November 2021.(3)

One concern regarding adolescent immunisation is a rare side effect of inflammation of the heart muscle (myocarditis) that has been observed after receipt of the second dose of BNT162b2, especially in young men.(5) Reports from the USA Centre for Disease Control (CDC) describe that:

'As of July 30, 2021, VAERS has received 1,249 reports of myocarditis or pericarditis among people ages 30 and younger who received COVID-19 vaccine. Most cases have been reported after mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna), particularly in male adolescents and young adults. Through follow-up, including medical record reviews, CDC and FDA have confirmed 716 reports of myocarditis or pericarditis.(15) Based on this dataset, Public Health England report that:

'Data from the USA suggests that, in males aged 12 to 17 years, 9.8 cases of myocarditis were reported per million first doses given. This rises to 67 per million after the second dose.'

Fortunately, most cases of myocarditis are benign and self-limiting, although long term effects are uncertain.(5)

The possibility of using alternatives to a full dose of BNT162b2 as the second dose of vaccine is therefore being considered, and could also help deploy available stocks of vaccine as effectively

as possible. Recent data from a Phase 2/3 study which enrolled 2268 participants between 5 and 11 years of age showed that a homologous two-dose regimen of 10 µg of BNT162b2 achieved comparable immunogenicity (was non-inferior) when compared to a two-dose regimen of 30 µg administered to participants aged 16 to 25 years of age [SARS-CoV-2-neutralizing antibody geometric mean titre (GMT) 1,197.6 (95% CI 1106.1, 1296.6) in participants aged 5-11 years compared to 1146.5 (95% CI 1045.5, 1257.2) in 16-25 year olds]. These new data suggest that a lower dose (one third) in the adolescent age group may have the potential to provide an equal level of immunogenicity but with an improved reactogenicity profile (16). A potential approach is therefore to use a lower dose of BNT162B2 COVID-19 vaccine. In addition to being possibly less reactogenic than, and comparably immunogenic to, a full dose, this would also allow greater numbers to be immunised with the available supply of vaccines.

The use of heterologous prime/boost schedules of COVID-19 vaccines has been studied in COMCOV and COMCOV2, to facilitate flexible immunisation programmes. The COMCOV study showed a schedule with ChAdOx1 nCOV-19 as the first dose, followed by BNT162b2 as the second dose is highly immunogenic and is now deployed routinely in non-elderly populations in Canada and many northern European countries. However, restrictions on the use of ChAdOx1 nCOV-19 in younger adults due to concerns regarding vaccine induced thrombotic thrombocytopenia mean that this would not be a suitable option for a mixed schedule in adolescents.

Another potential option for the second dose is NVXCoV2373. While not yet licensed, a phase 3 study of this vaccine showed it to be 89.7% effective at preventing SARS-CoV-2 infection in adults, without any significant safety concerns.(16) A phase 3 study currently underway in the USA (NCT04611802) includes an adolescent cohort (N=3000), in which over 1400 participants have received NVXCoV2373 with no safety concerns raised (Novavax, personal communication). Furthermore, data generated in COMCOV2 (unpublished) has shown that a schedule employing BNT162b2 followed by NVXCoV2373 is no more reactogenic than a homologous BNT162b2/BNT162B2 schedule in participants aged over 50 years.

Accordingly, this study will determine the side effect profile, and the immune responses, following schedules using BNT162b2 as a first dose (administered in this study or in the community), and a second dose administered at least 8 weeks later of either BNT162b2 (full or one third dose) or NVXCoV2373 (full dose). Following the JCVI recommendation on 29th November 2021 that all 12 to 15 year-olds should be offered a second dose of BNT162b2 vaccine, the study design was amended to focus on immune response to BNT162b2. After this date,

participants will be randomised 1:1 to either full or one-third dose BNT162b2 for their second vaccination. Participants will no longer be randomised to the Novavax arm of the study to prioritise the arms of the study that are likely to be more policy relevant. This does not reflect any concern regarding the safety or immunogenicity of the Novavax vaccine. A further review of the study design will be undertaken following an interim analysis in late 2021, and with input from the study Trial Steering Committee.

Many young people in the UK have already been infected with COVID-19. It is important to understand the response to vaccination in this group. Therefore, participants enrolled in this study will include those with previous proven or suspected COVID-19.
Young people aged 12 to 17 years are now being invited to receive Pfizer-BioNTech vaccine, and many may have already received one dose by the time the study commences. Individuals who have received one dose of Pfizer-BoiNTech vaccine in the community will be eligible to enrol in the study at least 8 weeks after receiving their first dose.

5.1. Potential benefits

A 2-dose schedule of BNT162b2 COVID-19 vaccine is approved for use from the age of 12 years and older in the UK, and is highly effective against COVID-19. JCVI recommendations (current on 29th November 2021) for paediatric COVID-19 immunisation are:

- Two doses of COVID-19 vaccines for all 16 to 17 year- olds, given at least 12 weeks apart(3)
- Two doses of COVID-19 vaccines, given at least 8 weeks apart, for 12 to 17 year-olds with specific underlying health conditions that put them at increased risk of COVID-19, or for household contacts of those who are severely immunocompromised(17)
- Two doses of COVID-19 vaccines for all 12 to 15 year-olds, given at least 12 weeks apart(4)

The opportunity to receive a second dose of COVID-19 vaccine a month earlier than it would be given in the national vaccination programme is a potential benefit that participation in this study would provide. It is possible that using a fractional dose of BNT162b2 for the second vaccination will reduce the risk of myocarditis.

The approved schedule of two full doses of BNT162b2 will be received by half of participants in this study from 29th November 2021. All other participants will receive a single full dose of BNT162b2, which is thought to provide 80% protection against hospitalisation.(2) A second dose of the vaccines included in this study is expected to further increase protection against infection.

The age group to be enrolled in this study (12 to 16 years of age) has a lower risk of severe COVID-19 disease than older age groups. Nevertheless, they are at risk of the Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).(18) SARS-Cov-2 infection results in exclusion from school for the child, and potentially leads to a need to self-isolate for the family. The prevention of SARS-COV-2 infections in this age group is therefore of direct benefit to participants.

It is hoped that the information gained from this study will contribute to the development of a safe, effective and versatile vaccine programme against COVID-19.

5.2. Potential risks

5.2.1. Unapproved schedules and vaccines

A subset of participants will be receiving a second vaccination different from the full dose BNT1622b that is now recommended in the current UK approved schedule. Furthermore, those randomised to receive NVXCoV2373 will be receiving a vaccine that is yet to receive MHRA emergency approval. However, NVXCoV2373 has been administered to over 1400 adolescents in an ongoing clinical trial, without raising significant safety concerns. Also, a mixed BNT162b2/ NVXCoV2373schedule has already been studied in COMCOV2 and similarly found to be well tolerated with no safety concerns.

There is the potential for the schedules with a heterologous or fractional dose boost to be less immunogenic than the approved schedule with two full doses of BNT162b2 COVID-19 vaccine.

There may be implications for domestic and international travel for participants receiving heterologous or fractional dose for the second vaccination. This is further discussed in Section 9.5.

Adolescents with underlying health conditions which place them at increased risk of COVID-19 or household contacts of those who are severely immunocompromised, who have been recommended to receive two doses of a COVID-19 vaccine according to JCVI guidelines as of 3rd September 2021, will not be eligible to participate in this study, and will be advised to receive COVID-19 vaccines through the NHS.

In order to ensure that participants are not significantly disadvantaged to their peers, a “booster” vaccine dose may be offered to participants if any of the vaccine schedules used in this study are found to be less immunogenic compared to standard vaccine schedules. The decision to offer participants additional vaccine doses will be determined based on the advice of the DSMB and TSC.

BNT162b2 COVID-19 vaccine has been administered to many millions of individuals (including 12 – 16 year-olds), and NVXCoV2373 has been administered to over 50000 participants in clinical trials, including over 1400 in adolescents. They therefore have a well-established safety profile. Specific concerns have been raised regarding a risk of myocarditis following a second dose of BNT162b2 in young males aged 12 to 17 years (9.8 per million first doses, rising to 67 per million after the second dose). Participants will be made aware of this at the time of enrolment and this will be specified in participant and parent information sheets. Participants will be advised to seek medical attention should they experience any of the cardinal symptoms of myocarditis (chest pain or pressure; palpitations; breathlessness after exercise, at rest or lying down; sweatiness). The diagnostic criteria for myocarditis are documented in Appendix D.(19)

5.2.2. Associated with phlebotomy

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will not be documented as AEs if they occur. Blood volumes collected will adhere to EC directive 2001/20/EC for paediatric blood volume sampling which states that 'per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time'. Based on these calculations, we will take 16ml per sampling timepoint from participants aged 12-16 years on each visit for immunology bloods. Some participants will turn 17 during the trial and become eligible for blood donation; they will be asked to refrain from this for the duration of their trial involvement.

5.2.3. Associated with saliva sampling

Participants may find the saliva collection process unsavoury as it is involves drooling and spitting. This will be an optional element of the study.

5.2.4. Associated with nasal fluid sampling

Localised discomfort can occur in the nostril. Infrequently, this can result in a small amount of epistaxis, which can be controlled with pressure to the affected area. This will be an optional element of the study.

5.2.5. Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is known to occur in approximately 2.5 to 4.7 per million recipients of mRNA COVID-19 vaccines,(20) and more generally in around 1 in 1,000,000 doses of all vaccines, but can occur in response to any vaccine or medication.(21)

5.2.6. Behaviour change

Participants might feel they can modify their COVID-19 risk behaviours on the assumption that they are protected once vaccinated. Participants will be counselled that they should continue to follow all up to date government advice in relation to COVID-19 precautions during the trial.

5.2.7. Specific risks from vaccines

Please refer to section 11.8 for full details.

5.2.8. Receiving a sub-optimal vaccine schedule

It is possible that one or more of the combinations of vaccine schedule used in this trial is, on analysis found to generate a humoral or cellular immune response lower than that of the licensed homologous BNT162b2 schedule. If this were to be the case, advice would be sought from the DSMB and TSC, who might recommend further doses of vaccine to any disadvantaged participant, if possible (either via the study or through the NHS).

5.2.9. Unwanted media attention

Trial participants can be subjected to unwanted attention from the media. They will therefore be provided with access to a document outlining some suggested media guidance.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	Timepoint(s)
Primary	To evaluate the reactogenicity of heterologous boost at least 8 weeks following BNT162B2 prime vaccine administered to adolescents.	Solicited systemic reactions	7 days after boost immunisation
Secondary	To assess safety of heterologous boost COVID-19 vaccines	Serious adverse events Adverse events of special interest	Throughout the study
	To characterise immunogenicity of heterologous & homologous boost schedules	Anti-spike immunoglobulins	D0*, 56, post prime D 14, 28, 132, 236 post boost
		Anti-nucleocapsid immunoglobulins	D0*, 56 post prime D132, 236 post boost
		Cellular immune responses by ELISpot	D0*, 56 post prime

			D 14, 132, 236 post boost
	To assess reactogenicity and safety of heterologous and homologous boost schedules of COVID-19 vaccines	Solicited local reactions	7 days after prime* and boost immunisation
		Unsolicited reactions	28 days after prime* and boost immunisation
	To evaluate immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment, compared with seronegative	Immunogenicity, safety & reactogenicity endpoints as outlined above	Timepoints as outlined above
Exploratory	To assess incidence of SARS-CoV-2 infection in participants receiving heterologous & homologous prime/boost schedules	Self-reported SARS-CoV-2 infection, from community testing	Throughout the study
	To further characterise the blood antibody response	Neutralizing and Functional antibody assays	D0*, 56 post prime D 14, 28, 132, 236 post boost
	To characterise and compare the mucosal immune response to immunisation with homologous and heterologous COVID-19 vaccines using nasal fluid (collected using SAM-strips) and saliva samples	IgA & IgG ELISA and exploratory immunological assays	D0*, 56 post prime D14 post boost
	To determine normal ranges of markers of cardiac muscle damage in adolescents, and to assess change post-immunisation	High sensitivity troponin and N-terminal pro B-type natriuretic peptide (NT-proBNP)	D0*, 56 post prime D14, 28 post boost

* Only for participants receiving prime vaccination in the study

7. TRIAL DESIGN

A single-blind, randomised, phase II multi-centre study to determine the reactogenicity and immunogenicity of heterologous boost COVID-19 vaccine schedules.

7.1. Setting

Multicentre study conducted through academic and NHS clinical trials sites.

7.2. Trial duration

Total duration of each participant will be approximately 26 weeks (for those primed in the community) or 34 weeks (those primed in the study). The total trial period will be approximately 10 months.

7.3. Study groups

A total of up to 270 (+ up to an additional 10%) participants will be enrolled and randomised (1:1:1) as below:

Group	Arm	Prime (Day 0)	Boost (day 56)
	1	BNT162b2	BNT162b2
	2	BNT162b2	BNT162b2 (one-third dose)
	3	BNT 162b2	NVXCov2373

After 29th November 2021, the enrolment of participants who have received their first dose of COVID-19 vaccine in the community will be temporarily suspended. Only participants who have received their first dose of COVID-19 vaccine in the study will be randomised to a second dose. They will be randomised (1:1) as below:

Group	Arm	Prime (Day 0)	Boost (day 56)
	1	BNT162b2	BNT162b2
	2	BNT162b2	BNT162b2 (one-third dose)

Randomisation will be performed at the time of the second dose, and stratified by study site and anti-nucleocapsid IgG status at baseline where available.

The study will be single-blind, i.e. while staff involved in study delivery will be aware of what vaccine schedule the participant is receiving, the participant themselves will remain blinded to their boost vaccine. This blind will be maintained by applying a masking tape over the vaccine syringe as detailed in the study clinical study plan. Laboratory staff will also be blinded to the vaccine schedule received.

7.4. Participants testing COVID-19 positive

Participants who acquire new infection with SARS-CoV-2 (as determined by SARS-C0V-2 antigen or PCR tests) will be asked to record this in their electronic/paper diary, and may continue in the study.

The UKHSA recently recommended increasing the interval between COVID-19 infection and vaccination from 4 weeks to 12 weeks in healthy 12 to 17 year olds. This is in part because young people are likely to have high levels of protection for at least 3 months after COVID-19 infection, meaning an earlier vaccine boost might not be necessary. It is also possible, though not confirmed, that a longer interval between infection and vaccination might reduce further the very small existing risk of myocarditis. The recommendation adopts a highly precautionary approach. However, 12 to 17 year olds at "high risk" and all adults are still advised to wait 4 weeks between infection and vaccination. On the advice of our independent Trial Steering Committee, we will still be offering a second dose of vaccination from 4 weeks after the first positive COVID-19 test confirming infection. This is in line with the recommendation for 'high-risk' 12 to 17 year olds. This is to allow as many adolescents as possible to take part in this study, and to enable us to provide results as quickly as possible to the JCVI.

8. PARTICIPANT IDENTIFICATION

8.1. Trial participants

Volunteers aged 12 to 16 years inclusive at enrolment. Comorbidities of clinical definition mild/moderate/well-controlled will be permitted. Individuals of all ethnicities will be recruited, with recruitment of those identifying as Black, Asian and Minority Ethnic particularly encouraged.

8.2. Inclusion criteria

- Parent/legal guardian/Participant is willing and able to give written informed consent for participation in the trial*
- Aged 12 to 16 years inclusive at enrolment
- In good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity, as long as this would not render them considered as belonging to a 'high -risk' cohort at particular need of 2 doses of COVID-19 vaccine (see exclusion criteria below) as part of the national roll out
- Able and willing (in the Investigator's opinion) to comply with all study requirements

- Registered with a GP, and willing to allow the investigators to discuss the participant's medical history with their General Practitioner and access all medical records when relevant to study procedures.

  * Parent/legal guardian to provide informed consent for participants under the age of 16. Participants aged 16 years will be assumed to be able to provide consent for themselves, however parental support will be encouraged and investigators will reserve the right to refuse enrolment if concerns arise.

8.3. Exclusion criteria

The participant may not enter the trial if ANY of the following apply:

- Previous receipt of more than one dose of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2
- Belonging to a 'high risk' cohort advised to receive 2 doses of a COVID-19 vaccine (participants at increased risk of COVID-19, or household contacts of immunocompromised, based on JCVI and 'Green Book' guidelines current on 13th September 2021).
- First degree relative of a study site staff member
- Any confirmed or suspected immunosuppressive or immunodeficient state; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting ≤14 days)
- History of anaphylaxis, allergic disease or reactions likely to be exacerbated by any component of study vaccines (e.g. hypersensitivity to the active substance or any of the SmPC/IB-listed ingredients of any study vaccine). This includes latex and polyethylene glycol/macrogol (PEG)
- Pregnancy, lactation or unwillingness to practice effective contraception from enrolment to 3 months post booster vaccination, for post-menarcheal females only
- Malignancy requiring receipt of immunosuppressive chemotherapy or radiotherapy for treatment of solid organ cancer/haematological malignancy within the 6 months prior to consent.
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
- Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
- Any serious chronic illness requiring hospital specialist supervision
- Congenital cardiovascular conditions

- Severe and/or uncontrolled respiratory disease, gastrointestinal disease, liver disease, renal disease, rheumatological disease, and neurological illness (mild/moderate well controlled comorbidities are allowed)
- History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis)
- Significant renal or hepatic impairment
- Scheduled elective surgery requiring overnight admission and/or general anaesthetic during the trial
- Insufficient level of English language to undertake all study requirements in opinion of the Investigators
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks
- Note that a prior history of confirmed or suspected COVID-19 is NOT an exclusion criterion for this study, provided the participant otherwise satisfies the health screening criteria for the study.

8.3.1. Temporary exclusion criteria

If the volunteer has any of the following, they will not be immunised that day.

- Acute respiratory illness (moderate or severe illness with or without fever)
- Fever (oral temperature greater than 37.8°C)
- Receipt of any vaccine (licensed or investigational) within 7 days before enrolment, or intent to receive within 7 days of the COVID-19 vaccines
- Proven COVID-19 infection, first confirmed less than 4 weeks previously (see Section 7.5)

9. TRIAL PROCEDURES

See APPENDIX A: SCHEDULE OF PROCEDURES

9.1. Recruitment

9.1.1. Identification of volunteers

Volunteers will be recruited by methods that may include use of an advertisement +/- registration form formally approved by the ethics committee(s) and distributed or posted by means such as:

- In public places, including buses and trains, with the agreement of the owner / proprietor
- In newspapers or other literature for circulation

- On radio and/or television via announcements
- On a website or social media site operated site or sponsor or with the agreement of the owner or operator (including on-line recruitment through the Oxford Vaccine Group website)
- By e-mail distribution to a group or list only with the express agreement of the network administrator or with equivalent authorisation
- By email distribution to individuals who have already given consent to be contacted for any clinical trial at the Oxford Vaccine Centre and at trial sites including COVID-19 vaccine research
- Direct mail-out using National Health Service databases: These include the National Health Applications and Infrastructure Services (NHAIS) via a NHAIS data extract or equivalent. Initial contact to potential participants will not be made by the study team. Instead, study invitation material will be sent out on our behalf by an external company, CFH Docmail Ltd, in order to preserve the confidentiality of potential participants. CFH Docmail Ltd is accredited as having exceeded standards under the NHS Digital Data Security and Protection Toolkit (ODS ID – 8HN70). Potential participants will be invited to either register their interest directly online using a link to complete our approved 'Pre Screening Questionnaire' on the trial website or to return the reply slip in the sealed freepost envelope. Replies will be processed and stored in accordance with local procedures surrounding the handling of identifiable data.
- Oxford Vaccine Centre databases and study site databases: We may contact individuals from databases of groups within the CCVTM (including the Oxford Vaccine Centre database) and other study sites of previous trial participants who have expressed an interest in receiving information about all future studies for which they may be eligible.
- Using local GP practices or Trusts as Participant Identification Centres (PICs)

9.2. Screening and eligibility assessment

9.2.1. Initial screening

Once parents/guardians or participants express an interest in joining the trial, they will be directed to a 2-part online screening process. The first part will assess for obvious exclusion criteria. If they pass this part, they will be asked to indicate their electronic consent to cover:

- Reporting the potential participant's medical history, including any history of SARS-CoV-2 infection identified by antigen detection, PCR testing or detection of SARS-CoV2 spike or nucleocapsid antibodies in the absence of COVID-19 vaccination
- Telephone screening visits to review their medical history (if required). Requirement to be determined by review of responses to Part 2 of online questionnaire)
- Permission to contact the participant's GP for further clarification of past medical history and vaccine status, should this be clinically indicated

Once Part 1 and consent have been completed, they may progress to Part 2. Here they will be asked to give details of any medical comorbidities or medications.

Participants without a past medical history or drug history that requires further review may be invited directly to enrolment/vaccination visits.

9.2.2. Telephone screening visit(s)

Participants for whom further clarification of eligibility is required, may be invited for telephone screening visit(s), which would then be completed by member(s) of the clinical team, based on the assessment of the part 2 responses. This will be recorded in a screening CRF. This will reduce the amount of time participants have with the clinical team during their screening procedures, should they progress to Visit 1.

We may also contact the participant's general practitioner with the permission of the volunteer. GPs will be notified at the time of enrolment (vaccination) that the subject is taking part in the study.

Volunteers will be asked to contact the study team if there are significant changes to their health status between screening and their Visit 1.

9.2.3. Screening

The final eligibility screening will be performed at the first visit.

9.3. Informed consent

Participants aged 16 years or over will be self-consenting as per the National Institute of Health Research guidelines. However, with the participant's permission, parents/guardians will be provided with information about the study by the trial team and via information available on the trial website, and the study team will request a parent/guardian to be at the first visit. If a participant aged 16 years declines parental notification, this will necessitate contact with their

named GP to corroborate their medical history before they are enrolled. This is to safeguard vulnerable young adults.

Consent will be taken by clinical staff (registered doctor or nurse) with appropriate experience and training. Where interested participants have vulnerabilities that may impair their capacity to provide informed consent, additional input or support from the individual's parents/ guardians will be sought. If there is ongoing doubt about an individual's ability to provide informed consent, then they will not be enrolled in the study.

Children/adolescents aged under 16 of years will require full parental written consent as well as signed assent from the participant themselves. Individually each participant (and their parent/guardian) will have the opportunity to question an appropriately trained and delegated researcher before signing the consent form. Participants who turn 16 years during the course of the study will be required to sign a full informed consent form at the visit occurring after their 16th birthday.

Prior to consent, the participant (and their parent/guardian) will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasised:

A written version and verbal explanation of the Participant Information Sheet and Informed Consent will be presented to the participant of the participant detailing:

- The exact nature of the study
- What it will involve for the participant
- The implications and constraints of the protocol
- The known side effects and any risks involved in taking part
- The sample handling protocol – participants will be informed that anonymised samples taken during the study may be shared with study collaborators
- Individual results will not be shared with participants.
- The Participant Information Sheet will be made available to the participant for an appropriate amount of time (where possible this will be a minimum of 24 hours) prior to consent being obtained. A video presentation of the Participant Information Sheet may be screened to an audience, or made available for participants to access remotely. Participants will have the opportunity to individually question an appropriately trained and delegated researcher before signing consent.
- The following general principles will be emphasised:

- Participation in the study is entirely voluntary
- Refusal to participate involves no penalty or loss of medical benefits
- The participant may withdraw from the study at any time
- The participant is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The participant will be informed that they will not know whether they have received an approved COVID-19 vaccine schedule. This may have implications for any travel or other activities that may require individuals to be considered 'fully immunised'.

Participants, like the general population, will not be exempt from following the contemporaneous government COVID-19 guidance to minimise viral transmission.

Samples taken as part of the study may be sent outside of the UK and Europe to laboratories in collaboration with the University of Oxford. These will be de-identified. Volunteers will be asked if they consent to indefinite storage of any leftover samples for use in other ethically approved research; this will be optional.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of the participant/parent/guardian dated signature, and dated signature of the person who presented and obtained the informed consent. The person obtaining the consent must be suitably qualified and experienced, and be authorised to do so by the Chief/Principal Investigator and listed on the delegation log. A copy of the signed informed consent will be given to the participant/parent/legal guardian. The original signed form will be retained at the research study site, in the CRF.

9.4. Randomisation

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three study groups. After 29th November 2021, participants will be randomised 1:1 to the two study groups.

Participants will be randomised using block randomisation. Random block sizes of 3 and 6 will be used before 29th November 2021, and random block sizes of 2 and 4 will be used after29th November 2021. Randomisation will be performed at the time of the second dose, and stratified by study site and anti-nucleocapsid IgG status at baseline (where available).

9.5. Blinding and code-breaking

The study will be single-blind. Staff involved in study delivery will be aware of which vaccine the participant is receiving (arm allocation); the participant will remain blinded to their boost vaccine allocation up until the day 84 visit, at which point participants will advised of their immunisation arm. Vaccines will be prepared out of sight of the participant and the blind will be maintained by applying a masking tape over the vaccine syringe. Laboratory staff will also be blinded to the vaccine schedule received.

If the clinical condition of a participant necessitates unblinding of the participant prior to the day 84 visit, this will be undertaken according to a trial specific working instruction and group allocation sent to the attending physician. This will be done if unblinding is thought to be relevant and likely to change clinical management.

In order not to disadvantage participants in a rapidly changing landscape of rules affecting national and international travel as well as event attendance, we will make every effort to liaise with appropriate parties to ensure participants' vaccination status is recorded in the most suitable manner.

As of the 11th June 2021, the Department of Health and Social Care has confirmed that for any future domestic certification of vaccination status, clinical trial participants will not be disadvantaged, and will be offered an "immunised" status regardless of the licencing status or vaccine schedule received. This status would be available to trial participants while blinded, and also after unblinding even if they have received an unlicensed vaccine schedule.

9.6. Visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the schedule of attendances (Each visit is assigned a time-point and a window period, within which the visit will be conducted. If a participant cannot attend a visit, where possible, this will be re-arranged to an in-person visit within the time window. A telephone visit may be conducted instead of the in-person visit to ascertain as much relevant information as possible if the participant is unable to attend a visit in person because of quarantine or self-isolation restrictions and the participant will be out of window if the visit is postponed.

Participants may enrol in the study either before receiving a COVID-19 vaccine (study-prime) or after receiving a first dose of Pfizer-BioNTech vaccine in the community (community-prime). The details of the D0 and D56 visits will differ for these two scenarios, as described below.

9.6.1. Visits for participants receiving their first dose of COVID-19 vaccine in the study

9.6.1.1. D0: Final eligibility check, enrolment and vaccination visit

9.6.1.1.1. Informed consent

The participant will have informed consent taken as described in Section 9.3 , before proceeding to the final eligibility check component of D0 visit. A video presentation of the aims of the study and all tests to be carried out may be screened to an audience or accessed remotely before informed consent is taken. This will be pitched at a level which should generally be comprehensible to the youngest participants. Individually, each volunteer and parent/legal guardian (if applicable) will have the opportunity to question an appropriately trained and delegated researcher before signing the assent/consent form.

9.6.1.1.2. Final eligibility check D0

During the final eligibility check component of D0 visit:

If written consent is obtained, the procedures indicated in the schedule of attendances will be undertaken including:

- Confirmation of medical history, including SARS-CoV-2 infection
- Physical examination (if required, determined according to past medical history)
- Height and weight
- Observations (temperature, heart rate)
- Urine pregnancy test in females

The eligibility of the volunteer will be reviewed by a study doctor. Decisions to exclude the volunteer from enrolling in the trial or to withdraw a volunteer from the trial will be at the discretion of the Investigator.

As per Section 8.3.1 “Temporary exclusion criteria”: If a volunteer has an acute respiratory illness (moderate or severe illness with/without fever) or a fever (oral temperature > 37.8°C) at D0/D56 visit screening, or a history of proven COVID-19 infection first confirmed less than 4 weeks earlier, the volunteer will not be enrolled that day, but may be considered for enrolment if they recover in sufficient time.

9.6.1.1.3. Samples taken at D0

- Blood tests including:
  - COVID-19 immunogenicity bloods
  - Markers of cardiac stress
- Nasal fluid and saliva sample (both optional, and at selected sites only)

9.6.1.1.4. Vaccination at D0

Participants will be considered enrolled to the trial at the point of receipt of the first vaccine administered by the study team. All vaccines will be administered intramuscularly according to specific SOPs. The participant will stay in the trial site for observation for at least 15 minutes, in case of immediate adverse events. Participants will be issued with an NHS COVID-19 vaccination record card at the first immunisation with entry of "BNT162b2" and batch number. This will be updated at the second immunisation, but boost vaccine type or batch number will not be added as this would unblind participants; instead, "COVID-19 vaccine", "Com-COV3 Trial" will be added. We will correspond with holders of the participant's medical information records (e.g. GPs) to enable updating of these records.

9.6.1.1.5. eDiary

Participants/parents/guardians will be given an oral thermometer, tape measure and diary (electronic, but for those who are unable to use an electronic diary, a paper version will be made available), with instructions on use. All participants will be given the emergency 24-hour telephone number to contact the on-call study physician if needed. Participants/parents/guardians will be instructed on how to self-assess the severity of the solicited and unsolicited AEs they are entering in the diaries. There will also be space in the diary to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms. It will also log any serious medical illnesses or hospital visits which may have occurred over the entire course of the study and any diagnosis of SARS-CoV-2 infection. Given the potential for physical exercise to raise troponin and NT-proBNP independently of myocardial inflammation, there will be a space in the diary to record episodes of strenuous physical activity ("defined as anything that makes you feel really out of breath") in the period between the booster vaccine and the D70 visit. Participants/parents/guardians will be asked to report on solicited AEs for 7 days from prime and boost dose (and longer if symptoms persist at day 7, until resolution or stabilisation of symptoms) and unsolicited AEs for 28 days. The Diary will collect information on the timing and severity of the following solicited AEs:

Table 1 Solicited AEs collected on post vaccination diary cards

Local solicited AEs	Pain, Tenderness, Redness, Warmth, Itch, Swelling, Induration
Systemic solicited AEs	Fever, Feverishness, Chills, Joint pains, Muscle pains, Fatigue, Headache, Malaise, Nausea, Vomiting, Diarrhoea

Post-vaccination (7 and 28 day) diary information will be reviewed by a clinician daily, and participants may be telephoned to discuss further, should there be any clinical concerns.

The diary will contain an instruction to contact the trial team by telephone should any encounter be a hospitalisation, or if they have concerns about their health.

9.6.1.1.6. Safety pause

Given that a) the homologous BNT162b2 vaccine schedule is licensed for use in 12 to 16 year-olds, b) Data from COMCOV2 demonstrates that BNT162b2 prime followed by NVXCoV2373 boost is no more reactogenic that homologous BNT162b2/BNT162b2 and c) employing fractional dose vaccines as the boost dose are expected to be less reactogenic than full dose regimens, there will be no planned safety pause or expedited review of reactogenicity data. Should significant safety concerns arise at any point (e.g. an AESI) then the DSMB will be consulted as appropriate.

9.6.1.2. Subsequent visits

Follow-up visits will take place as per the schedule of attendances described in APPENDIX A: SCHEDULE OF PROCEDURES. Participants will be assessed for local and systemic adverse events, interim history, review of diaries (paper or electronic) and blood, saliva/ nasal fluid sampling performed at these time points as detailed in the schedule of attendances. Observations and physical exam will be performed as and when clinically indicated.

Vaccination procedures will be as for D0 visit, adapted to the specific vaccine being administered as outlined in the clinical study plan. Scheduling of the second vaccination visit (D56) should be mindful of any planned routine non-COVID-19 immunisation outside the study (e.g. seasonal influenza vaccine), to avoid administration of the study COVID-19 vaccine within a period 7 days before or after the planned routine vaccine. If necessary, in this situation scheduling of the D56 visit can be delayed beyond the specified D56 study window, but must not be brought forward to less than 8 weeks following D0.

If participants experience adverse events which the investigator (physician), CI and/or DSMB chair deem to require further close observation, the participant may be admitted to an NHS

hospital for observation and further medical management under the care of the Consultant on call.

9.6.2. Visits for participants receiving their first dose of COVID-19 vaccine in the community

The screening visit for these participants will include all the procedures for informed consent and eligibility assessment described above (section 9.6.1.1.1 and 9.6.1.1.2) including date of first dose of COVID-19 vaccination in the community.

The screening visit may be combined with the D56 visit, or be scheduled to occur separately, at some time before the D56 visit.

At the D56 visit blood samples will be taken (as will nasal fluid and saliva samples, if consent has been given for this); booster vaccine will be determined by randomisation and administered; an e-diary will be supplied. These procedures will occur in the same way as described for those participants receiving their first dose of COVID-19 vaccine in the study.

Visits after D56 (i.e. D 14, 28, 132, 236 post boost), will involve the same procedures for all participants, whether or not they received their first dose of COVID-19 vaccine in the study or community. These are described in APPENDIX A: SCHEDULE OF PROCEDURES.

9.6.3. Participants under quarantine

Given the evolving epidemiological situation both globally and in the UK, should a participant be unable to attend any of their scheduled or unscheduled visits, a telephone consultation will be arranged in order to obtain core study data where possible. Participants should not attend for in-person visits if they are in their period of self-isolation/quarantine.

9.6.4. Admission of participants to hospital with COVID-19 infection

With the participant's/parent's/guardian's consent, the study team will request relevant sections of medical notes on any COVID-19 episodes resulting in hospitalisation. Any data which are relevant to assessing for disease enhancement will be collected. These are likely to include, but not limited to, information on ICU admissions, clinical parameters such as oxygen saturation, respiratory rates and vital signs, need for oxygen therapy, need for ventilatory support, imaging and blood tests results, amongst others.

9.7. Sample handling

Please refer to APPENDIX C: BLOOD SAMPLING for schedule of frequency and volume of blood sampling.

9.7.1. Sample handling for trial purposes

Immunogenicity will be assessed by a variety of immunological assays. This will include antibodies to SARS-CoV-Spike and non-Spike antigens by ELISA, ex vivo ELISpot assays for interferon gamma secreting T cell assays, and (potentially) neutralising and other functional antibody assays. Other exploratory immunological assays including cytokine analysis and other antibody assays, DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity and gene expression studies amongst others may be performed at the discretion of the Investigators.

Collaboration with other specialist laboratories in the UK, Europe and outside of Europe for further exploratory tests may occur. This would involve the transfer of serum, plasma, PBMC and/or other study samples to these laboratories, but these would remain anonymised. The analyses and which laboratories carry these out will be specified in the laboratory analysis plan.

Participants will be informed that there may be leftover samples of their blood (after all testing for this study is completed), and that such samples may be stored indefinitely for possible future research (exploratory immunology), including genotypic testing of genetic polymorphisms potentially relevant to vaccine immunogenicity. Participants will be able to decide if they will permit such future use of any leftover samples. With the participant's informed consent, any leftover cells and serum/plasma will be frozen indefinitely for future analysis of COVID-19 and other coronaviruses related diseases or vaccine-related responses. If a participant elects not to permit this, all of that participant's leftover samples will be discarded at the end of the trial.

Samples that are to be stored for future research will be transferred to the OVC Biobank (REC 21/SC/0161). If the participant/parent/legal guardian (as applicable) does not consent to storage in the Oxford Vaccine Centre Biobank, then all samples will be destroyed at the end of the study.

9.7.1.1. Nasal fluid & saliva samples

An exploratory analysis of mucosal immunity will be conducted at some sites using nasal fluid collected at V1, V2 and V3 using SAM-strips (synthetic absorptive matrix) and saliva samples. Analysis will be conducted initially with IgA and IgG ELISAs, with further exploratory immunology assays conducted based on results – more detail will be included in the laboratory analysis plan.

The same statements regarding collaboration, storage and use of samples as for blood in Section 0 apply here.

9.7.1.2. Sample handling for markers of cardiac stress

These will be centrifuged and frozen at sites before shipping to a central NHS laboratory, and tested for troponin and NT-proBNP. Residual samples will then be destroyed in accordance with standard NHS processes.

9.7.2. Sample handling for pregnancy testing

Urinary pregnancy testing: For female participants urine will be tested for beta-human chorionic gonadotrophin (β-HCG) immediately prior to vaccination. This will be a point of care test and no sample will be stored.

9.8. Early discontinuation/Withdrawal of participants

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a participant has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the participant at any time in the interests of the participants' health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).
- Significant protocol deviation
- Participant non-compliance with study requirements
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the volunteer, until the AE has resolved, stabilised or a non-trial related causality has been assigned. The DSMB or DSMB chair may recommend withdrawal of participants.

If the participant chooses to withdraw after receipt of the first dose of vaccine, they will not need to be formally unblinded, as they will all have received BNT162b2. If they withdraw after the second dose of vaccine, they will not be unblinded, unless criteria as described in 9.5 are met. since at present there is no recommendation for routine second dose in the age group being studied.

If a participant withdraws from the study, storage of samples will continue unless the participant specifically requests otherwise. Any data collected before their withdrawal will still be used in the analysis for safety and trial integrity; if the participant requests this could be de-identified following the end of the study.

In cases of participant withdrawal, long-term safety data collection, including some procedures such as safety bloods, may continue as appropriate if participants have received any vaccine doses through the trial, unless they decline any further follow-up.

9.9. Definition of end of trial

The end of the trial is the date of the last assay conducted on the last sample collected.

10. TRIAL INTERVENTIONS

See APPENDIX A: SCHEDULE OF PROCEDURES for details

10.1. Investigational Medical Product(s) (IMP) Description

Table 2: The marketing authorisation and IMP labelling status of the vaccines:

Vaccine	UK Marketing authorisation status	IMP labelling status
Pfizer/BioNTech BNT162b2	Approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012.	Not IMP labelled, product will be used as supplied by manufacturer for national supply
Novavax SARS-CoV-2 rS/Matrix-M1 Adjuvant NVXCoV2373	No marketing authority or emergency use approval currently	IMP labelling required

10.1.1. VACCINE A – Pfizer BioNTech (BNT162b2)

BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. BNT162b2 encodes the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation and more closely mimic the intact virus with which the elicited virus-neutralizing antibodies must interact. mRNA vaccines use the pathogen's genetic code as the vaccine; this then exploits the host cells to translate the code and then make the target spike protein. The protein then acts as an intracellular antigen to stimulate the immune response. The mRNA is then degraded within days. The vaccine RNA is formulated in lipid nanoparticles (LNPs) for more efficient delivery into cells after intramuscular injection.

10.1.1.1. Dosage, scheduling and packaging

The dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine. Each pack of the Pfizer BioNTech vaccine contains 195 vials with 6 full doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules. Participants randomised to the one third dose BNT162b2 vaccine group will receive a 0.10 ml dose.

10.1.2. VACCINE B – Novavax, NVXCoV2373

Novavax, NVXCoV2373 is a nano-particle vaccine. It is constructed from the full-length wild-type (prototype Wuhan sequence) pre-fusion trimers of SARS-CoV2 spike glycoprotein. The native protein has been modified with several substitutions to limit protease cleavage and enhance thermal stability (the putative native furin cleavage site has been modified from RRAR to QQAQ and 2 proline substitutions (positions K986P and V987P) in the HR1 domain). It has also been optimised for expression in insect (Spodoptera frugiperda) Sf9 cells. The recombinant S-protein genes are cloned into a baculovirus vector before being transferred into Sf9 cells. These cells then produce the protein which is extracted and purified. It is co-formulated with a saponin-based adjuvant, Matrix-M1™.

10.1.2.1. Dosage, scheduling and packaging

The dose of NVXCoV2373 is 5 µg recombinant spike protein with 50 µg Matrix-M1 adjuvant (0.5ml). The vaccine is supplied in 10 full dose vials.

10.2. Blinding of IMPs

See Section 9.5 for details.

10.3. Storage of IMP

Vaccines will be stored in accordance with manufacturers' recommendations.

All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms. To allow for participants to receive the vaccine in a short time period, multiple clinic locations may be used. In this instance vaccines will be transported in accordance with local SOP's and approvals as required.

10.3.1. Vaccine A - Pfizer BioNTech (BNT162b2)

The Pfizer BioNTech vaccine should be stored at -70°C +/- 10°C and has shelf life of 6 months. Once thawed, the vaccine may be stored for one month (for the purposes of this study, this is

considered to be 30 days) at 2 to 8°C. It should be used as soon as practically possible and within 6 hours of dilution.

10.3.2. Vaccine B – Novavax, NVXCoV2373

SARS-CoV-2 rS and Matrix-M1 adjuvant should be stored at 2°C to 8°C and not frozen.

10.4. Compliance with trial treatment

All vaccinations will be administered by the research team and recorded in the CRF. The study medication will be at no time in the possession of the participant and compliance will not, therefore, be an issue.

10.5. Accountability of the trial treatment

Accountability of the IMPs will be conducted in accordance with the relevant SOPs.

10.6. Concomitant medication

As set out by the exclusion criteria, volunteers may not enter the study if they have received any vaccine within 7 days before enrolment (which is defined as occurring at the time of receipt of the first study vaccine), or intend to receive within 7 days after the COVID-19 vaccine, and the subsequent COVID-19 immunisation should be scheduled to given at least 7 days before or after any non-study vaccine. Volunteers may not enter the study if they have participated in another research trial involving an investigational product in the previous 12 weeks, or if they have used immunosuppressant medication within 6 months prior to enrolment or if receipt is planned at any time during the study period (except topical steroids and short course of low dose steroids < 14 days). Concomitant medications taken at enrolment will be recorded, as will new medications within the 28 days after each immunisation.

10.7. Post-trial treatment

Decisions regarding the need for a boost dose in any of the heterologous prime/boost schedules, the nature of any boost dose and mode of delivery (e.g. NHS vs study site) will be made in consultation with the DSMB and trial steering committee.

10.8. Other treatments (non-IMPs)

Participants will be advised that they may take paracetamol prophylactically after vaccine administration. This will be from the participants own supplies rather than supplied by the study team.

10.9. Other interventions

There are no additional interventions other than those specified in this protocol.

11. SAFETY REPORTING

11.1. Safety reporting window

Safety reporting for the trial will commence once the first participant is consented; and will end 10 months after the last participant has received the second dose of an IMP for SAEs and Adverse Events of Special Interest (AESIs).

For individual participants the reporting period begins when they are consented, in person at the V1, and ends 12 months after the first dose of vaccine for SAEs and AESIs.

All adverse events (AEs) that result in a participant's withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the participant consents to this).

11.2. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Adverse Events of Special Interest (AESI)	Adverse events identified as being of particular relevance to the IMP's. These will also be reported as an SAE, if meeting SAE criteria (e.g. hospitalisation)
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: - Results in death - Is life-threatening - Requires inpatient hospitalisation or prolongation of existing hospitalisation - Results in persistent or significant disability/incapacity - Consists of a congenital anomaly or birth defect

	Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: 1. In the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product 2. In the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

11.3. Assessment results outside of normal parameters as AEs and SAEs

11.3.1. Clinical

Abnormal clinical findings from medical history or examination will be assessed as to their clinical significance throughout the trial. If an abnormal finding is deemed to be clinically significant, the participant will be informed and appropriate medical care arranged with the permission of the participant as per Section 9.5.

11.4. Assessment of severity

The severity of clinical adverse events will be assessed according to scales listed in the Clinical Study Plan and in Tables 3and 4 below.

Table 3: Severity grading for local adverse events

Adverse Event	Grade	Intensity
Pain at injection site	1	Pain that is easily tolerated
	2	Pain that interferes with daily activity
	3	Pain that prevents daily activity
	4	A&E visit or hospitalization
Tenderness	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
Erythema at injection site*	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
Induration/Swelling at injection site	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 - 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
	4	Necrosis
***erythema ≤2.5cm is an expected consequence of skin puncture and will therefore not be considered an adverse event**		

Table 4: Severity grading for local and systemic AEs

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
GRADE 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
GRADE 4	Potentially Life-threatening: Requires assessment in A&E or hospitalisation

11.5. Assessment of causality

For every recorded AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the CI-delegated clinician. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy. Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality of SAEs will be assigned by the reporting investigator at the time of reporting, as described in SOP OVC005 Safety Reporting for CTIMPs. For all other AE's causality assessment will take place during planned safety reviews, interim analyses (including if the study is paused by the DSMB due to safety concerns) and at the final safety analysis. Causality assessment will be recorded on the eCRF.

Table 1: Guidelines for assessing the relationship of vaccine administration to an AE.

0	No relationship	No temporal relationship to study product and Alternate aetiology (clinical state, environmental or other interventions); and Does not follow known pattern of response to study product
1	Unlikely	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	Possible	Reasonable temporal relationship to study product; ***or*** Event not readily produced by clinical state, environmental or other interventions; ***or*** Similar pattern of response to that seen with other vaccines
3	Probable	Reasonable temporal relationship to study product; ***and*** Event not readily produced by clinical state, environment, or other interventions ***or*** Known pattern of response seen with other vaccines
4	Definite	Reasonable temporal relationship to study product; ***and***

Event not readily produced by clinical state, environment, or other interventions; ***and***
Known pattern of response seen with other vaccines

11.6. Procedures for reporting Adverse Events

11.6.1. Solicited AEs

Participants will be asked to record local and systemic AEs for 7 days (and longer if symptoms persist at day seven, until resolution or stabilisation) following vaccination in the electronic/paper diary (solicited AEs).

11.6.2. Unsolicited AEs

All local and systemic AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the participant, whether or not attributed to study medication, will be recorded in electronic/paper diaries or study database. All AEs that result in a participant's withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the participant consents to this) as per Section 9.8.

SAEs and AESIs will be actively solicited at each study visit throughout the entire trial period.

11.7. Reporting procedures for Serious Adverse Events

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported to members of the study team immediately the Investigators become aware of their occurrence, as described in the clinical study plan. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The DSMB will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the chair of DSMB will be notified immediately (within 24 hours) of the sponsor being aware of their occurrence. SAE/AESIs will not normally be reported immediately to the ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial participants, at the discretion of the Chief Investigator and/or DSMB. In addition to the expedited reporting above, the Investigator shall include all SAE/AESIs in the annual Development Safety Update Report (DSUR) report provided for COM-COV, COM-COV2 and COM-COV3.

In participants who have received the NVXCoV2373 vaccine in this study, SAE's will be reported to Novavax according to the conditions and timelines outlined in the contemporaneous version of the Clinical Trial Agreement between Novavax and the University of Oxford University for conduct of this study.

11.7.1. Events exempt from immediate reporting as SAEs

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event. A&E attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

11.8. Expectedness

11.8.1. SARs

11.8.1.1. Pfizer BioNTech (BNT162b2)

If an SAE is considered as being an SAR to BNT162b2, section 4.8 of the BNT162b2 Summary of Product Characteristics will be used as the reference safety information to determine expectedness. Potential SARs considered to be expected include:

- Anaphylaxis
- Myocarditis/pericarditis
- Lymphadenopathy
- Facial nerve palsy

11.8.1.2. Novavax, NVXCoV2373

No SARs expected

11.8.2. Foreseeable Adverse Reactions

The foreseeable ARs following vaccination are as follows:

11.8.2.1. Pfizer BioNTech (BNT162b2)

Very common	*Common*	*Uncommon*	*Rare*	*Unknown*
Headache	Injection site redness	Lymphadenopathy	Acute peripheral facial paralysis	Anaphylaxis
Arthralgia	Nausea	Insomnia		Hypersensitivity
Myalgia		Pain in extremity		Myocarditis
Injection site pain/swelling		Malaise		Pericarditis

Fatigue		Injection site pruritus		
Chills				
Pyrexia				

11.8.2.2. Novavax, NVXCoV2373

(From the IB report of data from clinical trials)

- Reactogenicity is generally mild, and vaccinations were well tolerated.
- Following first vaccination, local reactogenicity is more frequent for NVXCoV2373 than the unadjuvanted or placebo regimens.
- Tenderness and pain were the most frequent local AEs.
- Systemic reactogenicity were individually less frequent but were observed with greater frequency in the SARS-CoV-2 rS/Matrix-M1 adjuvant groups.
- Headache, fatigue, and myalgia were the most frequent systemic AEs.
- Following second vaccination, NVXCoV2373 induced greater local and systemic reactogenicity, but the majority of reported symptoms remained at grade ≤ 1.
- Mean duration of reactogenicity events was ≤ 2 days without appreciable change in duration with second vaccination.
- Severe reactogenicity was infrequent (2 events after Dose 1 and 8 events after Dose 2), occurring more often with second vaccination and for systemic events, with placebo subjects citing similar frequencies as those receiving SARS-CoV-2rS.

11.9. No subjects sought medical intervention or refused second vaccination because of reactogenicity

11.10. Adverse Events of Special Interest

Table 2: AESIs

Immunologic	Anaphylaxis	
Neurological	Isolated anosmia/ageusia* Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Aseptic meningitis	Meningoencephalitis Peripheral facial nerve palsy Generalised convulsion Myelitis

Haematological	Thrombosis** Stroke Thrombocytopaenia*** Eosinophilia****	Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed and stroke)
Cardiac	Acute cardiovascular injury (includes myocarditis#, pericarditis#, arrhythmias, heart failure, infarction)	
Dermatological	Chilblain-like lesions Single organ cutaneous vasculitis	Erythema multiforme Alopecia
Gastrointestinal	Acute liver injury †† †	Appendicitis Cholecystitis*****
Respiratory	ARDS††	
Renal	Acute kidney injury	
Other	COVID-19 disease† PIMS-TS †† ††	SARS-CoV2 positivity on a validated test

*In the absence of COVID-19

** Excluding superficial thrombophlebitis (including line-associated)

*** G3 or above

**** This will be used as a marker of skewed Th2 responses and will be routinely monitored in participants attending the COVID-19 Pathway and follow-up visits. Only G2 and above.

***** Added as an expected AR to the IB for NVXCoV2373 in Addendum 1 dated 27 Sept 2021. A further update (Addendum 2 dated 11th January 2022) removed cholecystitis as an expected AR for NVXCoV2373. Cholecystitis is therefore not considered an expected AR, though it remains an AESI.

Brighton collaboration guideline definitions for myocarditis and pericarditis as outlined in appendix D

† In particular, any occurrence of suspected vaccine associated enhanced disease (VAED) as defined by most recent Brighton Collaboration Case Definition (22)

†† In the absence of an infective aetiology (including COVID-19)

†† † As defined in Hy's Law

†† †† The Royal College of Paediatrics and Child Health has outlined a case definition for PIMS-TS.

1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (Table 8) This may include children fulfilling full or partial criteria for Kawasaki disease.

2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice).
3. SARS-CoV-2 PCR testing may be positive or negative

AESIs should be collected and recorded in the AE reporting form in REDCap throughout the duration of this study. These should also be reported as SAEs if they fulfil the definition criteria for SAEs. All AESIs not already reported as SAEs should be included in the reports to the DSMB.

11.10.1. Disease enhancement following vaccination

Severe COVID-19 disease will be defined as hospitalisation, with further grading of severity according to the WHO ordinal scale (June 2020).(23) Cases of COVID-19 disease will be examined for the possibility of vaccine associated enhanced disease (VAED). This will be evaluated on the basis of the most recent recommendations of the Brighton Collaboration. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions, as they emerge. Investigations will be defined by the laboratory analysis plan.

11.11. SUSAR reporting

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

11.12. Development Safety Update Reports

A Development Safety Update Report (DSUR) will be prepared annually, reporting on this study, 'Comparing COVID-19 Vaccine Schedule Combinations (Com-COV) **(**Ethics Ref: 21/SC/0022**,** IRAS Project ID: 291055) and Comparing COVID-19 Vaccine Schedule Combinations -stage 2 (Com-COV2)(Ethics Ref: 21/SC/0119**,** IRAS Project ID 297443), within 60 days of the anniversary of the MHRA approval for the 'first' COMCOV study. The DSUR will be submitted by the CI to the Competent Authority, Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

11.13. Interim reviews

The safety profile will be assessed on an on-going basis by the Investigators. The CI and relevant Investigators (as per the trial delegation log) will also review safety issues and SAEs as they arise. The DSMB will evaluate safety data as required. The DSMB may also be consulted should safety concerns arise at any point.

11.14. Safety holding rules

There will be no formal pausing rules given the extensive safety database for all vaccines used in this study.

The study can be paused upon advice of the DSMB, Chief Investigator, Study Sponsor, regulatory authority, Ethical Committee(s), for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the participants or the reliability of the data.

11.15. Contraception and pregnancy

11.15.1. Contraception

Post-menarchal female participants are required to use an effective form of contraception from enrolment continuously until three months after boost immunisation.

Acceptable forms of contraception for volunteers of female sex include:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Total hysterectomy
- Bilateral Tubal Occlusion
- Barrier methods of contraception (condom or occlusive cap with spermicide)
- Male sterilisation, if the vasectomised partner is the sole partner for the subject
- True abstinence, when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence and withdrawal are not acceptable methods of contraception)

11.15.2. Pregnancy

Should a participant become pregnant during the trial, no further study IMP will be administered. They will be followed up for clinical safety assessment with their ongoing consent and in addition will be followed until pregnancy outcome is determined. We would not routinely perform venepuncture in a pregnant participant unless there is clinical need.

12. STATISTICS

12.1. Sample size

The total sample size of this trial will be up to 270 Since the primary endpoint analysis will be descriptive and therefore no formal sample size calculation is carried out to determine the sample size of the trial. The number has been therefore chosen based on practical constraints. The precisions on estimating the systematic reactions based on 90 per arm are:

True event rate	Precision (normal approximation)	95% exact binomial CI
5%	±4.5%	1.5%-11.7%
10%	±6.2%	4.7%-18.1%
25%	±8.9%	16.5%-35.2%
50%	±10.3%	39.3%-60.7%

For secondary endpoints of immunogenicity, the minimum geometric mean ratios that can be detected with 90% power at two-sided 0.05 based on 90 per arm are:

Standard deviation on log10 scale	Minimum GMR to detect
0.4	1.57 (or 0.64)
0.5	1.75 (or 0.57)
0.6	1.96 (or 0.51)

12.2. Description of statistical methods

A fully detailed statistical analysis plan will be developed and signed by the chief investigator prior to any data analysis being conducted. In brief, the analysis will incorporate the following:

Safety and reactogenicity

All SAEs will be presented for each group using descriptive analyses. Counts and percentages of each local and systemic solicited adverse reaction from diary cards, and all unsolicited AEs, and AEs of special interest will be presented for each group. Comparisons between the arms will made using Fisher's exact test.

Immunogenicity

Highly skewed ELISA data will be log-transformed prior to analysis. The geometric mean concentration (GMC) and associated 95% confidence interval (CI) will be summarised by computing the anti-log of the mean of the log-transformed data.

The GMRs and CIs post boost will be calculated for each of the heterologous arms when comparing to the homologous arm.

Spike-specific T cell responses (ELISPOT) will be presented as geometric means and confidence intervals, or medians and interquartile ranges if non-normally distributed after log-transformation.

Comparisons of continuous immunogenicity data between different arms or at different time points will be made using a t-test if normal distribution can be rendered after log-transformation. Otherwise, Mann Whitney U test will be used.

12.3. Missing data

Any missing data will be dealt with, if needed, using methods appropriate to the conjectured missing mechanism and level of missing.

12.4. Interim analyses

The analysis on the primary endpoint of reactogenicity, i.e. solicited AEs will be carried out once the 7-day e-diary data become available. The analysis on the secondary endpoint of immunogenicity will be carried out when the D70 immunogenicity data, i.e. 14 days post boost, become available. The interim analyses will provide evidence for policy making as to the recommendation on the second dose of COVID-19 vaccine among adolescents. The interim analyses will be carried out once the data is cleaned and the Study Analysis Plan is signed off. There will be no stopping rule for this interim analysis and the analysis will not affect the continuation of the trial.

After further discussion with Joint Committee on Vaccination and Immunisation (JCVI), the study team decided to carry out another interim analysis in December 2021. In this analysis, we will review the sero-status pre-boost as well as all the available immunogenicity data. These data will be shared with JCVI only to support decision making on boost dose among people aged 12-17. This interim analysis will be descriptive.

On 29th November 2021, the JCIV recommended that all 12 to 15 year-olds should be offered a second dose of BNT162b2 vaccine before reviewing the planned interim analysis in December 2021. The study design was amended to focus on immune response to full dose and one third dose of BNT162b2. The planned analysis in December will still be conducted and results will be

presented to JCVI to update their recommendation. The study's recruitment and sample size will then be reviewed on the basis of this analysis after discussing with JCIV, TSC and DSMB.

13. DATA MANAGEMENT

The Chief Investigator will be responsible for all data that accrues from the study.

13.1. Access to Data & Data Protection

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

13.2. Data Recording

All study data including participant diary will be recorded directly into an EDC system (REDCap) or onto a paper source document for later entry into EDC if direct entry is not available. This includes safety, laboratory and outcome data. Any additional information that needs recording, but is not relevant for the eCRF (e.g signed consent forms) will be recorded on separate paper source documents. All documents will be stored safely and securely in confidential conditions. The EDC online data is stored on University of Oxford servers.

All participant reported adverse event data (both solicited & unsolicited) will be entered onto electronic diary cards (e-diaries) for a maximum of 28 days following administration of the IMP. The e-diary provides a full audit trial of edits and will be reviewed at time-points as indicated in the schedule of events. Any adverse event continuing beyond the period of the diary will be copied into the eCRF as required for safety review.

The participants will be identified by a unique trial specific number and code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file, with the exception of the electronic diaries, for which consent will be obtained to store the participant email address for quality control purposes. Only site research staff and sponsor data managers have access to view the email address.

The EDC system (CRF data) uses a relational database (MySQL/ PostgreSQL) via a secure web interface with data checks applied during data entry to ensure data quality. The database includes a complete suite of features which are compliant with GCP, EU and UK regulations and

Sponsor security policies, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL and PostgreSQL database and the webserver will both be housed on secure servers maintained by the University of Oxford IT personnel. The servers are in a physically secure location in Europe. Backups will be stored in accordance with the IT department schedule of daily, weekly, and monthly retained for one month, three months, and six months, respectively. The IT servers provide a stable, secure, well-maintained, and high-capacity data storage environment. REDCap is a widely-used, powerful, reliable, well-supported system. Access to the study's database will be restricted to members of the study team by username and password.

13.3. Record keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s) and Host institution, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Following completion of the study, identifiable information such as contact details will be stored for a minimum of 5 years and until the youngest participant turns 21 years old. This includes storage of consent forms. Storage of these data will be reviewed every 5 years and files will be confidentially destroyed if storage is no longer required. Considerations at the time of this review will include the value of retaining this information for participant safety (e.g. to inform participants of unexpected safety signals emerging from post-licensing surveillance), as a resource for the participants (e.g. if they wish to check which vaccines they have received in the study) and any regulatory requirements. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, a record of this consent will be recorded, retained and stored securely and separately from the research data. If volunteers consent to have their samples stored and used in future research, information about their consent form will be retained and stored securely as per Biobanking procedures and SOP.

13.4. Source data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the participant file. Source documents are original documents,

data, and records from which the participant CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, GP response letters, laboratory records, diaries, medical records and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, adverse event data and details of vaccinations. All source data and participant files will be stored securely.

To prevent withdrawal of a participant due to relocation, if there is a nearby participating site and with the consent of the participant, copies of relevant participant research records (such as ICF, paper source documents) will be transferred to the local site using secure email addresses such as nhs.net or by password protected sheets. The electronic research data stored on REDCap will also be transferred to the new site. The original records will be retained by the recruiting site.

13.5. Data Quality

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs. If additional, study specific processes are required, an approved Data Management Plan will be implemented

14. Quality Assurance Procedures

14.1. Risk Assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2. Monitoring

Monitoring will be performed according to Good Clinical Practice (GCP) by an external monitor. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator sites will provide direct access to all trial related source

data/documents and reports for the purpose of monitoring and auditing by the Sponsor or the Host institution and inspection by local and regulatory authorities

14.3. Trial committees

14.3.1. Trial Steering Committee

A Trial Steering Committee will be formed to oversee the study, and advise the Study Management Committee on key issues of study conduct, including, but not limited to, study pauses due to safety concerns on the advice of the DSMB.

14.3.2. Safety Monitoring Committee

A Data Safety Monitoring Board (DSMB) will be convened. The DSMB will evaluate frequency of events, safety and efficacy data as specified in the DSMB charter. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons to the Trial Steering Committee.

The DSMB will review SAEs or AESIs deemed possibly, probably or definitively related to study interventions. The DSMB will be notified within 24 hours of the Investigators' being aware of their occurrence. The DSMB can recommend placing the study on hold if deemed necessary following a study intervention-related SAE.

14.3.3. Study Management Committee

Consists of the site Investigators and the Laboratory lead for Public Health England.

15. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be documented in a protocol deviation form according to SOP OVC027 and filed in the trial master file.

These will be managed as per SOP OVC027.

16. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

17.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject (i.e. as an Urgent Safety Measure).

17.4. Other Ethical Considerations

First degree family members of the study team are not eligible for inclusion in the trial given the potential for them to be unblinded to the vaccine the participant has received, and for this to influence completion of reactogenicity diaries.

17.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database. Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration by the CI or their delegate. Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

17.7. Participant confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of informed consent forms, participant ID log, electronic diaries and any other documents required for participant management. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the current data protection legislation.

17.8. Expenses and Benefits

Participants will be offered £10 reimbursement per visit towards travel and expenses. This may be in the form of gift cards/vouchers. Reimbursement may not be given at each visit (for example, we may give a £20 voucher at every other visit). The exact arrangements for reimbursement may vary between sites.

18. FINANCE AND INSURANCE

18.1. Funding

The study is funded by the UK Government through the National Institute for Health Research (NIHR).

18.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided and for the conduct of the research at NHS sites.

18.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

19. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Data from the study may also be used as part of a thesis for a PhD or MD.

20. DEVELOPMENT OF A NEW PRODUCT / PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

21. ARCHIVING

Study data may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the site. All essential documents will be retained for a minimum of 9 years (until the youngest participant turns 21) after the study has finished with 5 yearly reviews. The need to store study data for longer in relation to licensing of the vaccine will be subject to ongoing review. For effective vaccines that may be licensed, we may store research data securely at the site at least 15 years after the end of the study, subject to adjustments in clinical trials regulations. De-identified research data may be stored indefinitely, but with 5 yearly review.

General archiving procedures will be conducted in compliance to SOP OVC020 Archiving.

22. REFERENCES:

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23. APPENDIX A: SCHEDULE OF PROCEDURES

Study timeline	**Screening**	D0	D56	D14 post boost	D28 post boost	D132 post boost	D236 post boost
Study window		Within 120 days of screening	Day 56–70 post prime vaccine at D0 or Day 56 + post prime vaccination in community	Day 12-17 Post D56	Day 28-42 post D56	Day 112-152 post D56	Day 224-252 post D56
Pre - screening online consent	X*						
Informed consent	X	X					
Medical history	X	X					
Interim medical history		X	X	X	X	X	X
Physical examination (as required)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Urine test (Pregnancy) (if required)		(X)**	X				
COVID-19 vaccination		(X)**	X				

COVID-19 immunogenicity bloods		(X)**	X	X	X	X	X
Troponin and NT-proBNP blood test		(X)**	X	X	X		
Saliva and nasal fluid test (if participant consents)		(X)**	X	X			
Diary review			X	X	X		
SAE/AESI check			X	X	X	X	X

* Pre - screening online consent. Restricted to taking a limited medical history online, contacting the GP for further medical record if required and telephone screening visit(s)

**Procedures performed only if prime dose administered in the study

24. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
MHRA change request during MHRA review	1.1	27 Aug 2021	Hannah Robinson	Section 8.3 and 11.14 updated to specify that only post-menarchal females are required to use contraception during the specified period
1	2.0	10 Sep 2021	Philip de Whalley	• Sections 2, 3, 5.1, 5.2, 7.3, 10.1, 10.3 and 11.8 updated to change one arm of study from ½ dose Novavax to ½ dose Moderna • Section 0 updated to include additional DSMB member • Section 9.6 updated to include additional diary information to be collected • Sections 3, 6 and 25 updated to include D56 anti-nucleocapsid IgG testing for participants receiving first dose of COVID-19 vaccine in the community • Section 22 updated. Reference 15 added • Section 17.8 updated to clarify that reimbursement is towards travel and expenses • Section 3 updated to remove sentence about even distribution across age range • Section 23 updated to change D84 study window
2	2.1	20 Sep 2021	Iason Vichos	• Section 0 Key Trial Contacts: addition of Dr Philip Connor in the Trial Management Group as the Principal Investigator at Public Health Wales

3	2.2	14 October 2021	Sharon Tonner	• Section 0 Key Trial Contacts: addition of Dr David Turner in the Trial Management Group as the Principal Investigator at Cripps Health Centre
4	3.0	18 Oct 2021	Eimear Kelly, Philip de Whalley, Xinxue Liu	• IMP dosing for BNT162b2 booster arm 2 changed from 15 µg (0.15ml) to 10 µg (0.10ml) • Addition of interim analysis to be reported to JCVI in December 2021
5	N/A	05 November 2021	Sharon Tonner	• Creation of Invitation Letter (no impact on protocol).
6	4.0	15 Nov 2021	Eimear Kelly Emma Plested, Philip de Whalley	• Removal of Moderna arm • Reduction of total sample size to 270 • Change of last two visit timings to D140 and D238 • Addition of D56 antinucleocapsid IgG test for participants primed in the study • Update to national recommendations for 2nd dose of COVID-19 vaccines for 16 year olds. • Update to the exclusion criteria for those advised to receive two doses of a Covid-19 vaccine, that this only applies to the 'high risk' cohort as per the green book guidelines. • Clarification on how potential participants can respond to direct mailings to register their interest in the trial.
7	5.0		Philip de Whalley	• Change of D56 randomisation from 1:1:1 to 1:1, effective from 29th November 2021 • Updated JCVI recommendations • Amended Sections 2, 5.1 and 5.2 to account for latest JCVI recommendations

				• Clarified that participants with proven COVID-19 infection first confirmed less than 4 weeks previously will not be vaccinated (Sections 7.4 and 8.3.1) • Extended Day 70 visit window to between 12-17 days post Day 56
8	5.1	21 Dec 2021	Eimear Kelly	• Cholecystitis added as an AESI, and foreseeable adverse reactions for Novavax vaccine
9	6.0	18Jan 2021	Eimear Kelly	• Cholecystitis removed as a foreseeable adverse reaction to Novavax vaccine following issuing of Novavax Addendum 4.2, 11 Jan 2022 • Correction to labelling of Tables • Clarified the time points of the final two Com COV 3 visit. The penultimate visit will take place approximately 4 months post boost dose (Day 132 post -boost) and the final visit approximately 8 months post boost (Day 236 post boost). This will prevent the 28 day post boost and penultimate (previously D140) visits from coinciding for those participants recruited from the community. To avoid confusion study visits are now named in relation to prime and boost vaccines. • Addition of Troponin & NT proBNP analysis on Day 28 post boost samples on the advice of the DSMB. We will not be re-consenting participants for the change to the visit schedule and the addition of Troponin and NT proBNP analysis at d28 post

				boost (no additional blood volume required).

25. APPENDIX C: BLOOD SAMPLING

Study timeline	**D0**	**D56**	**D14 post boost**	**D28 post boost**	**D132 post boost**	**D236 post boost**
COVID-19 vaccination	**X**	**X**				
Secondary endpoints	Anti-spike IgG* Anti-nuclesocapsid IgG* ELIspot* Troponin & NT-proBNP*	Anti-spike IgG Anti-nucleocapsid IgG ELIspot Troponin & NT-proBNP	Anti-spike IgG ELIspot Troponin & NT-proBNP	Anti-spike IgG PBMC for storage Troponin & NT-proBNP	Anti-spike IgG Anti-nuclesocapsid IgG ELIspot	Anti-spike IgG Anti-nuclesocapsid IgG ELIspot
Total volume blood per visit	16	16	16	16	16	16
Total volume by end of study						96 ml

*** Procedures performed only if prime dose administered in the study**

26. APPENDIX D: DEFINITION OF MYOCARDITIS

Brighton Collaboration criteria provide a clinical definition of myocarditis.(19) They distinguish definitive, probable and possible cases, as follows:

Definitive case:

Histopathologic examination of myocardial tissue (autopsy or endomyocardial biopsy) showed myocardial inflammation

OR Elevated myocardial biomarkers (troponin T and/or troponin I), **AND**
Abnormal Imaging Study EITHER

Abnormal Cardiac Magnetic Resonance Study (at least 1 of the findings below):

1. Oedema on T2 weighted study, typically patchy in nature
2. Late gadolinium enhancement on T1 weighted study with an increased enhancement ratio between myocardial and skeletal muscle typically involving at least one non-ischemic regional distribution with recover (myocyte injury)

OR Abnormal Echocardiogram (at least 1 of the findings below):

1. New focal or diffuse left or right ventricular function abnormalities (e.g. decreased ejection fraction)
2. Segmental wall motion abnormalities
3. Global systolic or diastolic function depression/abnormality
4. Ventricular dilation
5. Wall thickness change
6. Intracavitary thrombi

Probable case:

Clinical symptoms

EITHER Cardiac symptoms (at least 1 finding below):

1. Acute chest pain or pressure
2. Palpitations

3. Dyspnea after exercise, at rest, or lying down
4. Diaphoresis
5. Sudden death

OR Non-specific symptoms (at least 2 findings below):

1. Fatigue
2. Abdominal pain
3. Dizziness/syncope
4. Oedema
5. Cough

OR In infants and young children (at least two finding below):

1. Irritability
2. Vomiting
3. Poor feeding
4. Tachypnoea
5. Lethargy

AND Testing supporting diagnosis (Biomarkers, ECHO and ECG)

EITHER Elevated myocardial biomarkers (at least 1 finding below):

1. Troponin I
2. Troponin T
3. CK myocardial band

OR Echocardiogram (ECHO) abnormalities (at least 1 of the findings below):

1. New focal or diffuse left or right ventricular function abnormalities (e.g. decreased ejection fraction)
2. Segmental wall motion abnormalities
3. Global systolic or diastolic function depression/abnormality
4. Ventricular dilation

5. Wall thickness change
6. Intracavity thrombi

OR Electrocardiogram abnormalities that are new and/or normalise on recovery (at least 1 of the findings below):

1. Paroxysmal or sustained atrial or ventricular arrhythmias (premature atrial or ventricular beats, and/or supraventricular or ventricular tachycardia, interventricular conduction delay, abnormal Q waves, low voltages)
2. AV nodal conduction delays or intraventricular conduction defects (atrioventricular block (grade I-III), new bundle branch block)

AND no alternative diagnosis for symptoms.

Possible case:

EITHER Cardiac symptoms (at least 1 finding below):

1. Acute chest pain or pressure
2. Palpitations
3. Dyspnea after exercise, at rest, or lying down
4. Diaphoresis
5. Sudden death

OR Non-specific symptoms (at least 2 findings below):

1. Fatigue
2. Abdominal pain
3. Dizziness/syncope
4. Oedema
5. Cough

OR In infants and young children (at least two finding below):

1. Irritability
2. Vomiting

3. Poor feeding
4. Tachypnoea
5. Lethargy

AND Biomarkers supporting evidence of infection (at least 1 finding below):

1. Elevated CRP
2. Elevated ESR
3. Elevated D-dimer

AND Non-Specific Electrocardiogram (EKG) Abnormalities that are new and/or normalize on recovery (at least 1 finding below):

1. ST segment or T wave abnormalities (elevation or inversion)
2. PACs and VCs

AND No alternative diagnosis for symptoms