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Evaluating COVID-19 Vaccination Boosters

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27/04/2021

Recruitment status
No longer recruiting

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13/05/2021

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Completed

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18/09/2023

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.

Vaccinations against COVID-19 have successfully been rolled out across the UK, with the majority of people having been vaccinated with either the Oxford/AstraZeneca vaccine (ChAdOx1-nCov19) or the Pfizer vaccine (BNT162b2). With the emergence of new variants of the SARS-CoV-2 virus which causes COVID-19 and the waning of immunity over time, it is likely that seasonal booster vaccinations may be required for high-risk groups. This study is to evaluate which booster vaccinations provide the best immune response, depending on which initial vaccination was used for the first 2 doses (known as a "prime-boost" regime).

Who can participate?
This study will enrol healthy adult volunteers aged 30 years or older from the JCVI priority groups 1 - 3 who received their first dose of COVID-19 vaccination in December 2020 or January 2021 who are at least 84 days post their second vaccination. Volunteers who are 70 days post second vaccine with Oxford/AstraZeneca may also be allowed to participate, due to differences in the roll out of vaccines in the NHS.

What does the study involve?
The study has 3 groups (A, B, and C) that are allocated to different sites which are running the study. Participants within groups A and B will be allocated to receive either one of 3 COVID-19 vaccines or a control group which will receive the Men ACWY vaccine (this protects against the Meningococcal bacteria which causes sepsis and meningitis). Participants in group B will be allocated to receive either one of 4 COVID-19 vaccines or a control group which will receive the Men ACWY vaccine.
Participants will be randomly allocated with an equal chance of receiving each of the vaccines (like tossing a coin). Group A will either receive Oxford/AstraZeneca, Novavax, Novavax half dose, or Men ACWY. Group B will either receive Pfizer, Valneva, Valneva half dose, Janssen, or Men ACWY. Group C will either receive Moderna, Curevac, Pfizer half dose, or Men ACWY

Participants will have a screening visit performed over the phone, then attend a screening and vaccination visit in person. They will have a medical review and blood tests for baseline immunity and safety. They will then receive their allocated vaccine. The participant will not know which vaccine they have received. They will wait 15 min after their vaccine to ensure they have no acute reaction. Following this participants will complete a diary of their symptoms for 28 days.

Participants will attend follow up visits at 28, 84 and 365 days after their vaccination to have blood tests to check their immune response. A subset of 25 participants from each vaccine group will be in the "Immunology" cohort, who will attend additional visits on days 7 and 14 for extra blood tests, and they will also provide samples of saliva and nasal fluid at the regular visits.

If participants receive a positive PCR swab for COVID-19 during the study, they will be asked to contact the study team and attend an extra visit where they will have a swab for COVID-19 with the study team as well as additional blood samples to check their immune response to the virus. After the NHS announced a national booster campaign and all participants completed their day 84 follow up visits, the participants allocated to the control arm were unblinded (other participants were informed they received an active vaccine, but not which one) and invited to be re-randomised to receive one of three COVID-19 vaccines as a booster: either Pfizer, a half dose of Pfizer, or a half dose of Moderna. This will allow us to compare the immune response of people who received a third dose booster approximately 3 months after their primary course of immunisation to the participants who received their boosters approximately 6 months after their primary course of immunisation.
There are several additional sub-studies of COV-BOOST
We have also invited participants of the Novavax clinical trial who received 2 doses the Novavax COVID-19 vaccine to receive a 3rd dose booster vaccine with Pfizer as part of the COV-BOOST study to monitor for side effects, and to see whether giving a different booster effects the immune response to this type of vaccine.
Participants who received the Pfizer vaccine as their third dose booster vaccine as part of the COV-BOOST study have been invted to participate in a fourth dose booster sub-study, where they will be randomised to receive either a fourth dose of the Pfizer vaccine or the Moderna vaccine, at a half dose (the same dose deployed as a third dose booster in the NHS). Participants will be followed up for a further 3 months to check for side effects and their immune response.
Young adults aged 18 – 30 who have not yet received a third dose booster have been invited to participate in our young adult fractional dosing sub-study. They will be randomised to received either a full dose of the Pfizer vaccine, a dose of one third of the Pfizer vaccine (the same as is administered to children aged 5 – 11 years), a half dose of the Moderna vaccine (the same as administered as a third dose booster via the NHS to adults) or a dose of one quarter of the Moderna vaccine. This study is to determine whether lower doses of these vaccines when given to young adults might have as good, or nearly as good an immune response as higher doses, and may have fewer side effects. Participants will be followed up for 8 months in 5 visits to check for side effects and their immune response.
Following the emergence of the Omicron variant, companies have produced vaccines which have been modified with the aim of training the immune system to target this variant more effectively than previous vaccines. COV-BOOST will undertake 2 sub studies containing variant adapted vaccines.
As part of the Omicron variant sub-study, we invited healthy adults who had received their third dose booster more than 84 days prior to be randomised to either a fourth dose booster with Moderna’s Omicron variant vaccine, or a fourth dose of the Pfizer vaccine. We will follow participants up and check their immune responses against both the Omicron and Delta variant to

see which produces the best immune response, and if there is any difference between the two. As it is a new vaccine, we will also be carefully monitoring participants for side effects. The follow up will be 5 visits over 8 months.

As part of the Omicron Bivalent sub-study, we invited healthy adults who had received their third dose booster more than 84 days prior to be randomised to either a fourth dose booster with Moderna's Bivalent vaccine, containing both the original and their updated Omicron mRNA, or a fourth dose of the Pfizer vaccine. We will follow participants up and check their immune responses against both the Omicron and Delta variant to see which produces the best immune response, and if there is any difference between the two. As it is a new vaccine, we will also be carefully monitoring participants for side effects. The follow up will be 5 visits over 8 months.

What are the possible benefits and risks of participating?
Administration of the third dose 'boost' of COVID-19 vaccine in this study (from 84 days after the second dose) may be administered earlier than it would be through routine immunisation, which is of potential benefit. This would not be the case for those who receive the MenACWY control vaccine.

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.

The risks of participating are as follows:
Drawing blood may cause slight pain and occasionally bruising at the site where the needle enters. Some people feel light-headed or even faint when having blood taken. During the course of the trial we will need to take between 30 ml and 77 ml of blood at a single visit. The total amount we will take over the period of the trial will be (approximately) 214-264ml if you are in the general cohort, or (approximately) 330-381 ml if you are in the immunology cohort. An additional 57-77 ml would be taken at the COVID-19 pathway visit if you were to develop confirmed COVID-19 during the study. If repeat bloods are requested for safety reasons at a visit this will be up to 7ml. These amounts over the course of the year, should be below the limit of 470 ml every 3-4 months for blood donations to the National Blood Transfusion Service.

If abnormal results or undiagnosed conditions are found during the course of the trial these will be discussed with you and, if you agree, your GP (or a hospital specialist, if more appropriate) will be informed. Any newly diagnosed conditions will be looked after within the NHS. Participants will not be informed of the results of their levels of post-vaccine immunity against the COVID-19 virus as these are not clinically validated tests.

Nasal fluid samples (optional) will involve insertion of a small bit of soft synthetic material about 2cm into your nostril and leaving it in there, pressed up against the inside of your nose for about one min. This can cause some eye-watering, but should not cause any damage to your nostrils. Some people might have more sensitive nostril linings and this might rarely cause a small amount of bleeding.

We aim to collect 1-1.5 ml saliva using a funnel and collection tube. Participants may find the saliva collection process unsavoury as it is involves drooling and spitting into a collection device. If you are having nasal fluid samples taken, we may also ask for optional saliva samples at routine visits from 28 days after your first vaccine dose. We would ask participants who are giving saliva samples not to eat, drink, smoke, chew gum, brush their teeth or use mouthwash for at least 30 min prior to their appointment.

Common side effects of vaccination are as follows:
1. People very often have tenderness, pain, warmth, redness, itching, swelling, or bruising, or less commonly have a small lump in their arm where they have been vaccinated
2. The symptoms of fatigue, headaches, flu-like symptoms (such as high temperature, sore throat, runny nose, cough and chills), muscle aches, joint aches, feeling unwell (malaise), and feeling sick or nauseated or vomiting can develop after vaccination and usually last for less than a week after vaccination (more commonly 24-48 h afterwards).

Other less common side effects include abdominal pain, decreased appetite, feeling dizzy, swollen lymph nodes (glands), and excessive sweating, itching skin or rash. These symptoms can be reduced by use of paracetamol around the time of immunisation and over the next 24 h. We would not routinely recommend the use of ibuprofen or other anti-inflammatory medication at this time.

After immunisation with the BNT162b2 (Pfizer/BioNTech) vaccine, difficulty sleeping has been observed in fewer than 1 in 100 people, and weakness of the muscles on one side of the face has been observed in fewer than 1 in 1000 people.

Data from studies comparing mixed prime-boost regimes of COVID-19 vaccination (e.g. Oxford /AstraZeneca followed by Pfizer) have found this may increase the risk of side effects following the second vaccine. It is possible that receiving a COVID-19 booster vaccine in this study which is different to your original prime-boost regime, this might increase the side effects of following vaccination.

With any vaccination, there is a small risk of rare serious adverse events, such as an allergic reaction. These may be related to the immune system or to the nervous system. Severe allergic reactions to vaccines (anaphylaxis) are rare (approximately 1 per million vaccine doses), but can be fatal. In case of this unlikely event, medication for treating allergic reactions is available and the researchers are appropriately trained in the management of anaphylaxis.

These are new vaccines, and there may be side effects that we are not yet aware of. Further information about vaccine safety is being actively gathered as the vaccines are being used in the UK and globally. participants will be informed of any significant change in the vaccine safety profile.

Participants will be provided with a 24 h trial mobile number. If they experience unexpected events or become in any way concerned they can use this to contact one of the trial doctors at any time. We will ask you them record these symptoms in the e-diary too.

Recently there have been reports of a very rare condition involving blood clots and unusual bleeding after vaccination. This is being carefully reviewed but the risk factors for this condition are not yet clear. Although this condition remains extremely rare there appears to be a higher risk in people shortly after the first dose of the AstraZeneca (AZ) or Janssen vaccine. Around 4 people develop this condition for every million doses of AZ vaccine doses given. This is seen slightly more often in younger people and tends to occur between 4 days and 2 weeks following vaccination. This condition can also occur naturally, and clotting problems are a common complication of COVID-19 infection. An increased risk has not yet been seen after other COVID-19 vaccines but is being carefully monitored. We do not know whether the risk of clots following vaccination with the Oxford/AstraZeneca or Janssen vaccine will be affected by receiving the first dose after already having had 2 doses of a different COVID-19 vaccine.

In the past, experimental vaccines were developed by different research groups against the SARS virus, which is in the same family as the COVID-19 virus and also infects the lungs. In some cases, animals that received certain types of experimental SARS vaccines appeared to develop more severe lung inflammation when they were later infected with SARS compared with unvaccinated animals. There has also been one report of this increased disease-associated inflammation being seen in a mouse study for a vaccine against MERS-CoV (another related virus), but this has not been observed in any other reported animal studies, and has not been seen in any of the trials of the vaccines being used in this trial. Importantly, this has not been seen in any of the human studies of these vaccines, which have shown immunisation with the vaccines used in this trial does provide protection against COVID-19 disease.

Where is the study run from?
The University Hospital Southampton (UHS) NHS Foundation Trust (UK). Several different sites around the UK are collaborating with UHS to run the study.

When is the study starting and how long does it run for?
From February 2021 to July 2023

Who is funding the study?
The National Institute for Health Research (UK)

Who is the main contact?
The study team can be contacted via email at UHS.SouthamptonCRF@nhs.net

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-002175-19

Integrated Research Application System (IRAS)

299180

Central Portfolio Management System (CPMS)
49379

Study information

Scientific Title
A randomised, phase II UK multi-centre study to determine reactogenicity and immunogenicity of booster vaccination against ancestral and novel variants of SARS-CoV-2

Acronym
Cov-Boost

Study objectives
To establish the optimum annual booster vaccination against COVID-19 depending on the initial homologous prime-boost vaccination regime

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 17/05/2021, South Central-Berkshire Research Ethics Committee (Easthampstead Baptist Church, South Hill Road, Bracknell, RG12 7NS, United Kingdom; +44 (0)207 104 8224; berkshire.rec@hra.nhs.uk), ref: 21/SC/0171

Primary study design
Interventional

Study design
Three-stage multicentre single-blinded randomized adaptive phase II non-inferiority study

Study type(s)
Prevention

Health condition(s) or problem(s) studied
COVID-19 (SARS-CoV-2 infection)

Interventions
Current intervention as of 17/08/2022:
Single-dose annual booster vaccination against ancestral and novel variants of SARS-CoV-2. A computer-generated randomisation list will be prepared by the study statistician. Participants in groups A and C will each be randomised 1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 4 available vaccines in each group using block randomisation. Random block sizes of 4 or 8 will be used. Participants in group B will each be randomised 1:1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 5 available vaccines in each group using block randomisation. Random block sizes of 5 or 10 will be used. The randomisation will be stratified by the study sites and age (<70 and ≥70 years). Participants, laboratory, and analysing statisticians will remain blind to treatment allocation.

ChAdOx1-nCov19: 5x10(10) vp (0.5 ml) one IM injection
BNT162b2: 30 µg (0.3 ml) one IM injection
mRNA-1273: 0.1 mg (0.5 ml) one IM injection
NVX-CoV2373: 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5 ml) one IM injection
NVX-CoV2373: 2.5 µg SARS-CoV-2 rS + 25 µg Matrix-M1 adjuvant (0.25 ml) one IM injection
VLA2001: 33 AU + 0.5 mg Aluminium hydroxide +1mg CPG (0.5 ml) one IM injection
VLA2001: 16.5 AU + 0.25 mg Aluminium hydroxide +0.5mg CPG (0.25 ml) one IM injection
CVnCoV : 12 µg (in 0.6 ml) one IM injection
BNT162b2: 15 mcg (0.15ml) one IM injection
Janssen : 5x10(10) vp/ml (in 0.5 ml) one IM injection
MenACWY: 0.5 ml one IM injection
BNT162b2: 10 mcg (0.1 ml) one IM injection
mRNA-1273: 25 mcg (prepared by dilution process) one IM injection
mRNA-1273.529: 50 mcg (0.25 ml) one IM injection
mRNA-1273.214: 50 mcg (0.25 ml) one IM injection

All participants will be followed up from 12 months post vaccination.

Participants in the unblinded control group will be randomised 1:1:1 to receive either a single dose of BNT162b2 (30 mcg), a half dose of BNT162b2 (15 mcg) or a half dose of mRNA-1273 (50 mcg) with additional visits at the day of vaccination, 14, and 28 days following the additional vaccination.

Participants of the external vaccine sub-study who have previously received 2 doses of NVX-CoV2372 will receive a single dose of BNT162b2, and will be followed up on day 14, 28, 84 and 242.

Participants in the fourth dose booster sub-study who were previously enrolled in COV-BOOST and received a full dose of BNT162b2 as their third dose booster, will be randomised 1:1 to receive either a single dose of BNY162b2 (30 mcg) or a half dose of mRNA-1273 (50 mcg). Follow up will be at day 14, 28 and 84 to monitor for adverse events and for immunology blood tests.

Participants in the young adult fractional dosing sub-study will be randomised 1:1:1:1 to receive either a single dose of BNT162b2 (30 mcg), a third dose of BNT162b2 (10 mcg), a half dose of mRNA-1273 (50 mcg) or a quarter dose of mRNA-1273 (25 mcg). Participants will be followed up on day 14, 28, 83 and 242 to monitor for adverse events and for immunology blood tests.

Participants in the Omicron fourth dose booster sub-study will be randomised 1:1 to receive either a single dose of BNT162b2 (30 mcg) or of mRNA-1273.529. Participants will be followed up on day 14, 28, 84 and 242 to monitor for adverse events and for immunology blood tests.

Participants in the Omicron Bivalent booster sub-study will be randomised 1:1 to receive either a single dose of BNT162b2 (30 mcg) or of mRNA-1273.214. Participants will be followed up on day 14, 28, 84 and 242 to monitor for adverse events and for immunology blood tests.

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Previous intervention as of 10/01/2022:
Single-dose annual booster vaccination against ancestral and novel variants of SARS-CoV-2. A computer-generated randomisation list will be prepared by the study statistician. Participants in groups A and C will each be randomised 1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 4 available vaccines in each group using block

randomisation. Random block sizes of 4 or 8 will be used. Participants in group B will each be randomised 1:1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 5 available vaccines in each group using block randomisation. Random block sizes of 5 or 10 will be used. The randomisation will be stratified by the study sites and age (<70 and ≥70 years). Participants, laboratory, and analysing statisticians will remain blind to treatment allocation.

ChAdOx1-nCov19: 5x10(10) vp (0.5 ml) one IM injection
BNT162b2: 30 µg (0.3 ml) one IM injection
mRNA-1273: 0.1 mg (0.5 ml) one IM injection
NVX-CoV2373: 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5 ml) one IM injection
NVX-CoV2373: 2.5 µg SARS-CoV-2 rS + 25 µg Matrix-M1 adjuvant (0.25 ml) one IM injection
VLA2001: 33 AU + 0.5 mg Aluminium hydroxide +1mg CPG (0.5 ml) one IM injection
VLA2001: 16.5 AU + 0.25 mg Aluminium hydroxide +0.5mg CPG (0.25 ml) one IM injection
CVnCoV : 12 µg (in 0.6 ml) one IM injection
BNT162b2: 15 mcg (0.15ml) one IM injection
Janssen : 5x10(10) vp/ml (in 0.5 ml) one IM injection
MenACWY: 0.5 ml one IM injection

All participants will be followed up from 12 months post vaccination.

Participants in the unblinded control group will be randomised 1:1:1 to receive either a single dose of BNT162b2 (30 mcg), a half dose of BNT162b2 (15 mcg) or a half dose of mRNA-1273 (50 mcg) with additional visits at the day of vaccination, 14, and 28 days following the additional vaccination.
Participants of the external vaccine sub-study who have previously received 2 doses of NVX-CoV2372 will receive a single dose of BNT162b2, and will be followed up on day 14, 28, 84 and 242.

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Previous interventions as of 03/06/2021:
Single-dose annual booster vaccination against ancestral and novel variants of SARS-CoV-2. A computer-generated randomisation list will be prepared by the study statistician. Participants in groups A and C will each be randomised 1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 4 available vaccines in each group using block randomisation. Random block sizes of 4 or 8 will be used. Participants in group B will each be randomised 1:1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 5 available vaccines in each group using block randomisation. Random block sizes of 5 or 10 will be used. The randomisation will be stratified by the study sites and age (<70 and ≥70 years). Participants, laboratory, and analysing statisticians will remain blind to treatment allocation.

ChAdOx1-nCov19: $5x10^{10}$ vp (0.5 ml) one IM injection
BNT162b2: 30 µg (0.3 ml) one IM injection
mRNA-1273: 0.1 mg (0.5 ml) one IM injection
NVX-CoV2373: 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5 ml) one IM injection
NVX-CoV2373: 2.5 µg SARS-CoV-2 rS + 25 µg Matrix-M1 adjuvant (0.25 ml) one IM injection
VLA2001: 33 AU + 0.5 mg Aluminium hydroxide +1mg CPG (0.5 ml) one IM injection
VLA2001: 16.5 AU + 0.25 mg Aluminium hydroxide +0.5mg CPG (0.25 ml) one IM injection
CVnCoV : 12 µg (in 0.6 ml) one IM injection
CVnCoV : 6 µg (in 0.3 ml) one IM injection

Janssen : 5x10¹⁰ vp/ml (in 0.5 ml) one IM injection
MenACWY: 0.5 ml one IM injection

All participants will be followed up from 12 months post vaccination.

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Previous intervention:
Single dose annual booster vaccination against ancestral and novel variants of SARS-CoV-2. A computer generated randomisation list will be prepared by the study statistician. Participants in groups A-C will each be randomised 1:1:1:1 within the 2 cohorts (ChaAdOx1 nCOV-19 and BNT162b2 homologous boost), to the 4 available vaccines in each group using block randomisation. Random block sizes of 4 or 8 will be used. The randomisation will be stratified by the study sites and JCVI priority groups (1 and 2).Participants, laboratory and analysing statisticians will remain blind to treatment allocation.

ChAdOx1-nCov19: 5x1010vp (0.5ml) one IM injection
BNT162b2: 30 µg (0.3ml) one IM injection
mRNA-1273: 0.1mg (0.5ml) one IM injection
NVX-CoV2373: 5 µg SARS-CoV-2 rS + 50 µg Matrix-M1 adjuvant (0.5ml) one IM injection
NVX-CoV2373: 2.5 µg SARS-CoV-2 rS + 25 µg Matrix-M1 adjuvant (0.25ml) one IM injection
VLA2001: 33 AU + 0.5mg Aluminium hydroxide +1mg CPG (0.5ml) one IM injection
VLA2001: 16.5 AU + 0.25mg Aluminium hydroxide +0.5mg CPG (0.25ml) one IM injection
CVnCoV : 12 µg (in 0.6ml) one IM injection
CVnCoV : 6 µg (in 0.3ml) one IM injection
MenACWY: 0.5ml one IM injection

All participants will be followed up from 12 months post vaccination.

Intervention Type
Biological/Vaccine

Phase
Phase II

Drug/device/biological/vaccine name(s)
ChAdOx1-nCov19 (Oxford/AstraZeneca), BNT162b2 (Pfizer), NVX-CoV2373 (Novavax), mRNA-1273 (Moderna), VLA2001 (Valneva), CVnCoV (Curevac), Men ACWY, mRNA-1273.529

Primary outcome(s)
1. Immunology measured using serum Anti Spike protein IgG levels at 28 days
2. Safety/Reactogenicity measured using the following from participant records:
2.1. Incidence and details of solicited adverse events between 0 and 7 days
2.2. Incidence and details of unsolicited adverse events between 0 and 28 days
2.3. Incidence and details of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) throughout the study

Key secondary outcome(s)
Current secondary outcome measures as of 17/08/2022:
1. Anti-spike immunoglobulins at 0, 84, and 365 days (and at 7, 14, 28 and 242 days for some cohorts)

2. Neutralising antibodies against SARS-CoV-2 at 0, 28, 84, and 365 days (and at 7, 14, 28 and 242 days for some cohorts)
3. Anti-nucleocapsid immunoglobulins at 0, 28, 84, and 365 days
4. Pseudo neutralising antibodies at 0, 28, 84, and 365 days (and at 7, 14 and 242 days for some cohorts)
5. Cellular immune responses by ELISpot at 0, 28, 84, and 365 days (and at 14 and 242 days for some cohorts)
6. Cellular immune responses by ICS (Th1/Th2) in the immunology cohort at 0 and 14 days (and at 28, 84 and 242 days for some cohorts)
7. Medically attended adverse events for up to 3 months post boost dose (i.e. 3 months from enrolment)
8. Changes in laboratory safety measures from baseline at 0 and 28 days
9. Changes in markers of cardiac muscle damage in participants receiving a 3rd dose COVID-19 booster vaccine approximately 6 months after 2nd dose, post initial vaccination course

Exploratory endpoints:
1. Evaluation of immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment
2. Characterisation of COVID-19 infections experienced following administration of vaccination and the immune response to those infections using anti-spike & anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
3. Genome sequencing of SARS-CoV-2 viruses isolated from infected participants from enrolment, and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
4. Characterisation of the mucosal immune response to SARS-CoV-2 booster vaccination in the immunology cohort using nasal fluid (collected using SAM-strips) and saliva samples IgA & IgG ELISA and exploratory immunological assays at 0, 28, and 365 days
5. Characterisation of the blood antibody response in the immunology cohort using functional antibody assays at 0, 28, and 365 days

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Previous secondary outcome measures as of 10/01/2022:
1. Characterisation of immunogenicity of booster vaccinations against SARS-CoV-2 measured using the following:
1.1. Anti-spike immunoglobulins at 0, 84, and 365 days (and at 7 and 14 days only for the immunology cohort)
1.2. Neutralising antibodies against SARS-CoV-2 at 0, 28, 84, and 365 days (and at 14 days only for the immunology cohort)
1.3. Anti-nucleocapsid immunoglobulins at 0, 28, 84, and 365 days
1.4. Pseudo neutralising antibodies at 0, 28, 84, and 365 days
1.5. Cellular immune responses by ELISpot at 0, 28, 84, and 365 days (and at 14 days only for the immunology cohort)
1.6. Cellular immune responses by ICS (Th1/Th2) in the immunology cohort at 0 and 14 days
2. Safety measured using medically attended adverse events for up to 3 months post boost dose (i.e. 3 months from enrolment) and changes in laboratory safety measures from baseline at 0 and 28 days
3. To characterise immune responses of 3rd dose booster vaccinations when administered approximately 6 months after 2nd dose, and in comparison to those administered after 3 months using the following:

3.1 Anti-spike immunoglobulins at 0, 14, and 28 days
3.2 Neutralising antibodies against SARS-CoV-2 at 0, 14, and 28 days
3.3 Pseudo neutralising antibodies at 0, 14, and 28 days
3.4 Cellular immune responses by ELISpot and ICS at 0, 14 and 28 days in the immunology subgroup
4. To assess changes in markers of cardiac muscle damage in participants receiving a 3rd dose COVID-19 booster vaccine approximately 6 months after 2nd dose, post initial vaccination course
5. To determine the reactogenicity of 3rd dose booster vaccinations when administered approximately 6 months after 2nd dose, and in comparison to those administered after 3 months measured using medically attended adverse events for up to 3 months post boost dose and changes in laboratory safety measures from baseline at 0 and 28 days
6. To characterise immune responses of 3rd dose booster vaccination with BNT162b2 when administered after a primary immunization course of purified protein technology (NVXCoV2373) using the following
6.1 Anti-spike immunoglobulins at 0, 14, 28, 84 and 242 days
6.2 Neutralising antibodies against SARS-CoV-2 at 0, 14, 28, 84 and 242 days
6.3 Pseudo neutralising antibodies at 0, 14, 28, 84 and 242 days
6.4 Cellular immune responses by ELISpot and ICS at 0, 14, 28, 84 and 242 days in the immunology subgroup
7. To determine the reactogenicity of 3rd dose booster vaccination with BNT162b2 when administered after a primary immunization course of purified protein technology (NVXCoV2373) measured using medically attended adverse events for up to 3 months post boost dose and changes in laboratory safety measures from baseline at 0 and 28 days

Exploratory endpoints:
1. Evaluation of immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment
2. Characterisation of COVID-19 infections experienced following administration of vaccination and the immune response to those infections using anti-spike & anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
3. Genome sequencing of SARS-CoV-2 viruses isolated from infected participants from enrolment, and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
4. Characterisation of the mucosal immune response to SARS-CoV-2 booster vaccination in the immunology cohort using nasal fluid (collected using SAM-strips) and saliva samples IgA & IgG ELISA and exploratory immunological assays at 0, 28, and 365 days
5. Characterisation of the blood antibody response in the immunology cohort using functional antibody assays at 0, 28, and 365 days

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Previous secondary outcome measures as of 03/06/2021:
1. Characterisation of immunogenicity of booster vaccinations against SARS-CoV-2 measured using the following:
1.1. Anti-spike immunoglobulins at 0, 84, and 365 days (and at 7 and 14 days only for the immunology cohort)
1.2. Neutralising antibodies against SARS-CoV-2 at 0, 28, 84, and 365 days (and at 14 days only for the immunology cohort)
1.3. Anti-nucleocapsid immunoglobulins at 0, 28, 84, and 365 days
1.4. Pseudo neutralising antibodies at 0, 28, 84, and 365 days

1.5. Cellular immune responses by ELISpot at 0, 28, 84, and 365 days (and at 14 days only for the immunology cohort)
1.6. Cellular immune responses by ICS (Th1/Th2) in the immunology cohort at 0 and 14 days
2. Safety measured using medically attended adverse events for up to 3 months post boost dose (i.e. 3 months from enrolment) and changes in laboratory safety measures from baseline at 0 and 28 days

Exploratory endpoints:
1. Evaluation of immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment
2. Characterisation of COVID-19 infections experienced following administration of vaccination and the immune response to those infections using anti-spike & anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
3. Genome sequencing of SARS-CoV-2 viruses isolated from infected participants from enrolment, and within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
4. Characterisation of the mucosal immune response to SARS-CoV-2 booster vaccination in the immunology cohort using nasal fluid (collected using SAM-strips) and saliva samples IgA & IgG ELISA and exploratory immunological assays at 0, 28, and 365 days
5. Characterisation of the blood antibody response in the immunology cohort using functional antibody assays at 0, 28, and 365 days

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Previous secondary outcome measures:
1. Characterisation of immunogenicity of booster vaccinations against SARS-CoV-2 measured using the following:
1.1. Anti-spike immunoglobulins at 0, 84, and 365 days (and at 7 and 14 days only for the immunology cohort)
1.2. Neutralising antibodies against SARS-CoV-2 at 0, 28, 84, and 365 days (and at 14 days only for the immunology cohort)
1.3. Anti-nucleocapsid immunoglobulins at 0, 28, 84, and 365 days
1.4. Pseudo neutralising antibodies at 0, 28, 84, and 365 days
1.5. Cellular immune responses by ELISpot at 0, 28, 84, and 365 days (and at 14 days only for the immunology cohort)
1.6. Cellular immune responses by ICS (Th1/Th2) in the immunology cohort at 0 and 14 days
2. Safety measured using medically attended adverse events for up to 3 months post boost dose (i.e. 3 months from enrolment) and changes in laboratory safety measures from baseline at 0 and 28 days

Exploratory endpoints:
1. Evaluation of immunogenicity, safety & reactogenicity of COVID-19 vaccines in participants sero-positive for SARS-CoV-2 nucleocapsid IgG at enrolment
2. Characterisation of COVID-19 infections experienced following administration of vaccination and the immune response to those infections using anti-spike & anti-nucleocapsid immunoglobulins, neutralising and pseudo-neutralising antibodies, cellular immune response by ICS and ELISpot within 1 week of a participant being found to be SARS-CoV-2 positive by external testing
3. Genome sequencing of SARS-CoV-2 viruses isolated from infected participants from enrolment, and within 1 week of a participant being found to be SARS-CoV-2 positive by external

testing
4. Characterisation of the mucosal immune response to SARS-CoV-2 booster vaccination in the immunology cohort using nasal fluid (collected using SAM-strips) and saliva samples IgA & IgG ELISA and exploratory immunological assays at 0, 7, 14, 28, 84, and 365 days
5. Characterisation of the blood antibody response in the immunology cohort using functional antibody assays at 0, 7, 14, 28, 84, and 365 days

Completion date
31/07/2023

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 17/08/2022:
1. Willing and able to give written informed consent for participation in the trial.
2. Aged 30 years or above and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until 3 months after boost immunisation
4. In the Investigator's opinion, is able and willing to comply with all trial requirements.
5. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
6. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
7. Agreement to refrain from blood donation during the study
8. Received priming dose of COVID-19 vaccination between December 2020 and January 2021 (inclusive) and booster dose no less than 84 days prior to day 0. Due to the NHS deployment timelines, some sites may need to invite people who have been prime-boosted with their second dose of AstraZeneca with a minimum of 70 days from their second dose. Sites need Sponsor approval for this prior to enrolment of people with a 70-83 day gap since their second dose in any study arm

For the External Vaccine Trial Participants sub-study, the inclusion criteria are:
1. Willing and able to give written informed consent for participation in the trial
2. Male or female aged 30 years or above
3. In the Investigator's opinion, is able and willing to comply with all trial requirements
4. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
5. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures
6. Primary immunization course (2 doses) of NVXCoV2373 COVID-19 vaccine
7. Plans to receive 1 or 2 doses of licensed vaccine (1 dose will be received as part of this trial, the second dose will not be provided by the trial but the participant may receive a second dose via the NHS if they wish to).

For the Fourth dose sub-study, the inclusion criteria are:
1. Participants from the main study in Group B who received a 3rd dose booster of BNT162b2 (regardless of whether primary course was BNT162b2 or ChAdOx1-nCov19) will be invited to participate.
2. Participants will be eligible for booster vaccination at the Fourth Dose Booster Sub-Study

unless they have had a previous severe adverse reaction to mRNA vaccines or have acquired an additional COVID-19 vaccine outside of the study since enrolling. Other medical criteria will be checked prior to immunisation (including diagnosis of cancer, autoimmune conditions, neurological conditions, blood clotting conditions and pregnancy), but will not be considered a contraindication to vaccination unless the investigator feels there is a specific clinical reason to withhold vaccination for the safety of the participant.

For the young adult fractional dosing sub-study, the inclusion criteria are:
1. Participant is willing and able to give written informed consent for participation in the trial.
2. Male or Female, aged 18 to 30 years and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. In the Investigator's opinion, is able and willing to comply with all trial requirements.
4. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
5. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
6. Agreement to refrain from blood donation during the study.
7. Has received 2 doses of BNT162b2 or mRNA-1273 and is at least 3 months (84 days) since their second dose by day 0

Following recruitment during the first half of 2022, and following discussions with both the funders (CEPI and the UK Vaccine Task Force/NIHR), changes to recruitment have been made in view of the small number of young adults who remain COVID-19 naïve, have not yet received a 3rd dose, and the lack of participant availability during the summer holidays. From June 2022, recruitment will close to participants with no history of confirmed COVID-19. Recruitment will pause from June 2022 until September 2022 for participants with a history of confirmed COVID-19. Upon reopening in September 2022, the inclusion criteria will be as follows:
1. Participant is willing and able to give written informed consent for participation in the trial.
2. Male or Female, aged 18 to 30 years and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. In the Investigator's opinion, is able and willing to comply with all trial requirements.
4. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
5. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
6. Agreement to refrain from blood donation during the study.
7. Has received 2 or 3 doses of BNT162b2 or mRNA-1273 and is at least 6 months (180 days) since their most recent dose by day 0
8. The participant self-reports a previous positive test result for COVID-19 (including via rt-PCR, lateral flow tests and saliva LAMP) at least 84 days prior to day 0 (a participant with any positive test within 84 days prior to day 0, or no history of a positive test is ineligible).
9. Participants who previously received their third dose of COVID-19 vaccine via the sub-study may be eligible to re-enrol and receive a fourth dose via the sub-study, so long as they received either the full dose of BNT162b2 (30mcg) or half dose of mRNA-1273 (50mcg) as their third dose, and they continue to meet the other inclusion and exclusion criteria.

For the Omicron fourth dose booster sub-study, the inclusion criteria are:
1. Participant is willing and able to give written informed consent for participation in the trial.
2. Male or Female, aged 30 years or over and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until

3 months after boost immunisation.
4. In the Investigator's opinion, is able and willing to comply with all trial requirements.
5. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
6. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
7. Agreement to refrain from blood donation during the study.

The inclusion criteria for the Omicron bivalent booster sub study are:
1. Participant is willing and able to give written informed consent for participation in the trial.
2. Male or Female, aged 30 years or over and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until 3 months after boost immunisation.
4. In the Investigator's opinion, is able and willing to comply with all trial requirements.
5. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
6. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
7. Agreement to refrain from blood donation during the study.
8. Has received 3 doses of approved COVID-19 vaccine, with the third dose being either BNT162b2 30 mcg or mRNA-1273 50 mcg and is at least 3 months (84 days) since their third dose by day 0.

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Previous participant inclusion criteria as of 10/01/2022:
1. Willing and able to give written informed consent for participation in the trial.
2. Aged 30 years or above and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until 3 months after boost immunisation
4. In the Investigator's opinion, is able and willing to comply with all trial requirements.
5. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
6. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
7. Agreement to refrain from blood donation during the study
8. Received priming dose of COVID-19 vaccination between December 2020 and January 2021 (inclusive) and booster dose no less than 84 days prior to day 0. Due to the NHS deployment timelines, some sites may need to invite people who have been prime-boosted with their second dose of AstraZeneca with a minimum of 70 days from their second dose. Sites need Sponsor approval for this prior to enrolment of people with a 70-83 day gap since their second dose in any study arm

For the External Vaccine Trial Participants sub-study, the inclusion criteria are:
1. Willing and able to give written informed consent for participation in the trial
2. Male or female aged 30 years or above
3. In the Investigator's opinion, is able and willing to comply with all trial requirements
4. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of

participation in the trial
5. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures
6. Primary immunization course (2 doses) of NVXCoV2373 COVID-19 vaccine
7. Plans to receive 1 or 2 doses of licensed vaccine (1 dose will be received as part of this trial, the second dose will not be provided by the trial but the participant may receive a second dose via the NHS if they wish to).

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Previous participant inclusion criteria:
1. Willing and able to give written informed consent for participation in the trial.
2. Aged 30 years or above and in good health as determined by a trial clinician. Participants may have well controlled or mild-moderate comorbidity.
3. Female participants of childbearing potential must be willing to ensure that they or their partner use effective contraception from 1 month prior to first immunisation continuously until 3 months after boost immunisation
4. In the Investigator's opinion, is able and willing to comply with all trial requirements.
5. Willing to allow their General Practitioner and consultant, if appropriate, to be notified of participation in the trial
6. Willing to allow investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
7. Agreement to refrain from blood donation during the study
8. Received priming dose of COVID-19 vaccination between December 2020 and January 2021 (inclusive) and booster dose no less than 84 days prior to day 0

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
2878

Key exclusion criteria
Current participant exclusion criteria as of 17/08/2022:
1. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on the interpretation of the trial data (e.g. adenovirus vectored vaccines, any coronavirus

vaccines)
3. Pregnant at enrolment or planning to become pregnant during the first 3 months of the trial period
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
5. 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)
6. History of 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-listed ingredients of the Pfizer vaccine)
7. Any history of anaphylaxis
8. Current diagnosis of or treatment for cancer, except basal cell carcinoma of the skin and cervical carcinoma in situ
9. Bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
10. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran, and edoxaban)
11. History of cerebral venous sinus thrombosis, antiphospholipid syndrome, or heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2)
12. Suspected or known current alcohol or drug dependency
13. Any other significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
14. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild /moderate well-controlled comorbidities are allowed)
15. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion.
16. Significant renal or hepatic impairment
17. Scheduled elective surgery during the trial
18. Life expectancy of <6 months
19. Have participated in another research trial involving an investigational product in the past 12 weeks. This does not exclude participants in trials of AZD1222 (ChAdOx1 nCOV-19) who were originally recipients of placebo and who received AZD1222 (ChAdOx1 nCOV-19) or BNT162b2 as part of the "national schedule" with AZD1222 (ChAdOx1 nCOV-19) or BNT162b2 dose 1 from mid-Dec 2020 through end February 2021 and then AZD1222 (ChAdOx1 nCOV-19) or BNT162b2 second dose 12 twelve weeks later (this is allowed by the COV001 and COV002 protocols)
20. Insufficient level of English language to undertake all study requirements in the opinion of the Investigators except where translation has been able to be provided and is available

For the External Vaccine Trial Participants Sub-Study the Exclusion criteria are:
1. Prior receipt of a third dose of COVID-19 vaccine
2. History of allergic disease or reactions likely to be exacerbated by any component of the study vaccine (e.g., hypersensitivity to the active substance or any of the SmPC-listed ingredients of the Pfizer vaccine)
3. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
4. 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)
5. Participant with life expectancy of less than 6 months

6. Any other significant disease, disorder, or finding which in the opinion of the investigator may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
7. Insufficient level of English language to undertake all study requirements in opinion of the Investigators except where translation has been able to be provided and is available.

For the young adult fractional dosing sub-study, the exclusion criteria are:
1. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on interpretation of the trial data (e.g. adenovirus vectored vaccines, any coronavirus vaccines)
3. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the 4. 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)
5. History of 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-listed ingredients of the Pfizer vaccine)
6. Any history of anaphylaxis
7. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
8. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
9. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
10. Suspected or known current alcohol or drug dependency
11. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data
12. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed)
13. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion
14. Significant renal or hepatic impairment
15. Participant with life expectancy of less than 6 months
16. Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
17. Insufficient level of English language to undertake all study requirements in opinion of the Investigators except where translation has been able to be provided and is available.

For the Omicron fourth dose booster sub-study, the exclusion criteria are:
1. Previous receipt of a fourth COVID-19 vaccine
2. Previous positive test for COVID-19, including rt-PCR, lateral flow or saliva/LAMP test.
3. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
4. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on interpretation of the trial data (e.g. COVID-19 variant specific investigational vaccines)

5. Participants who are pregnant at enrolment or planning to become pregnant during the first 3 months following vaccination.
6. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
7. 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)
8. History of 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-listed ingredients of the Pfizer vaccine)
9. Any history of anaphylaxis
10. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
11. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
12. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
13. Suspected or known current alcohol or drug dependency
14. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data
15. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed)
16. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion
17. Significant renal or hepatic impairment
18. Participant with life expectancy of less than 6 months
19. Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
20. Insufficient level of English language to undertake all study requirements in opinion of the Investigators except where translation has been able to be provided and is available.

The exclusion criteria for the Omicron bivalent booster sub study are:
1, Previous receipt of a fourth COVID-19 vaccine
2. COVID-19 infection (confirmed by rt-PCR, lateral flow tests or saliva LAMP) within 84 days before day 0
3. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
4. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on interpretation of the trial data (e.g. COVID-19 variant specific investigational vaccines)
5. Participants who are pregnant at enrolment or planning to become pregnant during the first 3 months following vaccination.
6. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
7. 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)
8. History of 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-listed ingredients of the Pfizer vaccine)

9. Any history of anaphylaxis
10. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
11. Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
12. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)
13. Suspected or known current alcohol or drug dependency
14. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data
15. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed)
16. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion.
17. Significant renal or hepatic impairment
18. Participant with life expectancy of less than 6 months
19. Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
20. Insufficient level of English language to undertake all study requirements in opinion of the Investigators except where translation has been able to be provided and is available.

Current participant exclusion criteria as of 10/01/2022:
1. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on the interpretation of the trial data (e.g. adenovirus vectored vaccines, any coronavirus vaccines)
3. Pregnant at enrolment or planning to become pregnant during the first 3 months of the trial period
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
5. 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)
6. History of 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-listed ingredients of the Pfizer vaccine)
7. Any history of anaphylaxis
8. Current diagnosis of or treatment for cancer, except basal cell carcinoma of the skin and cervical carcinoma in situ
9. Bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
10. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran, and edoxaban)
11. History of cerebral venous sinus thrombosis, antiphospholipid syndrome, or heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2)
12. Suspected or known current alcohol or drug dependency

13. Any other significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
14. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild /moderate well-controlled comorbidities are allowed)
15. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion.
16. Significant renal or hepatic impairment
17. Scheduled elective surgery during the trial
18. Life expectancy of <6 months
19. Have participated in another research trial involving an investigational product in the past 12 weeks. This does not exclude participants in trials of AZD1222 (ChAdOx1 nCOV-19) who were originally recipients of placebo and who received AZD1222 (ChAdOx1 nCOV-19) or BNT162b2 as part of the "national schedule" with AZD1222 (ChAdOx1 nCOV-19) or BNT162b2 dose 1 from mid-Dec 2020 through end February 2021 and then AZD1222 (ChAdOx1 nCOV-19) or BNT162b2 second dose 12 twelve weeks later (this is allowed by the COV001 and COV002 protocols)
20. Insufficient level of English language to undertake all study requirements in the opinion of the Investigators except where translation has been able to be provided and is available

For the External Vaccine Trial Participants Sub-Study the Exclusion criteria are:
1. Prior receipt of a third dose of COVID-19 vaccine
2. History of allergic disease or reactions likely to be exacerbated by any component of the study vaccine (e.g., hypersensitivity to the active substance or any of the SmPC-listed ingredients of the Pfizer vaccine)
3. Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ)
4. 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)
5. Participant with life expectancy of less than 6 months
6. Any other significant disease, disorder, or finding which in the opinion of the investigator may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
7. Insufficient level of English language to undertake all study requirements in opinion of the Investigators except where translation has been able to be provided and is available.

Previous participant exclusion criteria as of 03/06/2021:
1. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on the interpretation of the trial data (e.g. adenovirus vectored vaccines, any coronavirus vaccines)
3. Pregnant at enrolment or planning to become pregnant during the first 3 months of the trial period
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
5. 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)
6. History of 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-listed ingredients of the Pfizer vaccine)
7. Any history of anaphylaxis
8. Current diagnosis of or treatment for cancer, except basal cell carcinoma of the skin and cervical carcinoma in situ
9. Bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
10. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran, and edoxaban)
11. History of cerebral venous sinus thrombosis, antiphospholipid syndrome, or heparin-induced thrombocytopenia and thrombosis (HITT or HIT type 2)
12. Suspected or known current alcohol or drug dependency
13. Any other significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
14. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild /moderate well-controlled comorbidities are allowed)
15. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion.
16.Significant renal or hepatic impairment
17. Scheduled elective surgery during the trial
18. Life expectancy of <6 months
19. Have participated in another research trial involving an investigational product in the past 12 weeks
20. Insufficient level of English language to undertake all study requirements in the opinion of the Investigators except where translation has been able to be provided and is available

Previous participant exclusion criteria:
1. Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination (one week for licensed seasonal influenza vaccine or pneumococcal vaccine)
2. Prior or planned receipt of any other investigational or licensed vaccine or product likely to impact on the interpretation of the trial data (e.g. adenovirus vectored vaccines, any coronavirus vaccines)
3. Pregnant at enrolment or planning to become pregnant during the trial period
4. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccines
5. 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)
6. History of 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-listed ingredients of the Pfizer vaccine)
7. Any history of anaphylaxis
8. Current diagnosis of or treatment for cancer, except basal cell carcinoma of the skin and cervical carcinoma in situ
9. Bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture
10. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran, and edoxaban)
11. History of cerebral venous sinus thrombosis, antiphospholipid syndrome, or heparin-induced

thrombocytopenia and thrombosis (HITT or HIT type 2)
12. Suspected or known current alcohol or drug dependency
13. Any other significant disease, disorder, or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data
14. Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, an endocrine disorder, and neurological illness (mild /moderate well-controlled comorbidities are allowed)
15. History of active or previous auto-immune neurological disorders (e.g. multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion.
16. History of laboratory-confirmed COVID-19 prior to enrolment (history of SARS-CoV-2 detection by PCR, or positive antibody test to SARS-CoV-2 prior to having received COVID-19 vaccination)
17. Significant renal or hepatic impairment
18. Scheduled elective surgery during the trial
19. Life expectancy of <6 months
20. Have participated in another research trial involving an investigational product in the past 12 weeks
21. Insufficient level of English language to undertake all study requirements in the opinion of the Investigators except where translation has been able to be provided and is available

Date of first enrolment
01/06/2021

Date of final enrolment
30/06/2021

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
So166YD

Study participating centre

Addenbrookes Hospital
Hills road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Bradford Patient Recruitment Centre
Bradford Institute for Health Research
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Guys and St Thomas' NHS Foundation Trust
Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre
Leeds Teaching Hospitals
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
NHS Greater Glasgow and Clyde Clinical Research Facility
New Lister Building
10 Alexandra Parade
Glasgow
United Kingdom
G31 2ER

Study participating centre
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital

Oxford
United Kingdom
OX3 7LE

Study participating centre
Royal Devon and Exeter NHS Foundation Trust
Barrack Rd
Exeter
United Kingdom
EX2 5DW

Study participating centre
Stockport NHS Foundation Trust, Stepping Hill Hospital
Poplar Grove
Hazel Grove
Stockport
United Kingdom
SK2 7JE

Study participating centre
University College London Hospitals
235 Euston Rd
London
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NW1 2BU

Study participating centre
Royal Bournemouth Hospital
Castle Ln E
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BH7 7DW

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PO6 3LY

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University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Birmingham
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Study participating centre
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Study participating centre
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HA1 3UJ

Study participating centre
University Hospitals Sussex
Royal Sussex County Hospital
Eastern Road

Brighton
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BN2 5BE

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	28-day results of third dose	02/12/2021	03/12/2021	Yes	No
Results article	28-day results of fourth dose	09/05/2022	16/05/2022	Yes	No
Results article	3-month results of third dose	09/04/2022	21/04/2023	Yes	No
Results article	8-month results of third dose	19/04/2023	21/04/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 11.0	20/05/2022	18/08/2022	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes