Participant Information Sheet (Parent/Guardian): Com-COV3 Cohort B

Comparing COVID-19 vaccine schedule combinations in adolescents

A single-blind, randomised, phase II multi-centre study to determine reactogenicity and immunogenicity of heterologous prime/boost COVID-19 vaccine schedules in adolescents

Contents

1. Would your child like to participate in a COVID-19 vaccine study?

We would like to invite your child to take part in our COVID-19 vaccine study.

Taking part in research is entirely voluntary. Your child should only take part if they want to.

In this information sheet we explain the background for the study and describe what taking part would involve. Before your child makes a decision, it is important for them and you to understand why we are doing this research and what it would involve.

Please read the following information carefully and discuss it with your child. You may also want to consider discussing it with friends or relatives.

We will also provide an age-appropriate information sheet about the study to your child.

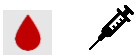
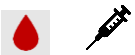
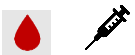
Participants younger than 16 years require the written consent of their parent or guardian to take part.

SUMMARY

- **Com-COV3 is a study looking at multiple options for immunising adolescents against COVID-19**
- **In this part of the study (Cohort B), we are looking at the immune response after a third dose of COVID-19 vaccine**
- **We are inviting young people aged 12 to 15½ years who have already received two doses of COVID-19 vaccine to take part**
- **For participants, the first study visit will take place 3 months or more after their second dose of COVID-19 vaccine**
- **We will give participants a third dose of COVID-19 vaccine**
- **380 participants will be allocated to one of five groups**
- **Participants in one of these groups will first be given two separate doses of a meningitis B vaccine; their third dose of COVID-19 vaccine will be given later**
- **There are 4 or 5 visits over a period of 6 or 7 months at CYARU**
- **A blood sample will be taken at each visit**
- **Participants will complete an online diary for 4 weeks after their vaccination(s)**

Participants who have completed a 2- dose (30 micrograms/dose) course of the adult Pfizer COVID-19 vaccine at least 3 months previously are randomised to groups 1 to 5 at enrolment.

The study design is summarised below:

	Study Visit				
	Visit1 Day0	**Visit 2 Day28**	**Visit 3 Day84**	**Visit 4 Day182**	**Visit 5 Day210 (Group 5 only)***
Groups 1-4					
Group 5					

*Only participants in Group 5 who receive the Pfizer bivalent COVID-19 vaccine will attend this visit and will have a blood sample taken.

 Blood test

 Vaccine

The vaccines to be given are summarised below:

Study Group	Visit 1	Visit 3	Visit 4
1	Full dose of adult Pfizer COVID-19 vaccine (=30 micrograms)		
2	One-third dose of adult Pfizer COVID-19 vaccine (=10 micrograms)		
3	Full dose of paediatric Pfizer COVID-19 vaccine (=10 micrograms)		
4	Full dose of Novavax COVID-19 vaccine		
5	MenB vaccine (Bexsero)	MenB vaccine (Bexsero)	Full dose of Pfizer bivalent COVID-19 vaccine (Original/Omicron BA.1) (=15 micrograms/15 micrograms)

2. Important information if your child is considering travelling abroad

Many countries now require evidence of COVID-19 vaccination to allow travellers to enter. Taking part in this study may mean that your child receives a schedule of vaccines which is not recognised for travel to certain countries. Regulations vary between countries and are constantly changing.

If your child is considering travelling abroad (especially in the next twelve months), please read the Appendix at the end of this information sheet. It contains information which will help them to decide whether or not to take part in this study.

3. Why has my child been asked to take part?

We are asking your child to take part because they are the right age and live in an area where we are doing the study.

4. Who is sponsoring, organising and funding the research?

The study is organised and sponsored by the University of Oxford. It is funded by the UK Vaccine Task Force and through financial support to the University of Oxford from the National Institute for Health Research (NIHR), which is a UK government funded research agency. It is being co-funded by the Coalition for Epidemic Preparedness Innovations (CEPI), an international foundation financing vaccine research. Novavax is providing its vaccine to be used in the study. The researchers are not paid for recruiting your child into this study.

5. Background information

Since early 2020, COVID-19 has spread around the world. It has killed over 160,000 people in the UK and 6 million people worldwide (by 8th March 2022). It has made many more people seriously ill.

Widespread vaccination is helping to save lives, reduce severity of illness and reduce spread of the disease. Most adults in the UK have now been vaccinated. By 8th March 2022, 91.6% of the UK population aged 12 years or over had received at least one dose of vaccine.

The vaccination programme in the UK initially mainly focussed on adults because older adults are more likely to suffer from severe disease or die from COVID-19 than younger people. Although children and young people usually do not become very ill with COVID-19, some do develop serious illness and a few have died. Young people with COVID-19 occasionally develop a serious inflammatory condition called paediatric multisystem inflammatory syndrome (PIMS-TS). In England, in the first year of the pandemic (until the end of February 2021), 251 under 18-year-olds (about 20 per million) were admitted to intensive care with COVID-19, and 25 (about 2 per million) died; 309 (about 26 per million) developed PIMS-TS.

Vaccinating young people may reduce their risk of severe disease and their likelihood of missing time in education.

In the UK, healthy 12 to 15 year olds are currently offered two doses of the Pfizer-BioNTech vaccine, given at least 12 weeks apart. Those with specific underlying health problems (such as Down's syndrome, cerebral palsy or conditions causing susceptibility to infections), who are at particular risk of serious COVID-19, are advised to have a third dose of Pfizer-BioNTech vaccine, as are those living with a person with impaired immunity. Those with a weakened immune system may be offered a fourth dose.

6. What is the purpose of this study?

The Com-COV3 study is divided into two different parts (or 'cohorts') to find out how well young people respond to different immunisation strategies for COVID-19. These two cohorts are:

a) Cohort A, which looked at the response to a second dose of COVID-19 vaccine (given in different combinations, or using a low dose of the Pfizer vaccine). This part of the study has completed recruitment.
b) Cohort B, which is looking at the immune response to a third dose of COVID-19 vaccine.

Your child is being invited to take part in **Cohort B,** and this part of the study is described in detail below.

After vaccination, immunity may gradually diminish with time. Giving a further dose of vaccine helps to boost immunity. A third (or "booster") dose of COVID-19 vaccine is now recommended in the UK for people aged 16 years or above. By 8th March 2022, a third dose had been given to over 38 million people in the UK.

We want to explore the immune responses in young people given various possible vaccines for the third dose. One possibility is to give the same dose of the Pfizer vaccine as for the first two vaccinations. Another possibility is to give the same vaccine but at a smaller dose. This might reduce the risk of unwanted effects from the vaccine, and would also enable the available supply of vaccine to be used for more people. It has been shown that giving a course of two vaccinations with one-third of the standard adult dose of Pfizer vaccine to children aged 5 to 11 years produces an immune response as good as that seen in adults after two full doses. It has also been found that adolescents tend to have a stronger immune response to COVID-19 vaccines than older people. Preliminary results from Cohort A of this study suggest that when used as a second dose, a reduced (one-third) dose of Pfizer vaccine may reduce the frequency and severity of common reactions observed after vaccination, while still generating a robust immune response. We now wish to see if this also applies when a reduced dose is used for the third vaccination.

The Pfizer vaccine is now available in two formulations, adult and paediatric (which contains one-third of the dose of the adult formulation). The two formulations are not made up in exactly the same way. We want to know if giving a one-third dose of the adult vaccine

produces the same effect as a dose of the paediatric version. This is important because the adult vaccine is likely to be more widely available around the world and cheaper to use than the paediatric formulation.

Another option which this study will examine is to use a different vaccine (Novavax) for the third dose. Novavax has recently been approved in the UK for use in adults and also in 12- to 17-year-olds, for the first two doses, as an alternative COVID-19 vaccine. It is a different type of vaccine from Pfizer. Novavax is a protein-based vaccine, whereas Pfizer is an mRNA vaccine. Previous studies in adults have shown that giving a dose of Novavax after one or two doses of Pfizer produces a good immune response with no safety concerns. However, these have mostly been in people without any previous COVID-19 infection, and it is important to study this in teenagers with a good representation from those who have, and have not, had a previous infection.

The study will include a "control group". One in nine of the study participants (11%) will be allocated to this group and receive two doses of a meningitis vaccine (Bexsero). They will then receive their third dose of COVID-19 vaccine (a full dose of the Pfizer-BioNTech bivalent vaccine, which targets both the original virus strain and the Omicron BA.1 variant) around 6 months after enrolment in the study. However, if this or a different COVID-19 vaccine were to be recommended for 12- to 15-year-olds in the UK before then, we would offer this recommended COVID-19 vaccine earlier, in line with the new guidelines. We would also seek expert advice from our Trial Steering Committee as to whether we should offer the other groups this recommended vaccine (assuming this is a different vaccine from what they have already received in the study), to ensure they are not disadvantaged compared to their peers outside of the study. If there are no new national recommendations then no additional vaccine will be offered and the control group will receive their COVID-19 vaccine at 6 months, as planned. The control group is very important to help us properly understand the effects of COVID-19 vaccination in the other groups.

We are also interested in learning about the effect of previous COVID-19 infection on response to COVID-19 vaccination. Young people are welcome to participate in the study whether or not they have previously had COVID-19.

The results of this study may be used to guide national vaccination policy.

7. What happens in the study (Cohort B)?

Participants will be required to make either four or five visits to the study site, and at each visit a blood sample will be taken. Most participants (those in groups 1 to 4) will receive a third dose of a COVID-19 vaccine at their first study visit (at least 3 months after their second dose). Participants in group 5 are expected to receive their COVID-19 vaccine at the fourth study visit, around 6 months after their first visit (or earlier if national guidelines change, as described above and in Section 17). All participants will be asked to record symptoms for 28

days after the study vaccination (a paper version of the diary is available, if required). At some sites, participants will also be asked to provide saliva samples and have a sample of nasal fluid taken at each visit; this is completely optional.

Visits will take place at CYARU.

8. Which vaccines are being used?

(a) Pfizer-BioNTech COVID-19 vaccine (Comirnaty 30 micrograms/dose; BNT162b2).

This was the first COVID-19 vaccine to be granted regulatory approval by the UK medicines regulator MHRA on 2nd December 2020. The approval was extended to include children aged 12 -15 years on June 2021, and the vaccine is being used for routine two-dose immunisation of this age group in the UK.

This is a messenger RNA (mRNA) vaccine. The vaccine enables human cells to produce a virus protein (the spike protein of the COVID-19 virus). The immune system then makes a protective immune response to the spike protein. This vaccine has been shown to be very effective at preventing severe COVID-19 disease. Millions of doses of this vaccine have now been given in the UK.

The following are the commonest side effects of this vaccine: injection site pain or swelling; tiredness; headache; general aches, or mild flu-like symptoms.

Symptoms following vaccination usually last less than a week.

Very rarely after this vaccine, inflammation of the heart (myocarditis) may occur. Most of these cases have been in younger men, usually a few days after the second vaccination. Generally, recovery occurs with rest and simple treatments. Recent information suggests that the risk of myocarditis after a third dose of Pfizer vaccine is at least as high as after a second dose.

It is important to understand that our study will not be large enough to compare the risk of myocarditis in those receiving the different schedules in this study, since myocarditis is such a rare event.

The characteristic symptoms of myocarditis are chest pain, shortness of breath and palpitations (the feeling of an abnormal heart rhythm). People experiencing any of these symptoms after receiving a COVID-19 vaccine are advised to ring 111 or see their GP.

(b) Comirnaty 10 micrograms/dose

This is the paediatric version of the Pfizer-BioNTech COVID-19 vaccine. It works in the same way, as described above. It is one-third of the dose of the full-dose adult vaccine. In the UK, Comirnaty 10 micrograms/dose was authorised by MHRA for use in children aged 5 to 11 years on 22nd December 2021. It is not licensed for use in older age groups.

The recognised side effects of this vaccine are the same as for Pfizer-BioNTech COVID-19 vaccine (including myocarditis), as described above.

(c) Novavax COVID-19 vaccine (NVXCoV2373)

Novavax was approved for use in adults by the UK regulator (MHRA) on 3rd February 2022 and was later approved for use in 12- to 17-year-olds on 26th August 2022 (as an alternative COVID-19 vaccine for the first two doses). It has been given to over 2200 adolescents in clinical trials, and no safety concerns have been raised in these studies. In adult clinical trials in the UK, the US, Mexico, and South Africa, this vaccine has been shown to be very effective at preventing symptomatic COVID-19 infection and severe COVID-19 disease. It has now been given to over 50,000 trial participants.

This vaccine is based on the spike protein from the COVID-19 virus combined with an adjuvant, a substance that increases the immune response to the protein. The adjuvant is called "Matrix-M1™" and consists of saponin (which is derived from the soapbark tree) and natural fats.

The following are recognised side effects of this vaccine:

Very common (may affect more than 1 in 10 people): injection site redness, tenderness, pain or swelling; tiredness; headache; nausea; vomiting; malaise; fever; chills.

Common (may affect up to 1 in 10 people): injection site itching.

Uncommon (may affect up to 1 in 100 people): enlarged lymph nodes; raised blood pressure; rash.

Up to August 2022 a small number (fewer than 40) cases of inflammation of the heart muscle (myocarditis) or inflammation of the lining of the heart (pericarditis) have been reported in some countries after Novavax vaccination. These cases have been detected through routine surveillance, after administration of over 700 000 doses of this vaccine. The risk appears similar to that previously reported following vaccination with the Pfizer-BioNTech COVID-19 vaccine. This is a very rare possible side effect (affecting less than 1 in 10,000 vaccine recipients). Now that this vaccine is licensed and will be given to much larger numbers of people, it is likely that rarer side effects may be seen. This means that continued monitoring for side effects (as with all newly licensed vaccines) is very important.

(d) Bexsero (4CMenB)

Bexsero is a licensed vaccine, which was introduced into the routine UK national immunisation programme in September 2015 to provide protection against group B meningococcus, an important cause of meningitis and sepsis in young children and teenagers. It is currently recommended to be given to infants at 2, 4 and 12 months of age, but not routinely recommended for teenagers in this country.

This vaccine is based on meningococcal proteins. The following are recognised side effects of this vaccine:

Very common (may affect more than 1 in 10 people): Headache; nausea; malaise; muscle pain; joint pain; injection site pain/redness/swelling/hardness.

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

(e) Pfizer-BioNTech bivalent COVID-19 vaccine (Comirnaty bivalent Original/Omicron BA.1)

The Pfizer-BioNTech bivalent COVID-19 vaccine was approved for use in individuals aged 12 years and above by the UK regulator (MHRA) on 3rd September 2022. The Joint Committee on Vaccination and Immunisation (JCVI) has advised that the vaccine be used in the COVID-19 booster vaccination programme for autumn 2022, currently restricted to adults over 50 years of age and to those who are "high risk" for COVID-19. It is a messenger RNA (mRNA) vaccine and works in the same way as the Pfizer-BioNTech COVID-19 vaccine described above.

In each dose of the vaccine, half of the vaccine (15 micrograms) targets the original virus strain, and the other half (15 micrograms) targets the Omicron (BA.1) variant. Based on clinical trial data, the vaccine has been shown to trigger a strong immune response against both Omicron and the original virus strain. Safety monitoring has shown that the side effects (including myocarditis) are the same as for the Pfizer/BioNTech COVID-19 vaccine, as described above.

9. Does my child have to take part?

No. It is up to you and your child to decide whether or not to take part. Your child will not be penalised in any way if they decide not to participate. Their decision will not affect their standard medical care. If they do decide to take part, they will be given an information sheet to keep (or be sent it electronically).

For children younger than 16 years, a parent or guardian must sign the consent form, but your child must show that they agree ('assent') to taking part. If they become 16 years old during the study, they will be asked to sign a consent form at the first study visit after their 16th birthday.

Your child is free to withdraw from the study at any time, without giving a reason (although we may request a follow up appointment if required for safety reasons).

10. Can my child take part?

In order to take part in Cohort B of this study, your child must already have received two doses of the adult Pfizer-BioNTech vaccine (with the second dose received at least 3 months prior to taking part).

Other requirements are that your child is:

- Aged between 12 and 15½ years on the day of enrolment.
- Able and willing (in the investigator's opinion) to comply with all study requirements.

- Willing to allow the investigators to discuss their medical history with their GP and access all medical records.

Your child **cannot** participate in this study if any of the following apply:

- They belong to a group advised by the JCVI to receive more than two doses of Pfizer-BioNTech vaccine because of specific underlying health problems. (Full details can be found in the "Green Book", Chapter 14a, https://www.gov.uk/government/publications/covid-19-the-green-book-chapter-14a)
- They have previously received more than two doses of COVID-19 vaccine (or they have received any COVID-19 vaccine other than Pfizer BioNTech).
- They have received meningitis B vaccine (Bexsero). Please note, this would not normally have been given to children born before 2015 (unless in a clinical study).
- They have received, or plan to receive, any non-study vaccine within 7 days of enrolment.
- They have recently received transfusions of blood products or immunosuppressant medication (except topical steroids or short-term oral steroids).
- They have a history of anaphylaxis or relevant allergies.
- For females, they are pregnant, breast feeding or are unwilling to practice effective contraception from enrolment in the study until at least 3 months after their last study vaccine.
- They have any serious chronic illness requiring hospital specialist supervision. Examples include: immune system disorders; congenital heart disease; malignant disease; bleeding disorders; auto-immune disorders; kidney and liver disease.
- They have surgery needing overnight admission and/or general anaesthetic planned during the study.
- They have participated in another study involving an investigational product in the past 12 weeks (Please note that this does not apply to participants who have completed the final visit (D236) in Cohort A of the study, and who are otherwise eligible to participate in Cohort B; they may enrol in Cohort B without waiting for 12 weeks to elapse).
- They are a close family member of a study team member.
- Their ability to understand English is insufficient to undertake all study requirements.

Mild to moderate conditions that are well-controlled would not automatically exclude your child from participating. If you are unclear whether they are eligible to be involved in the study, you can contact the study team who will be able to advise you.

If your child has previously had confirmed or suspected COVID-19 infection, they can still take part in the study, as long as they wait at least 4 weeks after a positive COVID-19 test before receiving any study vaccinations (see section 13 for full explanation).

11. What will happen if my child decides to take part?

If your child decides to take part in the study, you should complete the short online questionnaire to check that they are eligible. At the end of this, you will be asked if you agree to a researcher contacting you by phone to ask questions about your child's current health and discuss details of their medical history, if required. You will also be asked to agree to allow us to contact your child's GP for further information, if necessary, and for permission to access your child's NHS vaccination records. If your child is eligible, they will be invited to a face-to-face visit.

They would visit us either four or five times over the course of six or seven months. All visits will be arranged to take place outside of school hours.

The study visits are identified by numbers (e.g. D28). The number refers to the approximate number of days after the first study visit.

What happens at each study visit is summarised in the table below:

Visit	**D0**	**D28**	**D84**	**D182**	**D210** Group 5 only*
Week	0	4	12	26	30
Eligibility	✓				
Consent	✓				
Lateral flow test	✓			(✓)** Group 5 only	
Blood test	✓	✓	✓	✓	(✓) Group 5 only
Vaccine	✓		(✓) Group 5 only	(✓)** Group 5 only	
Diary	✓			(✓)** Group 5 only	

* Only participants in Group 5 who receive the Pfizer bivalent vaccine will be required to attend this visit and will have a blood sample taken at this visit.

**Participants in Group 5 who consent to receive the Pfizer bivalent vaccine will have a lateral flow test and receive a vaccine at the fourth visit.

The study visits are now described in more detail.

First visit (D0)

At this visit, we will re-check that your child is eligible to take part. Their temperature will be recorded (this is done at every study visit). Your child's heart rate, and height and weight will be recorded (at the first visit only). If necessary, a doctor may do a physical examination.

You and your child may be shown a video describing the study. You will both have the opportunity to ask any questions you want before you sign the consent form for the study. For participants under 16 years, a parent or guardian must sign the consent form. We will ask participants under 16 years old to sign an assent form to indicate their willingness to take part.

Your child will be asked to have a lateral flow test. If it is positive, the rest of this visit (including vaccination) will be deferred for at least 4 weeks. At some sites, we may also ask to take nasal fluid and saliva samples, which are to look at the immune response in the lining of the airways. This part of the study is entirely optional. If your child does not want these tests, they can still take part in the study. There will be a section in the consent form to indicate whether your child agrees to have these tests.

Your child will have a blood test. If they want the skin numbed with local anaesthetic cream, this can be provided. Their blood will be sent for analysis to measure various markers of immunity to COVID-19 (antibodies and T-cells).

Your child will be randomised to one of five groups (using a process which decides by chance). You and your child do not make the decision. There will be a greater chance (33%) of being allocated to either the one-third dose adult Pfizer COVID-19 vaccine group or to the one-third dose paediatric Pfizer COVID-19 vaccine group. We are prioritising these groups as it is important to find out whether a one-third dose of the Pfizer vaccine given using the adult formulation produces the same effect as a one-third dose given using the paediatric formulation. There is a lower chance (11%) of being allocated to one of the remaining three groups. Which group your child is assigned to will determine which vaccine(s) they receive, as shown on page 2.

You and your child will not know to which study group they have been allocated until shortly before their third study visit (D84).

Before giving a vaccine, we will check that your child is fit to be vaccinated on that day. If they have a fever, or if they have symptoms of a respiratory tract infection, the visit will be rescheduled. If required, a doctor may do a physical examination. We will also do a pregnancy test, as it is important that females who take part in the study are not pregnant and do not become pregnant during the course of the study. Anyone who could possibly be pregnant (considered to be any female whose periods have started, aged 12 and above) will be asked to provide a urine sample to check before they receive their vaccination.

Your child will be given the vaccine decided by the randomisation process described above. The vaccine will be given by injection into the muscle of the upper arm (deltoid). Your child will need to stay for at least 15 minutes after the vaccination.

Your child will be given a link to an online e-diary to record any symptoms they experience after the vaccination. A paper version can be provided instead if you are unable to access the

internet; the e-diary has the advantage that it enables the study team to view the entries on a regular basis. Your child will also be given a thermometer and tape measure. They will be asked to record local symptoms at the injection site (pain, tenderness, redness, warmth, itch, swelling and hardness) each day for seven days after vaccination. Similarly, they will be asked to record general symptoms (fever, chills, joint pains, muscle pains, fatigue, headache, malaise, nausea, vomiting and diarrhoea) each day for seven days. They will also be asked to record any other symptoms they experience in the 28 days after vaccination. They may need help from an adult to complete the diary.

Your child will be given a pack of lateral flow tests (with instructions) and asked to perform one test each week, up to and including the day of their second visit. You or your child will need to record the results in their study diary. Your child will also be asked to do a lateral flow test at any time they have symptoms of COVID-19 (fever, cough, sore throat, loss of taste or smell) whilst they are in the study, and then to repeat it three to four days later. These results are also to be recorded in the study diary.

Second visit (D28)

At this visit, your child will have a blood sample taken. We will review your child's diary entries.

Third visit (D84)

Ahead of this visit, your child will find out to which study group they have been allocated. Your child will have a blood sample taken. We will also enquire about any significant medical problems your child has experienced since their last visit.

Participants in Group 5 of the study only will be assessed for fitness for vaccination and given their second dose of Bexsero (Group B meningococcal) vaccine, as described above for the first visit. They will not have to fill in a symptom diary after this vaccination.

Fourth visit (D182)

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

Again, your child will have a blood sample taken. We will also enquire about any significant medical problems your child has experienced since their last visit.

Participants in Group 5 of the study only will be assessed for fitness for vaccination and given a dose of Pfizer-BioNTech bivalent vaccine (Comirnaty Original/Omicron BA.1, 15 micrograms/15 micrograms per dose). However, if national vaccination policy changes for this age group before their vaccine is due, a different vaccine may be offered to keep in line with this. Note that if your child is in the control group and declines a COVID-19 vaccine at this fourth visit, they will just have a final blood test and will not be required to attend their

fifth clinic visit. We ask that they (or you) let us know as soon as possible (and in advance of the fourth visit) if they decide they do not want a dose of COVID-19 vaccine. You and your child can discuss this with the study team at any time.

Participants in Group 5 (who have been vaccinated at this visit) only will be provided with a pack of lateral flow tests at this visit and asked to perform one test each week between this visit and the next. The results are to be recorded in the study diary.

Fifth visit (D210)

Only participants in Group 5 (who have received a vaccination at the fourth visit) will attend this visit, at which they will have a blood sample taken. We will review your child's diary entries and we will also enquire about any significant medical problems your child has experienced since their last visit.

12. What should my child avoid during the study?

Your child should not take part in other studies that involve the administration of drugs or vaccines, or studies testing other interventions for COVID-19. If your child needs to receive any vaccinations while enrolled in this study, you should inform the research team beforehand, so we can discuss with you the most appropriate time for the vaccination to be given.

13. What should I do if I believe my child has developed COVID-19 during the study?

The vaccinations in this study do not guarantee protection from COVID-19. Participants in the study should continue to follow all current government advice on COVID-19.

If your child is unwell, contact the NHS 111 service or phone 999.

We will provide your child with a pack of lateral flow tests. If you think they have symptoms of COVID-19 (fever, cough, sore throat, loss of taste or smell) at any time whilst they are in the study, they will be asked to do one of these tests and then repeat it 3 to 4 days later. The results should be recorded in the study diary. If your child is admitted to hospital during the study (for any reason), then you should inform the medical or nursing staff that your child is taking part in this study. We will provide a contact card for you to give to these staff.

It is important that you understand that if your child becomes seriously unwell and needs to be admitted to hospital, the standard referral routes within the NHS will be used. Participants will be treated the same way as the general population in this context of the COVID-19 pandemic. We are unable to offer extra medical support outside what is available within the NHS for the general public.

If your child is diagnosed with COVID-19, they should not come to any scheduled visit until they have fully recovered. Similarly, they should not attend during any period of self-isolation or quarantine. If your child is unable to attend for any of these reasons, please telephone us.

No-one who has current symptoms of COVID-19 or a recent positive test should accompany your child to study visits.

On 17th November 2021, the UK Health Security Agency 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 partly 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 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 at a minimum of 4 weeks after a positive COVID-19 test, 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 more rapid availability of results. This is important as the results from this study may advise future UK vaccine policy.

14. Are there any risks from taking part in the study?

a) Vaccine side effects

The potential side effects following immunisation are described in Section 8. One risk is a severe allergic reaction (anaphylaxis) after vaccination. This is extremely rare. If it occurs, it does so within minutes of the injection. This is the reason we ask your child to stay for at least 15 minutes after their vaccination. The study staff members are trained and equipped to recognise and treat anaphylaxis.

b) Blood tests

Having blood taken may cause some pain, although we will use anaesthetic cream to numb the skin if requested. Your child may feel light-headed or even faint. Your child may notice a bruise afterwards. Taking blood can sometimes be difficult. If we are unable to obtain the blood sample first time, we may ask your child permission for a second attempt.

c) Unwanted media attention

The media are very interested in reporting news about COVID-19. They sometimes approach study participants for "their story". We can give you advice about avoiding unwanted media attention if needed.

d) Implications of taking part in the study for travel and attending events

If your child is planning to travel abroad, please read with them the Appendix at the bottom of this information sheet.

e) Receiving a third dose of vaccine different from that which may be recommended in the future

It is important to be aware that it is possible a routine third dose of COVID-19 vaccine may be offered to 12 to 15 year-olds in the future. It is possible that a different COVID-19 vaccine, or a different dose of vaccine, from that your child is given in the study may be recommended. This is discussed further in Section 17 below.

It should be remembered that there is strong evidence that two doses of vaccine provide good levels of protection against severe disease. However, it is not known how long this protection lasts.

15. What are the advantages of taking part?

All 12 to 15 year-olds in the UK are currently offered two doses of Pfizer-BioNTech vaccine. However, by taking part in this study, your child will receive a third dose of a COVID-19 vaccine. It is expected that a third dose of COVID-19 vaccine will boost immunity, improving protection against disease.

Participants randomised to Group 5 of the study will also receive two doses of Bexsero (4CMenB) vaccine. This is not routinely given to adolescents. However, it has been shown to be 75% effective at preventing meningitis and sepsis due to Group B meningococcus (MenB) when administered to infants. When administered to adolescents, it has been shown to induce antibodies which kill the meningococcus bacteria and which persist for at least 4 years. Invasive Group B meningococcal disease has a mortality rate of about 5% in adolescents, and causes serious long-term complications (such as deafness) in many survivors. In England in the year 2019-2020, there were 55 cases of invasive Group B disease in 10 to 19 year-olds. There is some evidence that there may be a resurgence of Group B meningococcal disease in adolescents as social distancing restrictions are relaxed.

The results of this study may be used to guide future decisions about how best to vaccinate young people against COVID-19. By taking part in the study, your child will have contributed to this.

16. What is happening in the other parts of the Com-COV3 study?

The **first part** of the study (**Cohort A**) enrolled 149 young people aged 12 to 16 years from various sites in the UK. It has now completed recruitment. Participants received a first immunisation with a standard dose of Pfizer-BioNTech vaccine, and 8 weeks later received a second immunisation with either:

1. A full standard (adult) dose of Pfizer-BioNTech vaccine
2. A third of a standard (adult) dose of Pfizer-BioNTech vaccine
3. A standard dose of Novavax vaccine

Tests to assess the immune response were done at two and four weeks after the second vaccination. The results are being analysed and submitted for publication. The participants in

Cohort A will be followed up at about 11 and 26 weeks after their second vaccination, to assess how their immunity changes over time.

17. What happens if recommendations for routine COVID-19 immunisation change while my child is enrolled in the study?

At present, 12 to 15 year-olds in the UK are eligible to receive two doses of the Pfizer or Novavax COVID-19 vaccines. Those taking part in this study will receive a third dose of a COVID-19 vaccine.

It is possible that a routine third dose of COVID-19 vaccine may be offered to 12 to 15 year-olds in the future, and a different dose of the Pfizer vaccine from that given in the study, or another COVID-19 vaccine, may be recommended.

If the recommendations for routine immunisation change, then we will seek advice from the study Trial Steering Committee. They will consider what vaccines are offered routinely and the immune responses observed in this study. If they decide that one or more of the Groups in the study is significantly disadvantaged compared to their peers in the general population, those Groups may be offered an additional vaccination. For Group 5 (who will not receive a COVID-19 vaccine until their fourth visit) the vaccine offered will be a full dose of the Pfizer-BioNTech bivalent vaccine. If a change to the national vaccination policy occurs for this age group before their vaccine is due, a different COVID-19 vaccine may be offered to participants in this group, in line with the change to the national vaccination policy.

18. What if new information becomes available during the study?

Sometimes during the course of a study, relevant new information becomes available. If this happens, we would tell you and your child about it. We would discuss whether your child wants to, or should, continue in the study. If your child decides to continue to take part, you will be asked to sign an updated consent form. On receiving new information, we may consider it to be in your child's best interests to withdraw from the study. Your child's participation in this study may also be stopped at any time by the study doctor or the Sponsor for other reasons.

19. What will happen if my child does not want to carry on with the study?

If, at any time after agreeing to participate, your child changes their mind about being involved with this study, they are free to withdraw without giving a reason. If your child withdraws, we would not usually perform any more research procedures, although occasionally we might need to offer a follow up visit for safety purposes (for example, to check the injection site or a blood result). Your child would not be penalised in any way for their decision. Unless you request otherwise, any samples taken whilst your child has been in the study will continue to be stored and used for the research detailed above. You or your

child can request that the samples are destroyed at any time during or after the study. If your child chooses to withdraw from the study, their standard medical care will not be affected.

20. What if something goes wrong?

The investigators recognise the important contribution that volunteers make to medical research, and make every effort to ensure their safety and well-being. The University of Oxford, as the research Sponsor, has arrangements in place in the unlikely event that your child suffers any harm as a direct consequence of participation in this study.

In the event of harm being suffered, while the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that your child is properly represented in pursuing any complaint. The study doctor can advise you of further action and refer your child to a doctor within the NHS for treatment, if necessary. NHS indemnity operates in respect of the clinical treatment which may be provided if your child needs to be admitted to hospital.

21. What if I wish to complain?

If you wish to complain about any aspect of the way in which you or your child have been approached or treated during the course of this study, you should contact the research investigators who will do their best to address your concerns. You can contact us by e-mail at COMCOV3.HCRW@wales.nhs.uk. Alternatively, you may contact the University of Oxford Research Governance, Ethics & Assurance team (RGEA) office on 01865 616480, or the head of RGEA at rgea.sponsor@admin.ox.ac.uk

22. Will we be compensated for taking part?

Yes, we are able to reimburse you at a rate of £10 for each study visit, to help towards travel and other expenses. This may be given to your child as vouchers. Reimbursement may not be given at each visit (for example, we may give you a £20 voucher at every second visit). The exact arrangements for reimbursement may vary between sites.

23. Would my child's taking part in this study be kept confidential?

All information collected about your child during the course of the research will be coded with a study number and kept confidential. The information is available to the study team, authorised collaborators, ethical review committees Cardiff and Vale University Health Board, government regulatory agencies and the Sponsor (University of Oxford), who can ask to access the trial data. Responsible independent monitors may be given access to data for monitoring and/or audit of the trial to ensure we are complying with regulations. They are bound by the same confidentiality rules.

Every effort will be taken to maintain confidentiality. Information about your child may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at Children and Young Adults Research Unit. Study results may be published in

scientific journals, but nothing that could identify your child will be included in any report or publication.

24. What will happen to my child's data?

UK Data protection regulation requires that we state the legal basis for processing personal information. In the case of research, this is 'a task in the public interest.' The University of Oxford is the sponsor for this study, based in the United Kingdom. The University is the data controller and is responsible for looking after your child's information and using it properly.

We will be using information from your child's medical records in order to undertake this study and will use the minimum personally-identifiable information possible. We will keep identifiable information about your child, such as contact details, for a minimum of 5 years and until the youngest participant turns 21 years, as per the university requirements for studies that involve paediatric participants. The need to store this information for longer in relation to licensing of vaccines will be subject to ongoing review. De-identified research data will be stored indefinitely. If you have agreed that samples can be retained for future research, then your child's personally identifiable information will be kept with restricted access solely for the purposes of sample management for a minimum of five years after the last sample has been either used or disposed of in order to meet regulatory requirements. We will also store your consent form. Samples will be provided for future research only in a form that does not identify your child. We store research data securely at the University of Oxford indefinitely following removal of identifiable information. If you agree to your contact details being held so you can be contacted regarding future research, we will retain a copy of the consent form until such time as your details are removed from our database; we will keep the consent form and your contact details separately.

The study team will use your name and contact details to contact you about the research study; to make sure that relevant information about the study is recorded; for your health care health during the study; and to oversee the quality of the study. At the completion of the study, unless you consent otherwise (e.g. if you request to be informed of other studies), your personal details will not be used to contact you other than in exceptional circumstances. If you consent to take part in another study carried out by Children and Young Adults Research Unit, personal information and medical information, including blood test results, may be accessed to avoid unnecessary repetition.

Data protection regulation provides you with control over your personal data and how it is used. When you agree to your information being used in research, however, some of those rights may be limited in order for the research to be reliable and accurate. Further information about your rights with respect to your personal data is available at: https://compliance.web.ox.ac.uk/individual-rights

25. How will my child's General Practitioner (GP) be involved?

In order to enrol into this study, you will need to tick a box on an online form to say that you consent for us to contact your child's GP. The GP may be asked to share information about your child's medical history and give access to any other medical records as required. We will write to the GP to let them know when your child enrols in, and completes, the study, so medical records can be updated accordingly.

26. What will happen to any samples my child gives?

If you consent, any of your child's left-over samples can be stored and used for future research on vaccines or infectious diseases. This is optional; your child's participation in this study will not be affected by whether or not you decide to allow storage and future use of left-over samples. You may request at any time for your child's remaining samples to be destroyed.

Analysis of your child's samples, measuring immune response, will be done both at the University of Oxford and at other collaborating laboratories in the UK and overseas. Any samples or data sent to them would not include information that identifies your child.

27. Will any genetic tests be done?

With your specific permission, we will store your child's DNA obtained from his/her study samples. We may do tests on these samples, for example to look at the patterns of genes that regulate your child's own individual immune response (these are called Human Leukocyte Antigen genes). This helps us to work out which aspects of the immune response to vaccines are due to genetic differences between individuals. We may also look at the expression of certain genes which relate specifically to the immune response to COVID-19. Any samples and information recorded will be marked only with a study ID so that we cannot directly identify your child. However, your child's DNA is unique, and so will never be completely anonymous.

28. What will happen to the results of the research study?

The results of this research study will be presented to UK policy makers and at scientific meetings or conferences and published in scientific medical journals. This may not happen until one or two years after the study is completed. A copy of the results will be made available to you after the study. Your child will not be identified in any report or publication.

The de-identified data from this study will be shared with the collaborating partners who are organising and funding this research work. Data from this study may be used to file patents, licence vaccines or make profits in other ways. You will not be paid for any part of this. Data from this study may be used as part of a student post-graduate degree, for example an MD or PhD.

29. What happens when the study finishes?

Once all participants in the study have completed their visits, we will start the analysis and interpretation of the findings. Once complete, we will publish these results, and provide you with a link to the published paper on the Oxford Vaccine Group website. None of the reports will contain any information that might allow the readers to identify anyone who took part in the study. In addition to the published paper, we will also provide you with a summary of the key findings of the study.

30. Taking part in future vaccine-related research

With your consent, we would like to keep your contact details after your child's participation in this study is complete, so we may inform you of opportunities to participate in future vaccine related research. This is entirely optional and your participation in this study will not be affected by your decision to allow or not allow storage of your contact details at the end of this study. Being contacted does not oblige you to agree to take part in future research. Your details will be stored electronically on a secure server to which only authorised individuals at the Oxford Vaccine Group will have access. You can ask us to remove your contact details from our database at any time.

We will not, under any circumstances, share your contact details with any third-party institutions without your permission.

31. Who has approved the study?

This study has been approved by the NHS Research Ethics Service (RES) – Berkshire Research Ethics Committee. The Medicines and Healthcare products Regulatory Agency (MHRA), which regulates the use of all medicines in the UK, has reviewed the study design and has granted permission for use of any unlicensed vaccines in this clinical study.

32. Further information and contact details

We hope this information sheet has answered all of your questions. If you would like further information about participating in research, please visit the following website: http://www.nhs.uk/conditions/Clinical-trials/Pages/Introduction.aspx.

For independent advice about participating in this trial, you may wish to contact your GP.

If you would like to speak to one of our team members to discuss any aspect of this study, or **if you are interested in taking part, please contact us**:

COMCOV3.HCRW@wales.nhs.uk
Or
02921 847816

APPENDIX

HOW TAKING PART IN THE STUDY MAY AFFECT YOUR CHILD'S TRAVEL ARRANGEMENTS

For foreign travel, many countries require evidence of approved COVID-19 vaccination before allowing travellers into their country. Vaccination status can also make a difference to the requirements to quarantine in a foreign country on arrival. The vaccinations considered acceptable for these purposes vary between countries, as does the lower age limit applied. For example, some countries require adolescents to have received a COVID-19 vaccine, whereas others do not. Current requirements may change in future.

Please note that all participants in **Cohort B** will have already received two standard doses of an approved vaccine before being enrolled in the study. They would not be disadvantaged regarding travel arrangements compared with their peers unless a routine third vaccine were to be recommended which was different from the vaccine they are given in the study, and only then if the countries they are travelling to/from do not accept that vaccine.

COVID-19 vaccinations given during the study will be recorded on the participant's NHS record once the participant is informed of the vaccine they have received, not at the time of vaccination. For participants 12 years old and over, the vaccination will appear on their NHS COVID-19 Travel pass (often called the "vaccination passport") within a few days of being recorded on their NHS record. Prior to being informed of the vaccine they have received, a participant will not usually be able to use their trial vaccination as a qualifying vaccination for travel purposes.

International travel requirements, as specified by the UK and independently by foreign countries, can change at very short notice, and this is outside of the control of the research team.

If as a result of participation in this study, participants are required to take additional COVID-19 testing prior to travel, then consideration will be given to reimbursement of the cost of this testing (reimbursement up to £200 per participant on provision of receipt up to the time of final study visits).