



**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)

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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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**1 KEY TRIAL CONTACTS**

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<b>Funder(s)</b>	<p>UK Vaccine Task Force (VTF)  National Institute Health Research (NIHR)  Coalition for Epidemic Preparedness Innovations (CEPI)  Novavax (Vaccine supply)</p>
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<b>Committees</b>	<p><b>Data Safety Monitoring Board</b> Manish Sadarangani Guido Pieles Stephen Evans Hanna M. Nohynek Krishnan Bhaskaran</p> <p><b>Trial Steering Group</b> Mary Ramsay, Public Health England Robert Read, University of Southampton Paul Turner, Imperial College London Claire Cameron, Public Health Scotland</p> <p><b>Study Management Group</b> A Minassian T Lambe B Hallis Principal Investigator from each study site</p>

## **2 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.

A. Minassian is an investigator on the Cov001, Cov002 and Cov009 studies evaluating ChAdOx1nCoV19. These studies are funded by NIHR and receive logistical support from AstraZeneca. A. Minassian is currently, or has recently been, an investigator on studies funded +/- sponsored by vaccine manufacturers including Pfizer, GlaxoSmithKline, Janssen, Valneva SE and Novavax. She receives no personal financial benefit for this work.

## **3 LAY SUMMARY**

The successful roll-out of COVID-19 vaccines such as 'COVID-19 mRNA Vaccine BNT162b2' and the Oxford/AstraZeneca ChAdOx1 nCoV-19 vaccine has saved approximately 120 000 lives in the UK alone, up to 23<sup>rd</sup> September 2021.<sup>1</sup> Both of these vaccines are administered as a two-dose regimen, as is the adjuvanted protein COVID-19 vaccine from Novavax, NVXCoV2373, which was approved by the MHRA for use in adults on 3<sup>rd</sup> February 2022 and for use in 12 to 17 year olds on 26<sup>th</sup> August 2022 (as an alternative primary two-dose regimen).<sup>2</sup>

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 were reviewed by the JCVI in the second half of 2021, and on 13<sup>th</sup> September 2021 it was announced that a first dose of BNT162b2 was recommended for all 12 to 17 year olds in the UK.<sup>3</sup> On 15<sup>th</sup> 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.<sup>4</sup> 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 29<sup>th</sup> November 2021.<sup>5</sup>

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.<sup>6</sup> Mixed schedules with alternative vaccines used for the second dose, or using fractional doses of COVID-19 vaccines, could be alternatives that allow 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, Cohort A of this study will determine the side effect profile, and the immune responses of heterologous and/or fractional COVID-19 prime 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 29<sup>th</sup> November 2021 that all 12- to 15-year-olds should be offered a second dose of BNT162b2 vaccine, no new participants were enrolled and the study design for Cohort A was amended to focus on immune response to BNT162b2. After this date, participants recruited and not yet immunised with their second dose were randomised 1:1 to either full or one-third dose BNT162b2 for their second vaccination; participants were no longer randomised to the Novavax arm of the study to prioritise the arms of the study that were likely to be more policy relevant. This did not reflect any concern regarding the safety or immunogenicity of the Novavax vaccine. A further review of the study design was undertaken following an interim analysis, and on 3<sup>rd</sup> February 2022, the study Trial Steering Committee advised to stop recruitment for Cohort A. It was also decided to add a new cohort to the study to investigate possible strategies for a third dose of COVID-19 vaccine in adolescents, given a third dose is now recommended for those 16 years and above (as well as for younger high-risk groups).

Cohort B of this study will determine the side effect profile, and the immune responses to a third dose of COVID-19 vaccination in adolescents, given at least three months after completion of a two-dose prime schedule (two full doses of BNT162b2 given at least 8 weeks apart). Participants will be randomised to receive 30µg BNT162b2, 10µg BNT162b2 (given as 0.1ml of adult formulation), 10µg BNT162b2 (given as 0.2ml of paediatric formulation), NVXCov2373 (full dose) or two doses of 4CMenB (Meningococcal Group B vaccine, control group). The control group will be offered a full dose of Pfizer-BioNTech bivalent vaccine (Comirnaty Original/Omicron BA.1, 15µg /15µg per dose) 6 months after enrolment in the study (or earlier if a 3<sup>rd</sup> COVID-19 vaccine dose is routinely recommended for 12 to 15 year-olds before the 6 month timepoint). As a

consequence of challenging recruitment to the study, and following discussion with the study Trial Steering Committee, randomisation was changed from 1:1:1:1:1 to 1:3:3:1:1 to the five study groups (following approval of substantial amendment 13) on 9<sup>th</sup> June 2023, in order to prioritise recruitment to study groups 2 and 3 [i.e, the 10µg BNT162b2 (given as 0.1ml of adult formulation) and 10µg BNT162b2 (given as 0.2ml of paediatric formulation) groups]. This was done to achieve the participant numbers required to meet the study's key aim of comparing the immunogenicity between the two 10µg BNT162b2 groups. Following discussions with the Trial Steering Committee on 22<sup>nd</sup> March 2023, it was decided that recruitment to Cohort B would stop on 30<sup>th</sup> June 2023 following ongoing recruitment difficulties.

Further explanation of the rationale and design for Cohort B is given in Appendix E.

#### 4 SYNOPSIS

<b>Trial Title</b>	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)
<b>Internal ref. no. (or short title)</b>	Comparing COVID-19 Vaccine Schedule Combinations in adolescents (Com-COV3)
<b>Trial registration</b>	EudraCT: 2021-004267-27 ISRCTN: 12348322
<b>Sponsor</b>	University of Oxford, Clinical Trials and Research Governance, Joint Research Office, Boundary Brook House Churchill Drive, Headington Oxford OX3 7GB, United Kingdom
<b>Funders</b>	UK Vaccine Task Force (VTF) National Institute Health Research (NIHR) Coalition for Epidemic Preparedness Innovations (CEPI) Novavax (Vaccine supply)
<b>Clinical Phase</b>	Phase II
<b>Trial Design</b>	Single-blind, randomised homologous/heterologous-boost vaccine administration study using standard and/or fractional doses
<b>Trial Participants</b>	Cohort A: Adolescents aged 12 to 16 years (inclusive)

	Cohort B: Adolescents aged 12 to 15 years and 6 months (inclusive)		
<b>Sample Size</b>	<p>Cohort A: A total of up to 270 (+ up to an additional 10%) participants will be enrolled</p> <p>Cohort B: A total of up to 310 (+ up to an additional 10%) participants will be enrolled</p> <p>A participant is considered enrolled at the time they receive a vaccine in this study</p> <p>Cohort A &amp; B: A total of up to 580 (+ up to an additional 10%) will be enrolled</p>		
<b>Planned Trial Period</b>	<p>Cohort A: Approximately 26 or 34 weeks per participant. Total trial period approximately 10 months</p> <p>Cohort B: Approximately 6 or 7 months per participant</p> <p>Total trial period approximately 10 months</p>		
	<b>Objectives</b>	<b>Outcome Measures</b>	<b>Timepoint(s)</b>
<b>Primary</b>	<p>Cohort A: To evaluate the reactogenicity of heterologous boost* at least 8 weeks following BNT162b2 prime vaccine administered to adolescents</p> <p>Cohort B: To evaluate the reactogenicity of homologous and heterologous boost* (third dose) given to adolescents at least 3 months after a two-dose schedule of BNT162b2</p>	Solicited systemic reactions	<p>Cohort A: 7 days after booster immunisation</p> <p>Cohort B: 7 days after third dose</p>
<b>Co-Primary</b>	Cohort B: To determine whether the immune response with BNT162b2 (10 µg, 0.1ml adult formulation) is non-inferior to that with BNT162b2 (10 µg, 0.2ml paediatric formulation)	Anti-spike immunoglobulins	28 days post third dose
<b>Secondary</b>	Cohorts A and B: To assess safety of heterologous second and third dose COVID-19 vaccines	Serious adverse events Adverse events of special interest	Throughout the study
	<p>Cohort A: To characterise immunogenicity of heterologous &amp; homologous second dose schedules of COVID-19 vaccines</p> <p>Cohorts B: To characterise immunogenicity of heterologous &amp; homologous third dose schedules of COVID-19 vaccines</p>	Anti-spike immunoglobulins	<p>Cohort A: D0**, 56 post prime D14, 28, 132, 236 post boost</p> <p>Cohort B: D0, 28, 84, 182, 210***</p>

	when compared with unimmunized controls	Cellular immune responses by ELISpot	Cohort A: D0**, 56 post prime D14, 132, 236 post boost Cohort B: D0, 28, 84, 182, 210***
	Cohorts A and B: Characterisation of frequency of anti-SARS-CoV-2 nucleocapsid IgG seropositivity at enrolment, and subsequent seroconversion through the study	Anti-nucleocapsid immunoglobulins	Cohort A: D0**, 56 post prime D132, 236 post boost Cohort B: D0, 84, 182
	Cohorts A and B: To assess reactogenicity and safety of heterologous and homologous second and third dose schedules of COVID-19 vaccines	Solicited local reactions	Cohort A: 7 days after prime** and boost immunisation Cohort B: 7 days post third dose
		Unsolicited reactions	Cohort A: 28 days after prime** and boost immunisation Cohort B: 28 days post third dose
	Cohorts A and B: To evaluate immunogenicity, safety and reactogenicity of COVID-19 vaccines in participants seropositive for SARS-CoV-2 nucleocapsid IgG at enrolment, compared with seronegative	Immunogenicity, safety and reactogenicity endpoints as outlined above	Timepoints as outlined above
<b>Exploratory</b>	Cohorts A and B: To assess incidence of SARS-CoV-2 infection in participants receiving heterologous and homologous second and third dose schedules of COVID-19 vaccines	Self-reported SARS-CoV-2 infection, from community testing, or (Cohort B only) by the COVID-19 lateral flow tests provided by the study	Throughout the study
	Cohorts A and B: To further characterise the blood antibody response	Neutralising and Functional antibody assays	Cohort A: D0**, 56 post prime D14, 28, 132, 236 post boost Cohort B: D0, 28, 84, 182, 210***

	Cohorts A and B: 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 and IgG ELISA and exploratory immunological assays in participants at selected sites	Cohort A: D0*, 56 post prime D14 post boost Cohort B: D0, 28, 84, 182, 210***														
	Cohort A: 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														
	Cohort B: To explore the motivations and experiences of parents and participants taking part in the trial.	Parent and participant motivation and experience questionnaire	Questionnaire sent after 3 <sup>rd</sup> study visit (D84)														
Intervention(s) - IMP(s)	<p>* Refers to second dose in the context of Cohort A. For cohort B the boost refers to third dose</p> <p>** Only for participants receiving their first dose of COVID-19 vaccine in the study</p> <p>*** Group 5 (who receive Pfizer bivalent vaccine at D182) in Cohort B only</p>																
	<table border="1"> <thead> <tr> <th data-bbox="435 1032 836 1144">Vaccine</th> <th data-bbox="836 1032 1198 1144">Dose</th> <th data-bbox="1198 1032 1445 1144">Route of administration</th> </tr> </thead> <tbody> <tr> <td data-bbox="435 1144 836 1498">Pfizer BioNTech (BNT162b2)</td> <td data-bbox="836 1144 1198 1498">30 µg (0.3ml adult formulation), 10 µg (0.1ml adult formulation), 10 µg (0.2ml paediatric formulation)</td> <td data-bbox="1198 1144 1445 1498">Intramuscular</td> </tr> <tr> <td data-bbox="435 1498 836 1704">Novavax, NVXCoV2373</td> <td data-bbox="836 1498 1198 1704">5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)</td> <td data-bbox="1198 1498 1445 1704">Intramuscular</td> </tr> <tr> <td data-bbox="435 1704 836 1778">Bexsero (4CMenB)</td> <td data-bbox="836 1704 1198 1778">0.5ml</td> <td data-bbox="1198 1704 1445 1778">Intramuscular</td> </tr> <tr> <td data-bbox="435 1778 836 1935">Pfizer-BioNTech Comirnaty (Original/Omicron BA.1)</td> <td data-bbox="836 1778 1198 1935">15 µg/15 µg (0.3ml)</td> <td data-bbox="1198 1778 1445 1935">Intramuscular</td> </tr> </tbody> </table>	Vaccine	Dose	Route of administration	Pfizer BioNTech (BNT162b2)	30 µg (0.3ml adult formulation), 10 µg (0.1ml adult formulation), 10 µg (0.2ml paediatric formulation)	Intramuscular	Novavax, NVXCoV2373	5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)	Intramuscular	Bexsero (4CMenB)	0.5ml	Intramuscular	Pfizer-BioNTech Comirnaty (Original/Omicron BA.1)	15 µg/15 µg (0.3ml)	Intramuscular	
Vaccine	Dose	Route of administration															
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Novavax, NVXCoV2373	5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml)	Intramuscular															
Bexsero (4CMenB)	0.5ml	Intramuscular															
Pfizer-BioNTech Comirnaty (Original/Omicron BA.1)	15 µg/15 µg (0.3ml)	Intramuscular															



**5 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
VAED	Vaccine antibody enhanced disease
Vp	Viral particle
VTF	Vaccine Task Force
WHO	World Health Organisation
µg	Microgram
4CMenB	Bexsero Group B Meningococcal vaccine

## 6 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.<sup>7</sup> 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.<sup>8</sup> 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, by 25<sup>th</sup> February 2022, there had been 430,257,564 confirmed cases of COVID-19, including 5,922,047 deaths, reported to the WHO.<sup>9</sup>

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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>13</sup> Remdesivir, a direct anti-viral, has also been shown to reduce duration of symptoms in those who have only mild disease.<sup>14</sup>

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, was approved for use in adults by the MHRA on 3<sup>rd</sup> February 2022 and approved for use in 12- to 17-year-olds on 26<sup>th</sup> August 2022 (as an alternative primary two-dose regimen). 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, by 28<sup>th</sup> February 2022 more than 17 million 12 to 17 year-olds have received at least one dose of COVID-19 vaccine, and 14.5 million have received two doses.<sup>15</sup> The majority of COVID-19 vaccine doses in the USA have been the mRNA vaccines, predominantly BNT162b2. The potential benefits (and costs) of COVID-19 immunisation for adolescents in the UK was reviewed by the JCVI in the second half of 2021 and on 13<sup>th</sup> September 2021 it was announced that a first dose of BNT162b2 was recommended for all 12 to 17 year-olds in the UK.<sup>3</sup> A second dose of BNT162b2 was recommended for all 16 to 17 year-olds in the UK on 15<sup>th</sup> November 2021, and for all 12 to 15 year-olds on 29<sup>th</sup> November 2021.<sup>4,5</sup>

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.<sup>6,16</sup> An analysis of reports of myocarditis to the Vaccine Adverse Event Reporting System (VAERS) that occurred after mRNA-based COVID-19 vaccine administration in the USA between December 2020 and August 2021 has been published.<sup>17</sup> Rates of myocarditis were highest after the second vaccination dose in adolescent males aged 12 to 15 years (70.7 per million doses of the BNT162b2 vaccine) and 16 to 17 years (105.9 per million doses of the BNT162b2 vaccine). Fortunately, most cases of myocarditis are benign and self-limiting, although long term effects are uncertain.<sup>6,17</sup>

The possibility of using a fractional instead of a full dose of BNT162b2 for the second dose is therefore being considered, which could also enable available stocks of vaccine to be deployed 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 data suggest that a lower (one-third) dose in the adolescent age group may have the potential to provide a similar level of immunogenicity but with an improved reactogenicity profile.<sup>18</sup> Notably, this study was conducted using a bespoke paediatric formulation of the BNT162b2 vaccine, in which a diluent is used to increase the dose volume to 0.2 ml, and this paediatric formulation was licensed for use in 5 to 12 year-olds on 22<sup>nd</sup> December 2021. No studies have formally compared the immunogenicity and reactogenicity of a BNT162b2 10 µg dose when administered using 0.1 ml of the adult formulation versus the 0.2ml dose of the paediatric formulation.

The use of heterologous prime/boost schedules of COVID-19 vaccines has been studied in COMCOV and COMCOV2, to facilitate flexible immunisation programmes.<sup>19,20</sup> 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. 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.<sup>21</sup> It was licensed for use in 12 to 17 year olds by the MHRA on 26<sup>th</sup> August 2022 (as an alternative primary two-dose regimen). A phase 3 study in the USA enrolled 2247 adolescents aged 12 to 17 years and demonstrated 80% overall vaccine efficacy (at a time when the Delta variant was the predominant circulating strain) and a reassuring safety and reactogenicity profile.<sup>22</sup> Furthermore, data generated in COMCOV2 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.<sup>20</sup> More recently, an increased risk of myocarditis and pericarditis has been observed following vaccination with NVXCoV2373. These conditions can occur within days after vaccination, but most cases have occurred within 14 days. Cases have been detected through routine surveillance, after administration of over 700,000 doses of the vaccine. The exact risk is unknown but rare and appears to be similar to that reported for BNT162b2, affecting less than 1 in 10,000 vaccine recipients.<sup>23,24</sup>

Accordingly, Cohort A of 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). When enrolment to Cohort A of the study commenced, young people aged 12 to 17 years were being invited to receive one dose of Pfizer-BioNTech vaccine, and many had already been given this. Individuals who had received one dose of Pfizer-BioNTech vaccine in the community were eligible to enrol in the study at least 8 weeks afterwards.

Following the JCVI recommendation on 29<sup>th</sup> 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 were randomised 1:1 to either full or one-third dose BNT162b2 for their second vaccination. Participants were no longer randomised to the Novavax arm of the study in order to prioritise the arms of the study that were likely to be more policy relevant. This did not reflect any concern regarding the safety or immunogenicity of the Novavax vaccine. A further review of the study design was undertaken following an interim analysis and on 3<sup>rd</sup> February 2022, the study Trial Steering Committee advised to stop recruitment for Cohort A. It was also decided to add a new cohort to the study to investigate possible strategies for a third dose of COVID-19 vaccine in adolescents, following JCVI recommendation of a third dose to 16 and 17 year-olds (22<sup>nd</sup> December 2021).

Cohort B of this study will determine the side effect profile, and the immune responses to a third dose of COVID-19 vaccination in adolescents, given at least three months after completion of a two-dose schedule (two full doses of BNT162b2 given at least 8 weeks apart). Participants will be randomised to receive 30µg BNT162b2, 10µg BNT162b2 (given as 0.1ml of adult formulation), 10µg BNT162b2 (given as 0.2ml of paediatric formulation), NVXCov2373 (full dose) or two doses of 4CMenB (Meningococcal Group B vaccine, control group). The control group will be offered the Pfizer-BioNTech bivalent vaccine (Comirnaty Original/Omicron BA.1 (15µg/15µg)/dose) 6 months after enrolling in the study. As a consequence of challenging recruitment to the study, and following discussion with the study Trial Steering Committee, randomisation was changed from 1:1:1:1:1 to 1:3:3:1:1 to the five study groups (following approval of substantial amendment 13) on 9<sup>th</sup> June 2023, in order to prioritise recruitment to study groups 2 and 3 [i.e., the 10µg BNT162b2 (given as 0.1ml of adult formulation) and 10µg BNT162b2 (given as 0.2ml of paediatric formulation) groups] to achieve the participant numbers required to fulfill the study's co-primary endpoint of non-inferiority between the two BNT162b2 10µg groups. In light of

ongoing recruitment difficulties and following discussion with the Trial Steering Committee on 22<sup>nd</sup> March 2023, it was decided that recruitment to Cohort B would stop on 30<sup>th</sup> June 2023. . Further explanation of the rationale and study design for Cohort B is given in Appendix E.

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.

## **6.1 Potential benefits**

### **6.1.1 Current guidelines**

A 2-dose schedule of BNT162b2 (30 micrograms) 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. A 2-dose schedule of BNT162b2 (10 micrograms) is approved for use in 5-11 year-olds.

JCVI recommendations (current on 22<sup>nd</sup> December 2021) for adolescent COVID-19 immunisation are:

- 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 people who are severely immunocompromised: Two doses of BNT162b2, given at least 8 weeks apart, followed by a third dose at least 3 months after the second. Those who are severely immunocompromised should have a fourth dose.
- For all other 16 to 17 year- olds: Two doses of BNT162b2, given at least 12 weeks apart, followed by a third dose at least 3 months after the second.
- For all other 12 to 15 year-olds: Two doses of BNT162b2, given at least 12 weeks apart.

### **6.1.2 Potential benefits for participants in Cohort A**

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 29<sup>th</sup> November 2021. All other participants will receive a single full dose of BNT162b2, which is thought to provide 80% protection against hospitalisation.<sup>25</sup> A second dose of the vaccines included in this study is expected to further increase protection against infection.



### **6.1.3 Potential benefits for participants in Cohort B**

A potential benefit of participation in this study is the opportunity to receive a third dose of COVID-19 vaccine, which may boost the immune response to previous doses. Results from the adult multicentre randomised Phase II COVBoost trial showed significant boosting of responses elicited by a primary two-dose regimen by a heterologous third dose in adults over 30 years of age. If this boosting effect is also seen in adolescents a third dose may confer more prolonged protection against COVID-19 disease; however, this is not yet known. This potential benefit would no longer pertain if a routine third dose of COVID-19 vaccine were to be introduced nationally.

Participants randomised to Arm 5 of the study will also receive two doses of 4CMenB vaccine. This is not routinely given to adolescents. However, it has been shown to be 75% effective at preventing Group B meningococcal disease when administered to infants.<sup>26</sup> It has also been shown to induce bactericidal antibodies, which persist more than 4 years, when administered to adolescents.<sup>27</sup> Invasive Group B meningococcal disease has a mortality rate of about 5% in adolescents. In England in the epidemiological year 2019-2020, there were 55 cases of invasive Group B disease in 10 to 19 year-olds, and now there are early signs suggestive of an increase in cases in teenagers and young adults with normalisation of social mixing post-pandemic.<sup>28,29</sup>

### **6.1.4 Considerations for both Cohort A and Cohort B**

The age group to be enrolled in this study has a lower risk of severe COVID-19 disease than older age groups. Nevertheless, they are at a small risk of the Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).<sup>30</sup> SARS-Cov-2 infection results in exclusion from school for the child, and potentially leads to a need to self-isolate for the family (although the latter is no longer the case from 24<sup>th</sup> February 2022). The prevention of SARS-COV-2 infections in this age group may therefore be 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.

## **6.2 Potential risks**

### **6.2.1 Unapproved schedules and vaccines**

#### **6.2.1.1 Cohort A**

A subset of participants will be receiving a second vaccination different from the full dose BNT162b2 that is now recommended in the current UK approved schedule. Although NVXCoV2373 is not recommended in the current UK approved schedule, it has been approved

for use in 12- to 17-year-olds by the MHRA. Furthermore, it has been administered to 2247 adolescents in a Phase 3 clinical trial, without raising significant safety concerns.<sup>22</sup> A mixed BNT162b2/ NVXCoV2373 schedule has already been studied in COMCOV2 in those over 50 years of age and similarly found to be well tolerated with no safety concerns.<sup>20</sup>

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 a heterologous or fractional dose for the second vaccination. This is further discussed in Section 10.5.

#### **6.2.1.2 Cohort B**

Participants will receive an additional dose of COVID-19 vaccine compared to the current recommended schedule.

#### **6.2.1.3 Considerations for both Cohort A and Cohort B**

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 more than two doses of a COVID-19 vaccine according to the JCVI guidelines of 22nd December 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 compared with 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 current recommended vaccine schedules. The decision to offer participants additional vaccine doses will be informed by advice of the DSMB and TSC.

BNT162b2 COVID-19 vaccine has been administered to many millions of individuals (including 12 to 16 year-olds), and NVXCoV2373 has been administered to over 50000 participants in clinical trials, including over 2200 in adolescents. Both vaccines 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 (7 per million first doses, and 70 per million after the second dose in 12 to 15 year-old males).<sup>17</sup> Recent data suggest that the risk of myocarditis in young males following the third dose of BNT162b2 is at least as great as that following the second dose.<sup>31</sup> Similarly, a risk of myocarditis has been observed following vaccination with NVXCoV2373. The risk is very rare, similar to following BNT162b2 vaccination, affecting less than

1 in 10,000 vaccine recipients. 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.<sup>32</sup>

#### **6.2.2 Associated with phlebotomy (Cohort A and Cohort B)**

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 up to 20ml per sampling time-point from participants aged 12-16 years on each visit for immunology bloods. Some Cohort A 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.

#### **6.2.3 Associated with saliva sampling (Cohort A and Cohort B)**

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

#### **6.2.4 Associated with nasal fluid sampling (Cohort A and Cohort B)**

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.

#### **6.2.5 Allergic reactions (Cohort A and Cohort B)**

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product. Anaphylaxis is known to occur in approximately 2.5 to 4.7 per million recipients of mRNA COVID-19 vaccines,<sup>33</sup> and more generally in around 1 in 1,000,000 doses of all vaccines, but can occur in response to any vaccine or medication.

#### **6.2.6 Behaviour change (Cohort A and Cohort B)**

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.

**6.2.7 Specific risks from vaccines (Cohort A and Cohort B)**

Please refer to Section 12.8 for full details.

**6.2.8 Receiving a sub-optimal vaccine schedule (Cohort A and Cohort B)**

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).

**6.2.9 Unwanted media attention (Cohort A and Cohort B)**

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.

**7 OBJECTIVES AND OUTCOME MEASURES**

	<b>Objectives</b>	<b>Outcome Measures</b>	<b>Timepoint(s)</b>
<b>Primary</b>	<p>Cohort A: To evaluate the reactogenicity of heterologous boost* at least 8 weeks following BNT162b2 prime vaccine administered to adolescents</p> <p>Cohort B: To evaluate the reactogenicity of a homologous and heterologous boost* (third dose) given to adolescents at least 3 months after a two-dose schedule of BNT162b2</p>	Solicited systemic reactions	<p>Cohort A: 7 days after boost immunisation</p> <p>Cohort B: 7 days after third dose</p>
<b>Co-Primary</b>	Cohort B: To determine whether the immune response with BNT162b2 (10 µg, 0.1ml adult formulation) is non-inferior to that with BNT162b2 (10 µg, 0.2ml paediatric formulation)	Anti-spike immunoglobulins	28 days post third dose
<b>Secondary</b>	Cohorts A and B: To assess safety of heterologous second and third dose COVID-19 vaccines	<p>Serious adverse events</p> <p>Adverse events of special interest</p>	Throughout the study

	<p>Cohort A: To characterise immunogenicity of heterologous &amp; homologous second dose schedules of COVID-19 vaccines</p> <p>Cohorts B: To characterise immunogenicity of heterologous &amp; homologous third dose schedules of COVID-19 vaccines when compared with unimmunized controls</p>	<p>Anti-spike immunoglobulins</p>	<p>Cohort A: D0**, 56, post prime D 14, 28, 132, 236 post boost</p> <p>Cohort B: D0, 28, 84, 182, 210***</p>
		<p>Cellular immune responses by ELISpot</p>	<p>Cohort A: D0**, 56 post prime D14, 132, 236 post boost</p> <p>Cohort B: D0, 28, 84, 182, 210***</p>
	<p>Cohorts A and B: Characterisation of frequency of anti-SARS-CoV-2 nucleocapsid IgG seropositivity at enrolment, and subsequent seroconversion through the study</p>	<p>Anti-nucleocapsid immunoglobulins</p>	<p>Cohort A: D0**, 56 post prime D132, 236 post boost</p> <p>Cohort B: D0, 84, 182</p>
	<p>Cohorts A and B: To assess reactogenicity and safety of heterologous and homologous second and third dose schedules of COVID-19 vaccines</p>	<p>Solicited local reactions</p>	<p>Cohort A: 7 days after prime** and boost immunisation</p> <p>Cohort B: 7 days post third dose</p>
		<p>Unsolicited reactions</p>	<p>Cohort A: 28 days after prime** and boost immunisation</p> <p>Cohort B: 28 days post third dose</p>
	<p>Cohorts A and B: To evaluate immunogenicity, safety and reactogenicity of COVID-19 vaccines in participants seropositive for SARS-CoV-2 nucleocapsid IgG at enrolment, compared with seronegative</p>	<p>Immunogenicity, safety and reactogenicity endpoints as outlined above</p>	<p>Timepoints as outlined above</p>
<p><b>Exploratory</b></p>	<p>Cohorts A and B: To assess incidence of SARS-CoV-2 infection in participants receiving heterologous and homologous</p>	<p>Self-reported SARS-CoV-2 infection, from community testing, or (Cohort B only) by the</p>	<p>Throughout the study</p>

	second and third dose schedules of COVID-19 vaccines	COVID-19 lateral flow tests provided by the study	
	Cohorts A and B: To further characterise the blood antibody response	Neutralizing and Functional antibody assays	Cohort A: D0**, 56 post prime D14, 28, 132, 236 post boost Cohort B: D0, 28, 84, 182, 210***
	Cohorts A and B: 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 and IgG ELISA and exploratory immunological assays	Cohort A: D0**, 56 post prime D14 post boost Cohort B: D0, 28, 84, 182, 210***
	Cohort A: 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
	Cohort B: To explore the motivations and experiences of parents and participants taking part in the trial.	Parent and participant motivation and experience questionnaire	Questionnaire sent after 3 <sup>rd</sup> study visit (D84)

\* Refers to second dose in the context of Cohort A. For cohort B the boost refers to third dose

\*\* Only for participants receiving prime vaccination in the study

\*\*\* Group 5 (who receive Pfizer bivalent vaccine at D182) in Cohort B only

## 8 TRIAL DESIGN

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

### 8.1 Setting

Multicentre study conducted through academic and NHS clinical trials sites.

## 8.2 Trial duration

### 8.2.1 Cohort A

Total duration for 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.

### 8.2.2 Cohort B

Total duration for each participant will be approximately 6 months (for those in Arms 1, 2, 3 and 4) or 7 months (for those in Arm 5). The total trial period will be approximately 10 months.

## 8.3 Study groups

### 8.3.1 Cohort A

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 29<sup>th</sup> 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.

### **8.3.2 Cohort B**

The study design for Cohort B is described in Appendix E (Section 27.3). A total of up to 310 (+ up to an additional 10%) participants will be enrolled.

### **8.3.3 Blinding (Cohort A and Cohort B)**

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. In cohort B, participants randomised to control arm will be unblinded from day 56 after their first study vaccine.

### **8.4 Participants testing COVID-19 positive**

Participants who acquire new infection with SARS-CoV-2 (as determined by SARS-CoV-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.

## **9 PARTICIPANT IDENTIFICATION**

### **9.1 Trial participants**

For Cohort A participants will be aged 12 to 16 years (inclusive) at enrolment. For Cohort B participants will be aged 12 to 15.5 years (inclusive) at enrolment (*i.e.* up to 15 years and 6 completed calendar months, inclusive). 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.

## **9.2 Inclusion criteria**

### **9.2.1 Applicable to Cohort A only**

- Aged 12 to 16 years (inclusive) at enrolment

### **9.2.2 Applicable to Cohort B only**

- Age 12 to 15.5 years (inclusive) at enrolment
- To have already received two doses of 30µg BNT162b2, the second dose received at least 91 days prior to randomisation

### **9.2.3 Applicable to Cohort A and Cohort B**

- 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 additional 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/Participant is willing and able to give written informed consent for participation in the trial. 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.

## **9.3 Exclusion criteria**

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

### **9.3.1 Applicable to Cohort A only**

- Previous receipt of more than one dose of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2

### **9.3.2 Applicable to Cohort B only**

- Previous receipt of more than two doses of a COVID-19 vaccine, or a COVID-19 vaccine other than BNT162b2 30µg

- Previous receipt of the 4CMenB vaccine
- Participants in Cohort A are not eligible to be enrolled into Cohort B unless they received two full doses of BNT162b2 in Cohort A, and they have completed the Cohort A day 236 study visit. At this point they are eligible to enrol in Cohort B, in which case they will be treated as a new participant and receive a new, unrelated, participant number.

### 9.3.3 Applicable to Cohort A and Cohort B

- Belonging to a 'high-risk' cohort advised to receive additional 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 28<sup>th</sup> February 2022)<sup>34</sup>
- First degree relative of study team 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 study 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

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\* Study team member is deliberately loosely defined but at a minimum will include: anyone on the delegation log; anyone who might be anticipated that they could be placed onto the delegation log in the course of the study; anyone who has access to personal data on study participants (beyond name, contact details, DOB); and anyone who attends meetings where details of the study are discussed, for example safety updates.

- 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 (see exclusion criteria above for enrolment into Cohort B after participation in Cohort A of this study)
- 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

#### **9.3.4 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 8.4). Note that Cohort B participants who have a positive lateral flow test at the D0 visit will not be vaccinated on that day; the remainder of the visit will be deferred until at least 4 weeks after their positive test (if recruitment is ongoing at this point).

## **10 TRIAL PROCEDURES**

For Cohort A, see APPENDIX B: SCHEDULE OF PROCEDURES. For Cohort B, see APPENDIX E, Section 27.6.

## **10.1 Recruitment**

### **10.1.1 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)

Using direct SMS/text message, or emails to potential participants identified by GPs from their databases

Individuals who expressed an interest in taking part in Cohort A, but who did not enrol, may be contacted directly with information about Cohort B, using the contact information they have already provided

## **10.2 Screening and eligibility assessment**

### **10.2.1 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 access NHS vaccination records and 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.

### **10.2.2 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.

### **10.2.3 Screening**

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

### **10.3 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 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:
  - o Participation in the study is entirely voluntary
  - o Refusal to participate involves no penalty or loss of medical benefits
  - o The participant may withdraw from the study at any time
  - o 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
  - o 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.

#### **10.4 Randomisation**

##### **10.4.1 Cohort A**

Computer generated randomisation list will be prepared by the study statistician. Participants will be randomised 1:1:1 to the three study groups. After 29<sup>th</sup> 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 29<sup>th</sup> November 2021, and random block sizes of 2 and 4 will be used after 29<sup>th</sup> 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).

##### **10.4.2 Cohort B**

Computer generated randomisation list will be prepared by the study statistician. Participants were initially randomised 1:1:1:1:1 to the five study groups. After approval of substantial amendment 13 (9<sup>th</sup> June 2023), participants will be randomised 1:3:3:1:1 to the five study groups with higher probabilities to the 10 µg (0.1ml adult formulation) and 10 µg (0.2ml paediatric formulation) than the other three arms. This will prioritise recruitment to the two study groups relevant to the non-inferiority co-primary endpoint. However, as a result of ongoing recruitment challenges, final recruitment may still be insufficient to meet the non-inferiority endpoint, in which case the analysis will be descriptive.

Participants will be randomised using block randomisation. Random block sizes of 5 and 10 will be used. Randomisation will be performed at the time of the first study visit (D0), and stratified by study site and history of known COVID-19 infection. After the randomisation is changed to 1:3:3:1:1, a random block size of 9 will be used.

#### **10.5 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). Participants in Cohort A will remain blinded to their boost vaccine allocation up until the day 84 visit. Participants in Cohort B will remain blinded to their study arm allocation until day 56 after receipt of their first study vaccine, or earlier should



a recommendation for routine immunisation with a third dose of COVID-19 vaccine be introduced for 12 to 15 year-olds in the UK. 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 time-point described above, 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.

#### **10.6 Conducting 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.

#### **10.7 Cohort A visits**

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.

## **10.7.1 Visits for participants receiving their first dose of COVID-19 vaccine in the study**

### **10.7.1.1 D0: Final eligibility check, enrolment and vaccination visit**

#### **10.7.1.1.1 Informed consent**

The participant will have informed consent taken as described in Section 10.3, 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.

#### **10.7.1.1.2 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 9.3.4 “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.

#### **10.7.1.1.3 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)

#### **10.7.1.1.4 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.

### 10.7.1.1.5 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 (note that this is not applicable to Cohort B). 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*

<b>Local solicited AEs</b>	Pain, Tenderness, Redness, Warmth, Itch, Swelling, Induration
<b>Systemic solicited AEs</b>	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.

### 10.7.1.1.6 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 than 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.

#### **10.7.1.2 Subsequent visits**

Follow-up visits will take place as per the schedule of attendances described in APPENDIX B: 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.

#### **10.7.2 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 10.7.1.1.1 and 10.7.1.1.2) 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 B: SCHEDULE OF PROCEDURES.

### **10.8 Cohort B visits**

These are described in APPENDIX E, Section 27.8.

### **10.9 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.

### **10.10 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.

### **10.11 Sample handling**

For Cohort A, please refer to APPENDIX C: BLOOD SAMPLING for schedule of frequency and volume of blood sampling. For Cohort B, refer to APPENDIX E, Section 27.7.

#### **10.11.1 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.

#### **10.11.1.1 Nasal fluid and saliva samples**

An exploratory analysis of mucosal immunity will be conducted at some sites using nasal fluid collected (at V1, V2 and V3 for Cohort A; at all visits for Cohort B) 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 statements regarding collaboration, storage and use of samples in Section 10.11.1 also apply here.

#### **10.11.1.2 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.

#### **10.11.2 Sample handling for pregnancy testing**

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

### **10.11.3 Sample handling for lateral flow testing**

Proprietary COVID-19 lateral flow tests will be provided for participants in Cohort B. They will be used according to the instructions enclosed with the packaging. Results will be recorded in the study diary. This will be a point of care test and no sample will be stored.

### **10.12 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 participant's 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.

For **Cohort A**, 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 the criteria described in 10.5 are met.

For **Cohort B**, if the participant chooses to withdraw after receipt of their study vaccination, they may be unblinded 28 days after vaccination. They will only be unblinded earlier if the criteria described in 10.5 are met. If a participant in Group 5 of Cohort B decides they do not wish to receive the bivalent Pfizer vaccine at the 6-month time-point, they do not need to formally withdraw from the study. Instead, they will be invited to attend the D182 visit for a final blood test without vaccination; they will not be invited to attend the D210 visit.

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.

### **10.13 Definition of end of trial**

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

## **11 TRIAL INTERVENTIONS**

For **Cohort A**, see APPENDIX B: SCHEDULE OF PROCEDURES for details. For **Cohort B**, see APPENDIX E, Section 27.6.

## 11.1 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 Comirnaty 30 micrograms/dose BNT162b2	Approved for use in individuals over 12 years by the Medicines and Healthcare products Regulatory Authority (MHRA)	Not IMP labelled, product sourced from national supply
Pfizer/BioNTech Comirnaty 10 micrograms/dose BNT162b2 (Paediatric formulation)	Approved for use in children aged 5-11 years by the Medicines and Healthcare products Regulatory Authority (MHRA)	Not IMP labelled, product sourced from national supply
Novavax SARS-CoV-2 rS/Matrix-M1 Adjuvant NVXCoV2373	Approved for use in individuals over 12 years by the Medicines and Healthcare products Regulatory Authority (MHRA) It has been granted conditional marketing authorisation	Not IMP labelled, product supplied by the manufacturer. Product may also be sourced from national supply
Bexsero (4CMenB)	Approved for use in all age groups	Not IMP labelled, product sourced from national supply
Pfizer-BioNTech Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose	Approved for use in individuals over 12 years by the Medicines and Healthcare products Regulatory Authority (MHRA) It has been granted conditional marketing authorisation	Not IMP labelled, product sourced from national supply

### 11.1.1 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.

#### **11.1.1.1 Dosage, scheduling and packaging**

The dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine. Participants randomised to the one-third dose BNT162b2 vaccine group will receive a dose of 0.1ml of the diluted vaccine. Each pack of the Pfizer BioNTech vaccine contains 195 vials with 6 full doses per vial (975 doses per pack). Each vial comprises 0.45 mL concentrate in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a purple flip-off plastic cap with aluminium seal, which provides 6 doses. It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules. The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 0.9 solution for injection, using a 21 gauge or narrower needle.

#### **11.1.2 Vaccine B – Comirnaty 10 micrograms/dose**

This is the paediatric version of BNT162b2 (Vaccine A, described above). The active ingredient is the same.

##### **11.1.2.1 Dosage, scheduling and packaging**

The dose is 10µg contained in 0.2ml of the diluted vaccine. Pack size is 10 or 195 vials. 1.3 mL concentrate for dispersion is supplied in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and an orange flip-off plastic cap with aluminium seal. Thawed vaccine must be diluted in its original vial with 1.3 mL sodium chloride 0.9% solution for injection, using a 21 gauge or narrower needle. After dilution, vials of Comirnaty contain 10 doses of 0.2 mL of vaccine. In order to extract 10 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 mL. If standard syringes and needles are used, there may not be sufficient volume to extract 10 doses from a single vial.

#### **11.1.3 Vaccine C – 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™.

#### **11.1.3.1 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.

#### **11.1.4 Vaccine D – Bexsero (4CMenB)**

One 0.5ml dose of Bexsero contains:

Recombinant *Neisseria meningitidis* group B NHBA fusion protein (50µg);

Recombinant *Neisseria meningitidis* group B NadA protein (50µg);

Recombinant *Neisseria meningitidis* group B fHbp fusion protein (50µg);

Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4 (25µg)

The protein components are produced in *E. coli* cells by recombinant DNA technology and adsorbed on aluminium hydroxide.

#### **11.1.4.1 Dosage, scheduling and packaging**

The dose of Bexsero is 0.5ml. It is supplied as 0.5 ml suspension in a pre-filled syringe (Type I glass) with a plunger stopper (Type I bromobutyl rubber) and with a protective tip cap (Type I or Type II rubber) with or without needles. It is supplied in pack sizes of 1 or 10 syringes.

#### **11.1.5 Vaccine E - Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose**

This is an Omicron BA.1 variant-adapted version of BNT162b2 (Vaccine A, described above). In addition to the active ingredient in BNT162b2, it contains riltozinameran, an mRNA molecule encoding the viral spike protein of SARS-CoV-2 (Omicron BA.1), which exploits the host cells to translate the code and then make the target spike protein from the Omicron BA.1 subvariant of SARS-CoV-2. The protein then acts as an intracellular antigen to stimulate the immune response.

#### **11.1.5.1 Dosage, scheduling and packaging**

One dose (0.3 ml) of Comirnaty Original/Omicron BA.1 contains 15 micrograms of tozinameran and 15 micrograms of riltozinameran. Each vial contains 2.25mL dispersion supplied in a 2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a grey flip-off plastic cap with aluminium seal. Each pack contains 10 multidose vials with 6 doses per vial (60 doses per pack). This is a multidose vial which does not require dilution prior to use. In order to extract 6 doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more

than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

### **11.2 Blinding of IMPs**

See Section 10.5 for details.

### **11.3 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.

#### **11.3.1 Vaccine A - Pfizer BioNTech (Comirnaty 30 micrograms/dose; BNT162b2)**

The Pfizer BioNTech vaccine should be stored at -90°C to -60°C and has shelf life of 9 months. Within the 9-month shelf-life, unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C. 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. Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C. Thawed vials can be handled in room light conditions. Once thawed, the vaccine should not be re-frozen.

It should be used as soon as practically possible and within 6 hours of dilution.

#### **11.3.2 Vaccine B - Comirnaty 10 micrograms/dose**

Store in a freezer at -90 °C to -60 °C. Store in the original package in order to protect from light. During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light. The frozen vial has a shelf life of 6 months when stored at -90 °C to -60 °C. 10-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 4 hours, or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes. Once thawed, vials have a shelf life of 10 weeks at 2 °C to 8 °C, within the 6-month shelf life. Upon moving the vaccine to 2 °C to 8 °C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out. Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8 °C

and 30 °C. Thawed vials can be handled in room light conditions. Once thawed, the vaccine should not be re-frozen. Once diluted, it should be used as soon as possible (and within 12 hours).

### **11.3.3 Vaccine C – Novavax (NVXCoV2373)**

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

### **11.3.4 Vaccine D – Bexsero (4CMenB)**

Bexsero should be stored in a refrigerator (2°C – 8°C). Do not freeze. Store in the original package in order to protect from light.

### **11.3.5 Vaccine E - Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose**

The vaccine should be stored in a freezer at -90°C to -60°C. The frozen vial has a shelf life of 12 months when stored at -90°C to -60°C. Frozen vials should be transferred to an environment of 2°C to 8°C to thaw; a 10-vial pack may take 6 hours to thaw. Individual vials can be thawed at room temperature (up to 30°C) for 30 minutes. Upon moving the vaccine to 2°C to 8°C storage, the updated expiry date must be written on the outer carton and the vaccine should be used or discarded by the updated expiry date. The original expiry date should be crossed out. Prior to use, the unopened vials can be stored for up to 12 hours at temperatures between 8°C and 30°C. Thawed vials can be handled in room light conditions. Thawed unopened vials can be stored for up to 10 weeks at 2°C to 8°C within the 12-month shelf life.

## **11.4 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.

## **11.5 Accountability of the trial treatment**

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

## **11.6 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.

### 11.7 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.

### 11.8 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.

### 11.9 Other interventions

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

## 12 SAFETY REPORTING

### 12.1 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).

### 12.2 Adverse Event Definitions

<b>Adverse Event (AE)</b>	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.
<b>Adverse Reaction (AR)</b>	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	<p>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.</p> <p>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.</p>
<b>Adverse Events of Special Interest (AESI)</b>	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)
<b>Serious Adverse Event (SAE)</b>	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> <li>Results in death</li> <li>Is life-threatening</li> <li>Requires inpatient hospitalisation or prolongation of existing hospitalisation</li> <li>Results in persistent or significant disability/incapacity</li> <li>Consists of a congenital anomaly or birth defect</li> </ul> <p>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.</p> <p>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.</p>
<b>Serious Adverse Reaction (SAR)</b>	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.
<b>Suspected Unexpected Serious Adverse Reaction (SUSAR)</b>	<p>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:</p> <ul style="list-style-type: none"> <li>In the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product</li> <li>In the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question</li> </ul>

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.

### 12.3 Assessment of results outside of normal parameters as AEs and SAEs

#### 12.3.1 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 10.5.

#### 12.4 Assessment of severity

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

Table 3: Severity grading for local adverse events

Adverse Event	Grade	Intensity
<b>Pain at injection site</b>	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
<b>Tenderness</b>	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
<b>Erythema at injection site*</b>	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis
<b>Induration/Swelling at injection site</b>	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
<b>*erythema <math>\leq</math>2.5cm is an expected consequence of skin puncture and will therefore not be considered an adverse event</b>	

Table 4: Severity grading for local and systemic AEs

GRADE 0	None
<b>GRADE 1</b>	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
<b>GRADE 2</b>	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
<b>GRADE 3</b>	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
<b>GRADE 4</b>	Potentially Life-threatening: Requires assessment in A&E or hospitalisation

### 12.5 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 AEs 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.

<b>0</b>	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
<b>1</b>	Unlikely	Unlikely temporal relationship to study product <b>and</b> Alternate aetiology likely (clinical state, environmental or other interventions) <b>and</b> Does not follow known typical or plausible pattern of response to study product.
<b>2</b>	Possible	Reasonable temporal relationship to study product; <b>or</b> Event not readily produced by clinical state, environmental or other interventions; <b>or</b> Similar pattern of response to that seen with other vaccines
<b>3</b>	Probable	Reasonable temporal relationship to study product; <b>and</b> Event not readily produced by clinical state, environment, or other interventions <b>or</b> Known pattern of response seen with other vaccines
<b>4</b>	Definite	Reasonable temporal relationship to study product; <b>and</b> Event not readily produced by clinical state, environment, or other interventions; <b>and</b> Known pattern of response seen with other vaccines

## 12.6 Procedures for reporting Adverse Events

### 12.6.1 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).

### 12.6.2 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 10.12.

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

## **12.7 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, SAEs 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.

### **12.7.1 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.

## **12.8 Expectedness**

### **12.8.1 SARs**

#### **12.8.1.1 Pfizer BioNTech (Comirnaty 30 micrograms/dose; 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

**12.8.1.2 Comirnaty 10 micrograms/dose**

Expected SARs are as for BNT162b2, described above.

**12.8.1.3 Novavax (NVXCoV2373)**

If an SAE is considered as being a SAR to NVXCoV2373, section 4.8 of the NVXCoV2373 Summary of Product Characteristics will be used as the reference safety information to determine expectedness. Potential SARs considered to be expected include:

- Myocarditis/pericarditis

**12.8.1.4 Bexsero (4CMenB)**

No SARs expected.

**12.8.1.5 Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose**

Section 4.8 of the Comirnaty Original/Omicron BA.1 Summary of Product Characteristics will be used as the reference safety information to determine expectedness. Expected SARs are as for BNT162b2, described above.

**12.8.2 Foreseeable Adverse Reactions**

The foreseeable ARs following vaccination are as follows:

**12.8.2.1 Pfizer BioNTech (Comirnaty 30 micrograms/dose; BNT162b2)**

<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Unknown</i>
Headache	Injection site redness	Lymphadenopathy	Acute peripheral facial paralysis	Anaphylaxis
Arthralgia	Nausea	Insomnia		Facial swelling
Myalgia	Vomiting	Pain in extremity		Myocarditis
Injection site pain/swelling		Malaise		Pericarditis
Fatigue		Injection site pruritus		Swelling of vaccinated limb
Chills		Allergic reactions (eg. Rash, pruritus, urticaria)		Erythema multiforme
Pyrexia		Decreased appetite		
Diarrhoea		Asthenia		
		Hyperhidrosis or night sweats		

**12.8.2.2 Comirnaty 10 micrograms/dose**

The foreseeable ARs following vaccination are the same as those listed above for BNT162b2.

**12.8.2.3 Novavax (NVXCoV2373)**

<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Not known (cannot be estimated from the available data)</i>
Headache	Injection site pruritus	Lymphadenopathy	Myocarditis
Arthralgia		Hypertension	Pericarditis
Myalgia		Rash	
Injection site pain/tenderness/redness/swelling		Erythema	
Fatigue		Pruritus	
Malaise		Urticaria	
Pyrexia			
Nausea or vomiting			
Chills			
Pain in extremity			

**12.8.2.4 Bexsero (4CMenB)**

The Bexsero SPC lists the following adverse events in adolescents (from 11 years of age) and adults:

Very common: Headache; nausea; malaise; myalgia; arthralgia; injection site pain/redness/swelling/induration.

Frequency not known: Anaphylaxis; syncope; mild, transient signs of meningeal irritation (e.g. neck stiffness, photophobia); rash; fever; injection site nodule/blistering; swelling of vaccinated limb.

**12.8.2.5 Comirnaty Original/Omicron BA.1 (15/15 micrograms)/dose**

The foreseeable ARs following vaccination are the same as those listed above for BNT162b2.

**12.9 Adverse Events of Special Interest**

Table 2: AESIs

<b>Immunologic</b>	Anaphylaxis	
<b>Neurological</b>	Isolated anosmia/ageusia* Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Aseptic meningitis	Meningoencephalitis Peripheral facial nerve palsy Generalised convulsion Myelitis
<b>Haematological</b>	Thrombosis** Stroke Thrombocytopaenia*** Eosinophilia****	Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed and stroke)
<b>Cardiac</b>	Acute cardiovascular injury (includes myocarditis#, pericarditis#, arrhythmias, heart failure, infarction)	
<b>Dermatological</b>	Chilblain-like lesions Single organ cutaneous vasculitis	Erythema multiforme Alopecia
<b>Gastrointestinal</b>	Acute liver injury †† †	Appendicitis Cholecystitis*****
<b>Respiratory</b>	ARDS††	
<b>Renal</b>	Acute kidney injury	
<b>Other</b>	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 11<sup>th</sup> 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<sup>35</sup>

†† 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.

#### **12.9.1 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).<sup>36</sup> 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.

#### **12.10 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.

#### **12.11 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.

#### **12.12 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.

#### **12.13 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.

#### **12.14 Contraception and pregnancy**

##### **12.14.1 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)

##### **12.14.2 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.

## 13 STATISTICS

### 13.1 Sample size

#### 13.1.1 Cohort A

The total sample size of Cohort A 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)

#### 13.1.2 Cohort B

The sample size calculation is based on the primary outcome to determine the non-inferiority between the two BNT162b2 10µg formulations (adult vs paediatric) with paediatric being the reference group. From Com-COV3 day 28 data (Roche S assay) post second dose, the expected standard deviation is 0.30 in all participants with/without previous COVID-19 infection. A non-inferiority margin of 0.67 with a power of 90%, a type I error of two-sided 0.05, and 15% of loss of follow up was initially planned, which would require 76 participants to be recruited per arm, for an effective sample size of 64 per arm. However, as a result of recruitment challenges to the

study, the type 1 error was changed from a two-sided to a one-sided significance level of 0.05 which will require 62 participants per arm for an effective sample size of 52 per arm to achieve the co-primary outcome of non-inferiority between the two 10µg BNT162b2 formulation (adult vs paediatric) groups.

Using the same sample size of up to 62 for the remaining three groups (to simplify the randomisation and trial delivery), the total sample size will be up to 310.

### **13.2 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:

#### **13.2.1 Safety and reactogenicity (Cohort A and Cohort B)**

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 be made using Fisher's exact test if appropriate, otherwise only counts and percentages will be reported.

#### **13.2.2 Immunogenicity**

##### **Cohort A**

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.

**Cohort B**

The primary endpoint is anti-spike IgG at Day 28 days post third dose. The geometric mean concentrations (GMC) of anti-spike IgG will be compared between adult and paediatric formulation of BNT162b2(10µg) of under the hypothesis:

H0:  $GMC_{adult} / GMC_{paediatric} \leq 0.67$  or  $\log_{10} GMC_{adult} - \log_{10} GMC_{paediatric} \leq -0.174$ ;

H1:  $GMC_{adult} / GMC_{paediatric} > 0.67$  or  $\log_{10} GMC_{adult} - \log_{10} GMC_{paediatric} > -0.174$ ;

The anti-spike IgG titre will be transformed using logarithmic transformations (base 10) to render a normal distribution. We will test the above hypothesis using linear regression models on  $\log_{10}GMC$  adjusting for randomisation design variables, and the pre-specified prognostic factors, if any. The adjusted mean difference of  $\log_{10}GMC$  will be presented with the one-sided 95% confidence interval (CI). We will claim adult formulation is non-inferior to paediatrics formulation if the lower CI lies above -0.174.

The primary analysis will be conducted on a per-protocol basis among participants (regardless of baseline seropositivity and COVID-19 infection history at baseline) whose primary endpoint at D28 post boost is available, and who have had no self-reported COVID-19 infection within 28 days post vaccination or COVID-19 infection as indicated by a 2-fold increase in anti-nucleocapsid IgG from D0 to D28, and no protocol deviations (those can affect the immunogenicity, defined in the SAP), as the intent to treat analysis no longer produces the conservative estimation in non-inferiority trials. A modified intent to treat analysis will also be conducted as a sensitivity analysis to include those participants with protocol deviations. The primary analysis will be carried out when the primary endpoint data of D28 immunogenicity become available.

For the BNT162b2(30µg), NVX, and 4CMenB arm, the geometric mean and 95% confidence intervals will be presented at all the study time points. There will be no formal hypothesis testing between these arms, but we will calculate the GMR between the four vaccine arms and control to understand how long the benefit of booster (3<sup>rd</sup> dose) will last. The analysis on D28, D84, D182 and D210 immunogenicity will be on the mITT basis among participants with no confirmed COVID-19 infection.

**13.3 Missing data**

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

## **13.4 Interim analyses**

### **13.4.1 Cohort A**

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 reviewed the sero-status pre-boost as well as all the available immunogenicity data. These data were shared with JCVI only to support decision making on a boost dose among people aged 12-17 years. This interim analysis was descriptive.

On 29<sup>th</sup> November 2021, the JCVI 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 was conducted and results were presented to JCVI to update their recommendation. The study's recruitment and sample size were reviewed on the basis of this analysis after discussing with the JCVI, TSC and DSMB. On 3<sup>rd</sup> February 2022, the TSC advised to stop recruitment to the study. At this point, 149 participants had been enrolled.

### **13.4.2 Cohort B**

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 primary endpoint of immunogenicity will be carried out when the D28 immunogenicity data become available (or earlier, if data were to be requested by JCVI before all D28 immunogenicity data available, this does not include the adult and paediatric BNT162b2(10µg) arms as study is designed using the frequentist method). The interim analysis will provide evidence for policy making as to the recommendation on the third dose of COVID-19 vaccine among adolescents. The interim analysis will be carried out once the data is cleaned and the Statistical 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.

The cohort B arm of this study was powered based on standard deviation of anti-spike IgG observed in cohort A. Since we expected a higher proportion of participants with a history of COVID-19 infection in cohort B than cohort A, and we encountered a challenge in study recruitment, an additional interim analysis in cohort B was conducted by an independent statistician to check the assumption for sample size calculation, after the D28 data became available for ~100 participants. We found a similar standard deviation in the interim analysis and therefore no further change was made to the sample size calculation for the primary objective (i.e. the comparison between the 10 µg BNT162b2 arms) following the interim analysis. However, because the other three arms (BNT162b2 30 µg, NVXCoV2373, and control) will be used for descriptive analyses for the secondary objectives, the study team decided to drop the probabilities randomising to these three arms (change the randomisation from 1:1:1:1:1 to 1:3:3:1:1) to prioritise recruitment to the two study arms required to achieve the study's co-primary objective (non-inferiority between the two BNT162b2 10µg adult and paediatric formulation study groups). This change to randomisation will not affect the analysis of the co-primary objective of reactogenicity. Following discussions with the Trial Steering Committee on 22<sup>nd</sup> March 2023, and in light of ongoing recruitment difficulties, it was decided that recruitment to Cohort B would stop on 30<sup>th</sup> June. Consequently, the sample size calculation for the primary objective was amended to reduce the participant numbers required to meet the primary outcome of non-inferiority between the two BNT162b2 10µg formulations (adult vs paediatric) arms. This was achieved through a change in the type I error from a two-sided to a one-sided significance level of 0.05 which will require 62 participants per arm for an effective sample size of 52 per arm for study groups 2 and 3 to meet the co-primary outcome of non-inferiority. The total sample size will now be up to 310.

## **14 DATA MANAGEMENT**

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

### **14.1 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.

#### **14.2 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 trail 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.

### **14.3 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 may 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.

### **14.4 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.

#### **14.5 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

### **15 Quality Assurance Procedures**

#### **15.1 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.

#### **15.2 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

#### **15.3 Trial committees**

##### **15.3.1 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.

##### **15.3.2 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.

### **15.3.3 Study Management Committee**

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

## **16 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.

## **17 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.

## **18 ETHICAL AND REGULATORY CONSIDERATIONS**

### **18.1 Declaration of Helsinki**

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

### **18.2 Guidelines for Good Clinical Practice**

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

### **18.3 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).

### **18.4 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.

### **18.5 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.

### **18.6 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.

### **18.7 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.

### **18.8 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.

Due to a delay in the NHS National Immunisation Management System (NIMS) being updated to allow the recording of adolescent Novavax vaccinations, a small number of participants who received this vaccine have been unable to obtain an NHS Travel Pass to prove their vaccination status when travelling, impacting upon their upcoming travel arrangements. Accordingly, affected participants will be offered reimbursement of pre-departure COVID-19 testing (including PCR and antigen tests), if required, to ensure that they are not disadvantaged in this regard (reimbursement up to £200 per participant on provision of receipt, up to the end of active study visits). Once Novavax vaccinations are updated on NIMS and participants can obtain an NHS Travel Pass proving this vaccination status, the stated reimbursement will no longer apply from this timepoint onwards.

## **19 FINANCE AND INSURANCE**

### **19.1 Funding**

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

## **19.2 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.

## **19.3 Contractual arrangements**

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

## **20 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.

## **21 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.

## **22 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.

**23 APPENDIX A: 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	<p>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</p> <p>Section 0 updated to include additional DSMB member</p> <p>Section 9.6 updated to include additional diary information to be collected</p> <p>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</p> <p>Section 22 updated. Reference 15 added</p> <p>Section 17.8 updated to clarify that reimbursement is towards travel and expenses</p> <p>Section 3 updated to remove sentence about even distribution across age range</p> <p>Section 23 updated to change D84 study window</p>
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 Oct 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 Nov 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 2 <sup>nd</sup> 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 29 <sup>th</sup> 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	18 Jan 2022	Eimear Kelly	<p>Cholecystitis removed as a foreseeable adverse reaction to Novavax vaccine following issuing of Novavax Addendum 4.2, 11 Jan 2022</p> <p>Correction to labelling of Tables</p> <p>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.</p> <p>Addition of Troponin &amp; NT proBNP analysis on Day 28 post boost samples on the advice of the DSMB.</p> <p>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).</p>
10	N/A	21 Feb 2022	Sharon Tonner	Issue of new participant-facing document, providing a short update to participants/parents following the interim analysis on the above-named study (no impact on protocol).



11	7.0	01 Apr 2022	Philip de Whalley	<ul style="list-style-type: none"> <li>• Addition of Cohort B (Including in primary and secondary objectives)</li> <li>• Updating of secondary objectives to clarify that anti—nucleocapsid antibody testing is to define prevalence of SARS-CoV-2 infection, rather than assess immune response to vaccines</li> <li>• Updating of “Lay Summary” and “Background and Rationale” (Sections 3 and 6)</li> <li>• Updating and reformatting of References</li> <li>• Revised Section numbering</li> <li>• Re-ordering of Appendices</li> <li>• Addition of Appendix E</li> <li>• Addition of new funding body (CEPI)</li> <li>• Addition of new investigator (Professor Saul Faust)</li> <li>• Addition of Royal Free Hospital London as a new study site and addition of a new PI (Dr Kin Man) at this site</li> <li>• Addition of lateral flow testing (Cohort B)</li> <li>• Recruitment methods updated to include use of direct SMS/text messages, or emails to potential participants identified by GPs from their databases</li> </ul> <p>Addition of a letter to Novavax participants to offer reimbursement of pre-departure COVID-19 testing (including PCR and antigen tests), if required, given delays in the NHS NIMS system being updated to allow the recording of Novavax vaccinations thus impacting upon travel arrangements</p>
NSA4	7.1	09-May-2022	Grace Macaulay	<ul style="list-style-type: none"> <li>• Correction of minor typographical errors including in Cohort B tables 27.6 and 27.7.</li> <li>• Correction of wording in Temporary Exclusion Criteria</li> </ul>

				(Section 9.3.4) for Cohort B to align with other protocol sections and PIS documents regarding delaying remainder of D0 visit (including vaccination) if participant has a positive lateral flow test at this visit.
12	8.0	22-September-2022	Eimear Kelly	<ul style="list-style-type: none"> <li>• Change of trial CI from Professor Matthew Snape to Dr Angela Minassian</li> <li>• Addition of Conflict of Interest Statement for new CI Dr Angela Minassian</li> <li>• Addition of new investigator Dr Dominic Kelly (paediatrician - to support Oxford PI/CI)</li> <li>• Addition of previous receipt of 4CMenB as an exclusion criterion</li> <li>• Clarification of study staff member first degree relative exclusion criterion</li> <li>• Extension of Cohort B D84 and D182 visit windows</li> <li>• For Cohort B, making participation in Cohort A a temporary, rather than permanent exclusion criterion (subject to having received two full doses of BNT162b2 in Cohort A and completed all study visits in Cohort A)</li> <li>• Addition of MHRA approval of Novavax (NVXCoV2373) for use in 12 to 17 year olds</li> <li>• Updated/tabulated foreseeable ARs for Novavax</li> <li>• Approval of a 2-dose schedule of BNT162b2 (10 micrograms) for use in 5-11 year-olds</li> <li>• Addition of Comirnaty Original/Omicron BA.1 vaccine as an IMP</li> <li>• Addition of expected SARS and foreseeable ARs for Comirnaty Original/Omicron BA.1 vaccine</li> </ul>

				<ul style="list-style-type: none"> <li>• Change of control group COVID-19 vaccine to Comirnaty bivalent vaccine (Original/Omicron BA.1) and updates in Appendix E to reflect this addition</li> <li>• Included option for final study visit and blood test at D182 if participants in Cohort B Group 5 decline a bivalent vaccine</li> <li>• Attendance at D210 visit (and lateral flow testing at and between D182 and D210 visits) only for Group 5 participants receiving the bivalent vaccine at the D182 visit</li> <li>• Permission to access participants' NHS vaccination records as part of initial screening</li> </ul>
13	9.0	19-Dec-2022	Eimear Kelly	<ul style="list-style-type: none"> <li>• Minor clarifications and typographical corrections throughout</li> <li>• Change to Cohort B randomisation to 1:3:3:1:1</li> <li>• Addition of NVXCoV2373 carditis risk, in accordance with the vaccine SmPC. The SmPC will also be used as the RSI to determine expectedness in the event of a SAR.</li> <li>• Carditis added as a foreseeable AR for NVXCoV2373</li> <li>• Addition of an alternative supply source for NVXCoV2373 (i.e. through national supply)</li> <li>• Clarification of the approach to statistical analysis of the immunogenicity data for Cohort B (including the definition of COVID-19 infection and how the sensitivity analyses will be performed)</li> <li>• Marketing authorisation updated for BNT162b2 (30mcg/dose): approved for use in individuals over 12 years by MHRA</li> <li>• Marketing authorisation updated for BNT162b2 (10mcg/dose):</li> </ul>

				<p>approved for use in children aged 5-11 years by MHRA</p> <ul style="list-style-type: none"> <li>Marketing authorisation updated for NVXCoV2373: approved for use in individuals over 12 years by MHRA and has been granted conditional marketing authorisation.</li> </ul>
14	10.0	31 Aug 2023	<p>Melanie Greenland</p> <p>Eimear Kelly</p>	<ul style="list-style-type: none"> <li>Lay summary and Background sections 3 and 6 respectively, updated with details of change to Cohort B randomisation and recruitment deadline.</li> <li>Randomisation section 10.4 updated with additional detail regarding change to randomisation and recruitment challenges.</li> <li>Sample size section 13.1 updated with change to Cohort B total sample size and that required for groups 2 and 3 to meet the non-inferiority co-primary outcome as a result of change to type 1 error level of significance from one-sided to two sided.</li> <li>Interim analyses section 13.4 updated with recruitment deadline based on TSC advice and change to sample size for Cohort B.</li> <li>Cohort B Statistics section 27 in Appendix E updated with details regarding change to participant numbers required for groups 2 and 3 to meet non-inferiority co-primary endpoint.</li> <li>Correction of hypothesis labelling for Cohort B from H0 to H1 for the alternative hypothesis in Section 13.2.2.</li> <li>Minor grammatical corrections throughout.</li> </ul>
15	11.0	13 Dec 2023	<p>Eimear Kelly</p> <p>Melanie Greenland</p>	<ul style="list-style-type: none"> <li>Addition of a new document – Parent and Participant Questionnaire. A link to the questionnaire will be emailed to parents and participants to</li> </ul>

				<p>understand their motivations for and experiences of participating in the Com-COV3 study.</p> <ul style="list-style-type: none"><li>• Correction of wording for cohort B confidence interval for adjusted mean difference from 97.5% to 95%.</li></ul>
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## 24 APPENDIX B: SCHEDULE OF PROCEDURES (COHORT A)

Study timeline	Screening	D0	D56	D14 post boost	D28 post boost	D132 post boost	D236 post boost
<b>Study window</b>		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
<b>Pre - screening online consent</b>	X*						
<b>Informed consent</b>	X	X					
<b>Medical history</b>	X	X					
<b>Interim medical history</b>		X	X	X	X	X	X
<b>Physical examination (as required)</b>	(X)	(X)	(X)	(X)	(X)	(X)	(X)
<b>Urine test (Pregnancy) (if required)</b>		(X)**	X				
<b>COVID-19 vaccination</b>		(X)**	X				
<b>COVID-19 immunogenicity bloods</b>		(X)**	X	X	X	X	X
<b>Troponin and NT-proBNP blood test</b>		(X)**	X	X	X		
<b>Saliva and nasal fluid test (if participant consents)</b>		(X)**	X	X			
<b>Diary review</b>			X	X	X		
<b>SAE/AESI check</b>			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

## 25 APPENDIX C: BLOOD SAMPLING (COHORT A)

Study timeline	D0	D56	D14 post boost	D28 post boost	D132 post boost	D236 post boost
<b>COVID-19 vaccination</b>	<b>X</b>	<b>X</b>				
<b>Secondary endpoints</b>	Anti-spike IgG* Anti-nucleocapsid 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-nucleocapsid IgG  ELIspot	Anti-spike IgG Anti-nucleocapsid IgG  ELIspot
<b>Total volume blood per visit</b>	16	16	16	16	16	16
<b>Total volume by end of study</b>						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):

Oedema on T2 weighted study, typically patchy in nature

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):

New focal or diffuse left or right ventricular function abnormalities (e.g. decreased ejection fraction)

Segmental wall motion abnormalities

Global systolic or diastolic function depression/abnormality

Ventricular dilation

Wall thickness change

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):

Troponin I

Troponin T

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):

Acute chest pain or pressure

Palpitations

Dyspnea after exercise, at rest, or lying down

Diaphoresis

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

## 27 APPENDIX E: COHORT B

### 27.1 Rationale

Evidence of waning immunity following two-dose COVID-19 vaccine schedules and the emergence of SARS-CoV-2 variants has led to the recommendation for a third dose booster of COVID-19 vaccines in many high-income countries. In the UK, a third dose booster is now offered to healthy 16 to 17 year-olds and “at risk” 12 to 15 year-olds.<sup>37</sup> There is no current recommendation to offer a booster to healthy 12 to 15 year-olds.

Healthy adolescents are at low risk of serious illness or death from COVID-19.<sup>30,38</sup> There is an increased risk of myocarditis after receiving mRNA vaccines, highest in adolescent and young adult males.<sup>6,39</sup> This risk appears to be at least as high after a third dose as after the second dose of BNT162b2.<sup>31</sup> Use of a lower (fractional) dose or a different vaccine platform may potentially reduce this risk (though the risk is as yet unknown).

In adults, a booster dose of NVXCoV2373, given three months after completion of a two dose BNT162b2 schedule, produced a four-fold increase in anti-spike IgG GMC at 28 days post-boost, compared with controls.<sup>40</sup>

COVID-19 vaccines have been found to be more immunogenic in adolescents than older adults,<sup>22,41</sup> therefore fractional doses of mRNA vaccines may be adequately immunogenic in adolescents. Use of fractional doses has the advantage of enabling more people to be vaccinated with the available supply of vaccine. Fractional doses would be expected to cause fewer adverse reactions than full doses. Fractional doses may also be adequately immunogenic in populations with high background rates of natural infection.

A paediatric formulation of BNT162b2 vaccine (10µg, one-third of the adult dose) administered to children aged 5 to 11 years is highly immunogenic after two doses.<sup>18</sup> It is not known whether the immunogenicity of a 10mcg dose administered as a 0.1ml dose of the adult formulation is non-inferior to that administered using the paediatric formulation of BNT162b2 (10µg in 0.2ml). This is of relevance to the interpretation of the first part (Cohort A) of the study (which used a one-third dose of the adult formulation). It is also of practical relevance, as the adult formulation may be more widely available and its use more cost effective than the paediatric formulation.

The second part of the study (Cohort B) will investigate various options for a third dose booster in adolescents aged 12 to 15.5 years who have already received two doses of BNT162b2 30µg. It will include arms to compare 10µg BNT162b2 administered as either paediatric or adult formulation. For direct comparison, the study will include a blinded control group, receiving a

MenB vaccine (which is of similar reactogenicity to COVID-19 vaccines). The rapidly changing situation, with respect to proportion of population previously infected and dominant circulating COVID-19 variants, makes it preferable to use randomised rather than historical controls. The advent of bivalent COVID-19 vaccines, and licensing of these as booster doses in the UK during the study, led to the decision to give the control group participants Comirnaty bivalent Original/Omicron BA.1 vaccine. This targets two strains of the virus by combining 15 mcg of mRNA encoding the SARS-CoV-2 wild-type spike protein contained in BNT162b2 with 15 mcg of mRNA encoding the spike protein of the Omicron BA.1 variant. Data from a Phase 2/3 clinical trial of 1,234 adult participants demonstrated that the Omicron adapted vaccine elicited higher neutralising antibody responses against Omicron BA.1 when compared to BNT162b2 [GMR: 1.56 (95% CI: 1.17 to 2.08)]. Based on the safety and immunogenicity data from the trial, the vaccine has been approved by the UK regulator MHRA and recommended by the Committee for Medicinal Products for Human Use (CHMP). On the advice of the JCVI, it has also been included in the autumn COVID-19 booster vaccination campaign. The use of a bivalent vaccine in the study may provide more policy-relevant data and possibly provide better protection against SARS-CoV-2 and prevailing variants of the virus.

### **27.2 Participants and eligibility**

Participants aged 12 to 15½ years (up to 15 years and 6 completed calendar months, inclusive) who have already received two doses of BNT162b2 30µg vaccine will be enrolled. Inclusion and exclusion criteria are detailed in Sections 9.2 and 9.3 above.

### **27.3 Study design**

A total of up to 310 (+ up to an additional 10%) participants will be enrolled. Following discussions with the TSC on the 22<sup>nd</sup> March 2023, it was decided that recruitment to cohort B would stop on the 30<sup>th</sup> June 2023 following difficulty recruiting the target population.

Cohort B	Arm	Doses 1 + 2	Dose 3 given at D0	D84	D182
<b>n= up to 310</b>	1 (n= up to 62)	BNT162b2 30µg (x2)	BNT162b2 30µg		
	2 (n= up to 62)	BNT162b2 30µg (x2)	BNT162b2 10µg (0.1ml adult formulation)		
	3 (n= up to 62)	BNT162b2 30µg (x2)	BNT162b2 10µg (0.2ml paediatric formulation)		
	4 (n= up to 62)	BNT162b2 30µg (x2)	NVXCoV2373		
	5 (n= up to 62)	BNT162b2 30µg (x2)	4CMenB	4CMenB	Comirnaty Original/Omicron BA.1 (15/15µg)/dose

#### 27.4 Randomisation and blinding

Participants were initially randomised 1:1:1:1:1 to the five study arms, as described in Section 10.4.2. However, in light of ongoing recruitment challenges to the study and following discussion with the Trial Steering Committee on 11<sup>th</sup> December, it was decided to change randomisation to 1:3:3:1:1 in order to prioritise recruitment to study groups 2 and 3 (i.e., the fractional dose BNT162b2 10µg adult and paediatric formulation study groups) to achieve the participant numbers required to meet the study's co-primary endpoint (non-inferiority between the two BNT162b2 10µg adult and paediatric formulation study groups). The PIS will be updated to reflect this change to randomisation and participants will be informed at the time of consent that there is a greater chance of being allocated to either the fractional dose adult Pfizer COVID-19 study group or fractional dose paediatric Pfizer COVID-19 study group. The study will be single-blind as described in Section 10.5, and participants will be unblinded from day 56 after receipt of their first study vaccine. Participants in Group 5 (i.e., the control group) who are already consented and enrolled in the study (based on the original Cohort B PIS) will not receive communication regarding the change to their COVID-19 vaccine at D182 and updated PIS until after unblinding.

## 27.5 Statistics

Statistical methods are described in Section 13.2. Plans for interim analysis are described in Section 13.4.2. The Cohort B sample size calculation is based on the primary outcome to determine the non-inferiority between the two BNT162b2 10µg formulations (adult vs paediatric) with paediatric being the reference group. A non-inferiority margin of 0.67 with a power of 90%, a type I error of two-sided 0.05, and 15% of loss of follow up was initially planned, which would require 76 participants to be recruited per arm, for an effective sample size of 64 per arm. However, as a result of recruitment challenges to the study, the type 1 error was changed from a two-sided to a one-sided significance level of 0.05 which will require 62 participants per arm for an effective sample size of 52 per arm for study groups 2 and 3 to achieve the co-primary outcome of non-inferiority between the two 10µg BNT162b2 formulation (adult vs paediatric) groups. The total sample size will be up to 310.

**27.6 Schedule of procedures (Cohort B)**

Study timeline	COVID-19 vaccination	Screening	D0	D28	D84	D182	D210***
<b>Study window</b>		After second COVID-19 vaccination. At or before D0	Day 91+ post second dose COVID-19 vaccine	Day 28-42 post D0	Day 77-98 post D0	Day 162-210 post D0	Day 28-42 post D182
<b>Pre - screening online consent‡</b>		X					
<b>Informed consent</b>		X	X				
<b>Medical history</b>		X	X				
<b>Lateral flow test**</b>			X			X*	
<b>Interim medical history</b>				X	X	X	X***
<b>Physical examination (if required)</b>		(X)	(X)	(X)	(X)	(X)	(X)***
<b>Urine pregnancy test (if required)</b>			(X)		(X)*	(X)***	
<b>COVID-19 vaccination</b>	X						
<b>COVID-19 study vaccine</b>			X†			X***	
<b>MenB Vaccine*</b>			X*		X*		
<b>COVID-19 immunogenicity bloods</b>			X	X	X	X	X***
<b>Saliva and nasal fluid test (if participant consents)</b>			X	X	X	X	X***
<b>Diary review</b>				X			X***
<b>SAE/AESI check</b>				X	X	X	X***

\* Control group (Arm 5) only

† Arms 1, 2, 3 and 4 only (not control group)

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

\*\* Lateral flow test performed at Day 0 (all groups) and Day 182 [Control group (Arm 5) participants who consent to receive Comirnaty bivalent Original/Omicron BA.1 vaccine at the D182 visit. Participants who do **not** consent to receive the bivalent vaccine will **not** have a lateral flow test at this visit]. Lateral Flow tests will also be performed: weekly until the Day 28 visit (all groups), between the Day 182 and 210 visit [Control group (arm 5) participants who received Comirnaty bivalent Original/Omicron BA.1 vaccine at the D182 visit **only**] and when symptomatic throughout the study (all groups).

\*\*\*Applies only to control group (Arm 5) participants who receive the Comirnaty bivalent Original/Omicron BA.1 vaccine at the D182 visit. Participants who do not consent to receive the bivalent vaccine will not attend the D210 visit.



**27.7 Blood Sampling (Cohort B)**

Study timeline	D0	D28	D84	D182	D210*
<b>COVID-19 vaccination</b>	X†			X*	
<b>MenB vaccination*</b>	X*		X*		
<b>Secondary endpoints</b>	Anti-spike IgG  Anti-nucleocapsid IgG  ELISpot  PBMC for storage	Anti-spike IgG    ELISpot  PBMC for storage	Anti-spike IgG  Anti-nucleocapsid IgG  ELISpot	Anti-spike IgG  Anti-nucleocapsid IgG  ELISpot  PBMC for storage	Anti-spike IgG    ELISpot  PBMC for storage
<b>Total volume blood per visit (ml)</b>	20	20	16	20	20
<b>Total volume by end of study</b>					76ml† or 96ml*

\* Control group (Arm 5) only. Blood sampling will only take place at D210 for those participants in Arm 5 who have received Comirnaty Original/Omicron BA.1 bivalent vaccine. Participants who do **not** consent to receive this vaccine at the D182 visit will **not** attend the D210 visit and will **not** have any blood sample taken.

† Arms 1, 2, 3 and 4 only (not control group)

## **27.8 Visits**

The principles for the conduct of visits are described in Section 10.6. The schedule of procedures for Cohort B is shown in Section 27.6 above. Details of blood tests performed are shown in Section 27.7 above.

### **27.8.1 D0 Visit**

The participant will have informed consent taken as described in Sections 10.3 and 10.7.1.1.1. Once written consent is obtained, a final eligibility check will be made as described in Section 10.7.1.1.2. A COVID-19 lateral flow test will be performed. If this is positive, the remainder of the D0 visit will be deferred for at least 4 weeks (see section 9.3.4).

Blood will be taken for COVID-19 immunogenicity assays, as detailed in section 27.6. Nasal fluid and saliva samples will be taken at selected sites from participants who have given optional consent for this.

The participant will be randomised to one of the five study Arms, as described in Section 10.4.2. The randomised vaccine will be administered. All vaccines will be administered intramuscularly according to specific SOPs. Vaccination procedures will be adapted to the specific vaccine being administered, as outlined in the clinical study plan. The participant will stay in the trial site for observation for at least 15 minutes, in case of immediate adverse events. Participants will be considered enrolled to the trial at the point of receipt of the first vaccine administered by the study team.

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 for use, as described in Section 10.7.1.1.5. They will be provided with a pack of lateral flow tests, with instructions for use. They will be asked to perform a lateral flow test at home every week between the first and second visits (up to and including the day of the D28 visit), and to record the result in their diary. Participants will also be asked to perform a lateral flow test if they develop symptoms of COVID-19 (fever, cough, sore throat, loss of taste or smell) at any time while in the study, and to repeat the test 3 to 4 days later. Results should be recorded in the diary.

### **27.8.2 D28 visit**

Participants will be assessed for local and systemic adverse events and an interim history will be taken. Diaries (paper or electronic) will be reviewed. Observations and physical examination will be performed if clinically indicated.

Blood will be taken for COVID-19 immunogenicity assays, as detailed in Section 27.6. Nasal fluid and saliva samples will be taken at selected sites from participants who have given optional consent for this.

### **27.8.3 D84 visit**

Participants will be informed of the study Arm to which they have been randomised at or before this visit. Participants will be assessed for local and systemic adverse events and an interim history will be taken. Observations and physical examination will be performed if clinically indicated. Blood will be taken for COVID-19 immunogenicity assays, as detailed in Section 27.6. Nasal fluid and saliva samples will be taken at selected sites from participants who have given optional consent for this.

Participants in Arm 5 (control group) will be assessed for fitness for vaccination (see Section 9.3.4. for temporary exclusion criteria); this will include a urinary pregnancy test for female participants. They will be given their second dose of 4CMenB vaccine, according to specific SOPs and the clinical study plan. They will stay in the trial site for observation for at least 15 minutes after vaccination.

### **27.8.4 D182 visit**

Participants in Arm 5 only (controls) will have a lateral flow test (if they are receiving a vaccination at this visit). If this is positive, the remainder of this visit will be deferred for at least 4 weeks.

Participants will be assessed for local and systemic adverse events and an interim history will be taken. Observations and physical examination will be performed if clinically indicated.

Blood will be taken for COVID-19 immunogenicity assays, as detailed in Section 27.6. Nasal fluid and saliva samples will be taken at selected sites from participants who have given optional consent for this.

Participants in Arm 5 (controls) will be assessed for fitness for vaccination (see Section 9.3.4. for temporary exclusion criteria); this will include a urinary pregnancy test for female participants. They will then receive a dose of Comirnaty Original/Omicron BA.1 bivalent vaccine. The vaccine will be given according to specific SOPs and the clinical study plan.

Participants will stay in the trial site for observation for at least 15 minutes after vaccination. They will be provided with a pack of lateral flow tests, with instructions for use. They will be asked to perform a lateral flow test at home every week between this visit and the next (i.e. up to and including the day of the D210 visit), and to record the result in their diary. If a control group participant declines the Comirnaty Original/Omicron BA.1 bivalent vaccine at this D182 visit, they will only have a blood sample taken, and will therefore not need to attend the final (D210) study visit.

### 27.8.5 D210 visit

Only participants randomised to Arm 5 (who have received a vaccination at D182) will attend the D210 visit. Participants will be assessed for local and systemic adverse events and an interim history will be taken. Diaries (paper or electronic) will be reviewed. Observations and physical examination will be performed if clinically indicated.

Blood will be taken for COVID-19 immunogenicity assays, as detailed in Section 27.6. Nasal fluid and saliva samples will be taken at selected sites from participants who have given optional consent for this.

## 28 REFERENCES

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