Does temporarily suspending (stopping) methotrexate treatment for two weeks enhance response to COVID-19 vaccine booster - The VROOM Study (Vaccine Response On/Off Methotrexate)

PARTICIPANT INFORMATION SHEET

Version 3.0, 09Sep2021

We would like to invite you to take part in a research study.

Invitation to join the VROOM study

Before you decide whether to take part or not, it is important that you understand why we are doing this study and what it will involve.

Please take time to read the following information and talk to others about the study. If anything is unclear, or if you would like more information, please ask a member of the study team who will be happy to answer any questions.

What is the purpose of this study?

You may already know that methotrexate is used to treat inflammatory conditions such as rheumatoid arthritis and psoriasis. It often controls the condition, but it may also reduce the body's ability to fight infections. People who take methotrexate are known to have weaker responses to vaccines against the seasonal flu and pneumonia that those not on methotrexate.

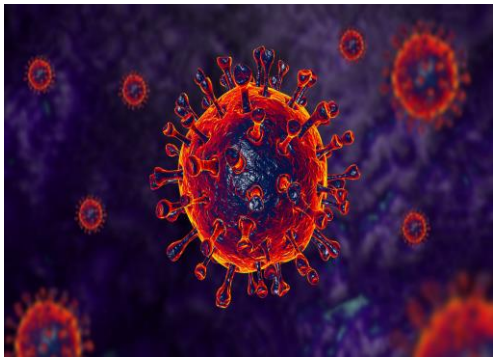
A recent study in Korea showed that a two week break in taking methotrexate after the flu vaccine increased the body's immune response to it. However, it is not known if such an interruption in methotrexate treatment would improve the protection provided by vaccines against COVID-19. Because there is no clear evidence on whether to temporarily stop methotrexate around the time of COVID-19 vaccinations, specialists across the world have given conflicting advice. The VROOM study aims to find out if we should stop or continue methotrexate around the time of COVID-19 booster vaccine. By booster vaccine we mean any COVID-19 vaccine given after the first two-doses e.g. a third or subsequent dose, regardless of whether it is called a booster or not.

If it does give more protection we also need to understand if there is a possible downside to temporarily stopping methotrexate, in the control of your disease. Potentially it could mean you get an increase in symptoms disease activity, which people often call flares. If the benefit of stopping is very small – is it better to continue taking your methotrexate as normal to prevent having issues with the control of your disease?

We have been funded by the UK Government organisation called the National Institute for Health Research (NIHR) to investigate if continuing or temporarily stopping methotrexate just after a COVID-19 booster vaccination results in a difference in the level of protection seen in the blood from the COVID-19 booster vaccine. By booster vaccine we mean any COVID-19 vaccine given after the first two-doses e.g. a third or subsequent dose, regardless of whether it is called a booster or not.

Interrupting methotrexate treatment for 2 weeks may increase the risk of disease flare up in some people. In this study we will also find out more about if there is any difference in the disease control between those that temporarily suspend treatment with methotrexate for two weeks or continue it as usual. People who develop a flare-up in the study will be allowed rescue treatment e.g. with steroids, anti-inflammatory medicines and creams as required.

Those who agree to take part in the VROOM study would be assigned to continue taking methotrexate as usual, or to skip methotrexate treatment for two weeks after the COVID-19 booster vaccination. The decision on who is advised to interrupt treatment and who is advised to continue treatment will be made by a computer programme and is similar to rolling a dice (this is called randomisation).



Note: *You should only stop taking medications prescribed by a doctor after talking to them – if you are suitable for this study and decide to take part in this study – you would only be entered if your hospital medical team have no objections to you temporarily stopping taking your methotrexate for two weeks. This invitation is being sent to you by your usual care team at your local hospital and they have assessed your condition to be suitable for a temporary interruption in methotrexate treatment. However, please do contact your usual care team if you would like to discuss this further.*

Who is taking part and why have I been invited to take part?

We hope to enrol 560 adults aged 18 years or older who have inflammatory conditions such as rheumatoid arthritis, psoriasis and psoriatic arthritis into this study. We will recruit from at least 20 NHS hospitals or centres providing NHS care.

You have been given this information sheet, and are invited to consider taking part in the VROOM study, because you are an adult aged 18 years or older, have an inflammatory condition that is treated with methotrexate either as tablets or by an injection for at-least 3 months. Those who take part also need to have received the first two COVID-19 vaccinations.

Do I have to take part in this study?

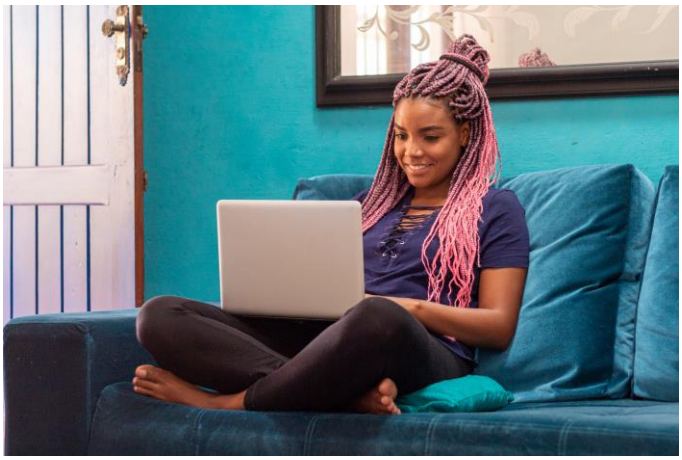
You are under no obligation to take part in the study. Deciding not to take part will not affect the treatment or care you receive from your medical team. It is up to you to decide whether or not to take part. Please keep this leaflet and use it to help you make your decision. If you decide to take part, you will be asked to sign a consent form to give your written permission. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

If you choose not to join the VROOM study, you will receive your standard routine NHS care, as you have already been receiving by your local treating team of healthcare professionals, in accordance with standard NHS guidelines.

What will happen to me if I take part?

Whether you decide to take part in the VROOM study or not – the timing of your booster appointment will not be affected. The NHS is centrally running the COVID-19 booster programme and the VROOM study has no effect on who, where and with which COVID-19 booster any individual is offered.

If you are happy to take part in this study, we would ask you to follow the link in the letter that came with this leaflet. This electronic link would take you to a secure page dedicated for the VROOM study.



Here you would be asked a couple of simple questions about your medical history to see if you might be suitable to take part in this study. If you are then you would be asked to give your name, address, date of birth, email address (if you have one), mobile phone (if you have one), home phone number (if you have one) and your GP surgery details, and Alternatively there is a paper form that you can complete asking for the same information that you could post in a FREEPOST envelope to the team organising the study at Oxford University, or you could call the study team directly on the number in the letter where a researcher will ask you the same simple questions about your medical history and ask for the above details from you to see if you might be able to take part in the study. Whichever method you choose to use if you decide you might be interested in taking part this should take no more than 10 minutes of your time.

If based on your answers the study team think that you may be suitable to take part in the VROOM study the study database or team (depending on how you have made contact with the study team) will let you know. If you may be suitable, we will contact the hospital that gave you this leaflet to let them know you are interested in taking part in the VROOM study.

You would then receive a call from a person at that hospital who is working on the VROOM study to arrange for you to come into the hospital at a convenient time for you and the researchers. This visit must be before you receive your COVID-19 booster vaccination. By booster vaccine we mean any COVID-19 vaccine given after the first two-doses e.g. a third or subsequent dose, regardless of whether it is called a booster or not.

At the hospital your suitability for the study will be checked again and if the hospital team are happy that you are suitable to participate in the VROOM study you will be asked to give your consent (permission) for this. The consent form you will asked to sign will be an electronic form on a tablet computer. A member of the VROOM team at your hospital will also sign it and then a copy of the form will be emailed to you or someone of your choosing. Paper consent forms will also be available if you would prefer to sign with a pen.

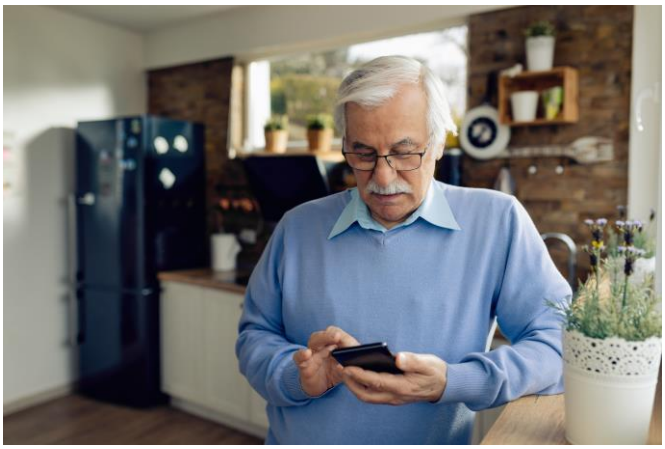
You will then be asked some questions about your condition, ask for your height and weight, take a short medical history, lifestyle factors, the dates of your previous COVID-19 vaccinations, if you had COVID-19 in the past and how you rate your general health in a very short questionnaire. These questions should take you no more than 10 minutes to answer. A member of the local study team would also look through your medical notes to record values of some blood-tests that are routinely checked for people with inflammatory conditions.

A small blood sample would then need to be taken to collect 7ml of blood – this is the equivalent of just over a teaspoonful. The blood would be sent to the University of Nottingham where scientists would separate it into tubes to be sent to laboratories in the UK to look at the levels of something called COVID-19 RBD (receptor binding domain) in your blood. High levels of RBD in your blood is a good thing as it shows you have protection against COVID-19 as it allows your body to produce antibodies to try to kill off any COVID-19 that comes into contact with your body's immune system. These tests will be undertaken at a Government laboratory managed by Public Health England.

Also 100 of the 560 participants who agree to take part will be chosen to see how much methotrexate is in your blood. These tests will be undertaken in a NHS Hospital laboratory in Manchester. The same 100 participants will also have their blood tested for something called COVID-19 neutralising antibodies. These tests will be undertaken in a university laboratory in London. Anyone who receives your samples to test will not be given your details so they could not identify you from them.

Whether you have one thing tested from your blood sample, or all 3 tests the same amount of blood would be taken from you (7mls – approximately the equivalent of just over one teaspoonful).

Waiting for your Booster Vaccination (COVID-19 vaccine given after first two-doses e.g. a third or later dose) Appointment:



If you agree, we will then send you a weekly text after your consent asking if you have yet received a date for your booster vaccination. (For those who don't agree to this you can opt to have a weekly phone call, or choose to contact the VROOM study team yourself when you have a booster vaccination date).

When you have a date for your booster vaccination appointment we ask that you let the VROOM study team at Oxford University know either through the study dedicated electronic pages or via a telephone call to the office team. The study team/study database will then ask you a few brief questions and provided you are willing to continue with the study, advise you to either:

- Continue to take your methotrexate as you currently do, or
- Temporarily stop taking your methotrexate for 2 weeks immediately after you receive your COVID booster vaccination.

You will be told which group you have been assigned to. You will have an equal chance of being allocated to either group.

A letter will then also be sent to your GP to let that know of your taking part in the VROOM study and which group you have been assigned to.

After your Booster Vaccination (COVID-19 vaccine given after first two-doses e.g. a third or later dose) Appointment:

After your booster, depending on your preferences we would then send you up to 6 text messages in the 2 weeks around your booster vaccination to remind you which group you were put into and to find out how you are and what methotrexate you have taken over the 2 weeks. (If you don't want to be texted, then a member of the study team could call you, or send you short emails).

The hospital where you gave your consent and first sample will then be contacted by the VROOM study team when you let us know your booster vaccination date. The hospital will then arrange with you a convenient date and time for you to return to the hospital to give another blood sample (approximately 7mls – just over a teaspoonful) and answer some questions at approximately 4 and 12 weeks after your booster vaccination including the same questionnaires/questions you had at your first visit about how you feel, whether your inflammatory condition is currently under control and how you would rate your general health in a very short questionnaire. We would also ask you for information about your COVID-19 booster vaccination, how you have been taking your methotrexate since your booster, and any disease flare ups and how you dealt with them.

To save time at your 4 and 12 week visits – if you have provided an email address and agree to receive the short questionnaires ahead of your visit these can be sent to you to answer in advance of your hospital visit by email or post. These questions should take you no more than 10 minutes to answer. If not when you come back to the hospital the questionnaire would be given to you to fill in and a small blood sample (7ml – the equivalent of just over a teaspoonful). We anticipate that each of these visits should take approximately 20 minutes. This would then end your participation in the study.

If your booster gets changed or delayed for any reason – the visits can be rearranged so that they are still approximately 4 and 12 weeks after your booster vaccination. Should this happen you just need to let the study team at the University of Oxford know.

You should not be out of pocket for taking part in this study, therefore reasonable travel expenses can be claimed from the study team for going to hospital for the 3 study visits and at the end of the study you will receive a small token of appreciation from the study team. At the moment the levels of what is being looked at in blood in this study (anti-RBD antibody) and the level of protection (immunity) from COVID-19 is not fully understood. At the end of the study, we will send you a copy of the results of the study if you wish and also what the results were of any of the blood tests that we conducted on your samples. There will also be a letter to explain what the results might mean and what the range of the results were in those taking part so you could see how your results compared to others taking part in the study. The levels of your antibodies are only part of the protection your body will use against COVID-19 and specifically measured for this study. The results are provided for your interest only and should not be used to make any decisions about your healthcare. You will get your samples results but other than what the ranges of other people taking part samples were – no-one will be identified to you or anyone else outside the VROOM study teams. If, for any reason, you do not have this study visit before your vaccine booster it will not be possible for you to be part of the study. It will not be possible to delete the information we have collected from you so far.

What are the benefits and risks of taking part in the study?

We hope that the valuable information from this study will give the NHS and other countries a clear answer to the question of "Whether temporarily stopping methotrexate for 2 weeks around the time of COVID-19 booster vaccination improves the vaccine response. We cannot promise that the study will help you directly, but the information we receive has the potential to benefit all those with inflammatory conditions who continue to be vaccinated against COVID-19 in the future. Thus, the results of this study may benefit you in the future.

There is a small risk of your condition flaring up on interrupting methotrexate treatment for two weeks. However, you will be able to access treatment for flare-up as usual.

People sometimes feel uncomfortable answering certain questions about their health, or may feel unable to answer certain questions. If you feel uncomfortable at any point, then you do not have to answer the questions.

Who will know that I am taking part?

VROOM research team and the healthcare professionals involved in your care. However, you can tell anyone that you would like to that you are taking part. The only people who will have access to information that identifies you will be people who need to contact you to about the study, or review your hospital record, or the central study team at who will let your GP know if you agree to take part in the study. This may include staff from the University of Oxford running the study on a day to day basis, the University of Nottingham who are in charge of the study, the NHS Trust or those delivering NHS care to you at non-NHS sites where you have your study appointments, and a specialist group of research nurses employed by a national research support organisation called the Clinical Research Network. The people who analyse the information will not be able to identify you, and will not be able to find out your name or contact details. Paperwork that is completed by the research team, or the treating clinical team, will be uploaded onto an electronic database managed by the University of Oxford.

We will contact your GP (family doctor) to tell them that you have agreed to take part in the VROOM study, and which group you were allocated to. However, we will not share any of your study questionnaire answers with them.

Will my details be kept confidential and what happens to my data?

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you and your medical records during the course of the research. This information will be kept **strictly confidential**, stored in a secure protected database at the University of Oxford. Under UK Data Protection laws the University of Nottingham is the Data Controller (legally responsible for the data security, although until the study finishes the data will also be controlled by the University of Oxford) and the Chief Investigator of this study (Professor Abhishek Abhishek) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information and to read our privacy notice at: https://www.nottingham.ac.uk/utilities/privacy.aspx

The data collected for the study will be looked at and stored by authorised persons from the Universities of Nottingham and Oxford who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being

carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

Where possible information about you which leaves the hospital (care centre) you were recruited at will have your name and address removed and a unique code will be used so that you cannot be recognised from it, however sometimes we need to ensure that we can recognise you to link the research data with your medical records so in these instances we will need to know your name and date of birth. We will also need this information to contact your GP to let them know if you have agreed to take part in the VROOM study. By signing the consent form you agree to the above.

Your contact information that you give in registering your interest will be kept by the University of Oxford for 12 months after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted) if you go on to be randomised. If you register your interest in the study but do not go on to be randomised for whatever reason – when randomisation closes your information will be deleted. This information will be kept separately from the research data collected and only those who need to will have access to it. All other data (research data) will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

What will happen if I don't want to carry on with the study?

You are free to withdraw from taking part in the study at any time without giving a reason. Please remember, it is your decision to take part. If you agree to take part now, but you change your mind during the study, this will not change the standard of care you receive from the NHS. If you were to decide to stop taking part in the study at any time, any data and samples collected on you would be kept. You would not be contacted about the study again or have any further data collected. If you lose consent capacity (i.e you become seriously unwell) during the study, we will keep the data and samples already taken by the study team, and we would stop contacting you with any questionnaires.

What happens at the end of the study?

We will share the results of this study with healthcare researchers and professionals to improve the care of patients who take methotrexate. Also, we will present the results in research reports and at scientific conferences, and publish them in scientific journals. The study results will also be publicly available at www.vroom-study.co.uk at the end of the study.

If you would like a copy of the results, please let us know this on your consent form. We will also be happy to share the results of any tests that are undertaken on your blood samples as part of the VROOM study, and what the results were in the different groups in the study with an explanation letter of what the results mean. Please let us know on the consent form if you would like to receive these results. *Any tests on your blood may not necessarily be undertaken straightaway – so any results from your tests would only be sent to you at the end of the study.*

We will not include any data that could identify you in the results. If any of the funders of this research ask us to make the study data available for other researchers or to themselves, we will first anonymise your information (i.e. we will take your name and other identifying details out) so that you cannot be identified.

What will happen to any samples I give?

We would also like to seek your consent so that any remaining samples may be stored and used in possible future research – this is optional (please indicate if you agree to this on the consent form). The samples will be stored with a code unique to you and securely at the University of Nottingham under the University's Human Tissue Research Licence (no 12265). Some of these future studies may be carried out by researchers other than current team of Professor Abhishek Abhishek, who ran the first study, including researchers working for commercial companies. Any samples or data used will be anonymised, and you will not be identified in anyway. If you do not agree to this any remaining samples will be disposed of in accordance with the Human Tissue Authority's codes of practice.

There will be no genetic tests undertaken on your samples.

Who is organising and funding the research?

The University of Nottingham is organising this study. It is being conducted by a research team led by Professor Abhishek Abhishek, a Consultant Rheumatologist, and Professor Rosemary Boynton, a leading scientist in infection. The study is also being supported by a nationally accredited Clinical Trial Unit called the Oxford Clinical Trials Research Unit (OCTRU), based at the University of Oxford. The study has been funded by the National Institute for Health Research.

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Who has approved this study?

A panel of independent researchers and patient representatives, as well as a Research Ethics Committee have reviewed and approved this study. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by Yorkshire & The Humber - Leeds West Research Ethics Committee. The study reference is IRAS: 303827.

What if I have concerns?

If you have any concerns or complaints about any aspect of the study, please contact the VROOM research team using the details below.

If you would prefer to speak with someone who is not involved in the study, then please contact your local Patient Advice and Liaison Service (PALS). PALS is a confidential NHS service that can provide you with support for any complaints or queries you have regarding the care you receive as an NHS patient. However, PALS cannot provide information about this research study.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Nottingham but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

If you have any questions about the study, please contact the VROOM team on:
Email: VROOM@ndorms.ox.ac.uk Telephone: 0808 196 2101

Thank you for reading this information leaflet and considering taking part.