A randomized, double-blind, placebo-controlled trial evaluating the influence of a concentrated foods pill and a probiotic pill on clinical outcomes among individuals with covid-19 viral infection

Information for patients and GP's

You have been invited to take part in a clinical trial by the doctors and the research team at Bedford Hospital. Before agreeing to take part, you should know exactly what taking part will mean to you, and what you are required to do. This Patient Information Leaflet supports the verbal explanation given to you by your doctor and research nurse or practitioner. This trial has been approved by the National Research Ethics Committee (Sheffield Committee) and has been sponsored by Bedford Hospital NHS Trust.

Why have I been invited to take part in this study? You have been asked to consider participating in this clinical trial because you have attended the A&E Department or designated Covid-19 pod at the Hospital after displaying symptoms of the coronavirus; and new continuous cough and a high temperature.

What is the study trying to find out? This study is trying to find out if a whole-food supplement, rich in natural plant-based chemicals (phytochemicals), could shorten recovery time and reduce complications from a likely Covid-19 (Corona virus) infection. It is also trying to find out whether it could reduce the chance of those who live in the same house as you from developing similar symptoms. The best way of finding out if the whole-food supplement is making a difference, is to do a randomized trial of the food supplement verses a placebo or dummy supplement. This will be discussed in more detail later on in this leaflet, but in this study you will have a 50% chance of being randomly selected to receive the food supplement capsule, over receiving a placebo or dummy supplement. Then a further 50% chance of receiving an additional probiotic capsule or not. We are aiming to recruit 132 patients into this trial.

Why is this study important? Management of the symptoms of Covid-19 are currently supportive until anti-viral medicines and preventive vaccines are developed. Most patients with the disease recover fully, but about 20% require hospital treatments and 10% require intensive care. Effective treatments for Covid-19 infection are in development but will take some time. We do not know whether dietary factors increase the risk of catching the virus but it is known that people with pre-existing health conditions or who are overweight are more vulnerable to the complications of infection. One possible explanation for this is a pre-existing gut bacterial flora could adversely affect immunity.

What if I do not agree to take part? Participation in this study is entirely voluntary. Agreeing, or not agreeing, to enter this study does not change in any way the other treatments that you will receive connected to your disease. If you do agree to participate, but later decide to withdraw from the trial at any stage, this would also not in any way influence future treatment decisions. We will also ask you if we can inform your GP you have entered this study. A doctor or nurse may need to access your hospital medical notes, especially if you are admitted to hospital.

Giving consent to take part in this clinical trial. Attached to this Patient Information Leaflet is a consent form. Because Covid-19 is highly infectious, if after you have read this leaflet and had the opportunity to discuss it with your family and / or a member of the research team, you wish to participate, you will be able to give your consent to a member of the research team over the telephone. We will also ask you if

we can inform your GP you have entered this study. We will ask you to sign and date the attached Consent Form at the same time, and return it in the pre-paid envelope.

However, we would ask that **you do not post it until you have been advised that you can end your self-isolation**. We will also ask you if we can inform your GP you have entered this study.

What will you have to do if you enter the study? If you agree to take part in the study, you will be asked some baseline questions about your current symptoms, past medical history, medication, diet, smoking habits and exercise levels (attached with this leaflet). Provided you are eligible, you will be randomised to receive 4-weeks supply of *either* the study food supplement *or* placebo, and you will be asked to take either one capsule, two times a day on its own are the same with a probiotic capsule. You will be sent the capsules with clear instructions how and when to take them. You will also be asked to record only **your** temperature every day, using the thermometer provided.

A member of the trials team will contact you three times a week (at dates and times convenient for you) to ask you:

- to give **your** daily temperature reading
- to score your cough according to the Cough Symptom Score (attached to this leaflet)
- to score how you have been feeling using the Subjective Well-Being (SWB) (attached to this leaflet)
- Have developed any other symptoms
- Had any change in medication, other treatments or visits to the hospital

What is randomisation? This means that it is down to chance whether you receive the food supplement or placebo. After consent, a member of the trials team will open an envelope (numbered consecutively), and within each envelope is a card stating 'capsule A' or 'capsule B', and this is the capsule that you will receive, which will be sent to you in the post. Neither you nor the research team will know whether capsule A or capsule B is the supplement or placebo, as both the capsules and the packaging, will look the same. You will have a 50% chance of receiving the food supplement, and a 50% chance of receiving the placebo (called 1:1 randomisation). On top of this there will be a 50% chance of also taking the probiotic pill.

About the capsules? The cylindrical capsule measures 21.4mm long, and is best taken with a drink. It can be taken with or without food. If you find it difficult to swallow the capsule whole, it can be opened up and added to food. The supplement and placebo have been produced by a fully licensed UK manufacturer who has fulfilled all necessary EU and UK regulations for nutritional and food products The capsule, given randomly to two thirds of the participants, will contain the dried food extracts of a citrus fruit, turmeric, Aloe Vera, pomegranate and chamomile. The other third of participants will receive a capsule which looks the same as the food supplement, but is actually a simple bulking agents thought to have no significant activity. This is known as a placebo. Neither you nor the research team will know which you have been randomised to. The probiotic pill contains a bacteria commonly found in foods called lactobacillus.

How long will the trial last? If you agree to take part in the study, you will be asked to take the pills for 4 weeks, from the date that you receive them. You will be contacted by a member of the research team three times a week, for up to 4 weeks, or until you have fully recovered from your Covid-19 symptoms. You can, of course, withdraw from the study whenever you wish.

Will you have to change your diet? No, you will not have to change your diet and you are completely free to choose whatever you wish to eat and drink, as are the people who live with you.

Possible side effects. Based on information from previous trials of these ingredients, the chance of side effects is small. About 8% experienced some mild flatulence (wind) or loose stools. Any possible side effects will be recorded in trials forms during your telephone consultations, but if in the meantime you get a symptom which began *after* you started taking the capsules, please feel free to contact the research team on 01234 795 787.

Possible interaction with other drugs. No person in a trial involving a similar supplement had any adverse effect on the blood pressure (if on anti-blood pressure medication), or INR (if on warfarin). People on warfarin are not excluded from this 4 week intervention.

All the information collected during the study be confidential? All the information you provide will be known only to the research team. Any trial results which are published in medical journals or at conference, will not identify you or any other individuals. We will make sure no-one can work out who you are from the reports we write. If you consent to take part in this study, your records will be kept within the research unit at The Primrose Unit for 10 years. All data collected during the study will be processed and stored in accordance with the guidelines set out in the Data Protection Act 2018 and the Good Clinical Practice (CGP) guidelines. Your GP will be informed of your participation in the study, unless you request otherwise on the consent form.

What are your choices about how your information is used?
You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- Via our leaflet available from The Hospital's information governance officer (Daniel Smith 01234 3551222 ex. 5082, email daniel.smith@bedfordhospital.nhs.uk
- by asking the head of the research team Madeleine Williams either by ringing us on 01234 795 787 or emailing madeleine. williams@bedfordhospital.nhs.uk or

Who is funding this study? This study is funded by the Primrose Unit Fund (folio account. 013096), which is part of Bedford Hospital Charitable Funds', registered charity number 1061003. The research team involved in the study are not being paid to recruit you into the study. There are no copyright or patents issued on any of the investigational products and the anonymised results of the study will be published the public domain.

Regulation and design: This trial has been approved by the Bedford Hospital NHS Trust Research and Development Department and the National Research Ethics Committee (number 282517). It has been registered on the international register (Eudract number 2020-001532-10Integrated Research Application Number System number 282517). The study will be independently audited by an external agency to ensure accuracy and probity.

What if you have any further queries about this trial? Please contact Madeleine Williams, Professor Thomas' Research Manager, on 01234 795 787.

Additional concerns. If you have any additional comments or concerns about this study, you may discuss these with the investigator. If you wish to go further and complain about any aspect of the way in which you have been approached or treated during the study, you should contact the Bedford

Hospital Patient Advice and Liaison Service Lead, Jessica Toraman, on 01234 355122 ext. 4624. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence you may have grounds for legal action for compensation against Bedford Hospital Trust but you may have to pay for legal costs. The National Health service complaints mechanisms will still be available to you.

The research team thank you for taking time to read this information sheet and for considering participating in this new research study.

Professor Robert Thomas MRCP MD FRCR
Consultant Oncologist Bedford and Addenbrookes
Hospital Visiting Professor University of Bedfordshire

Cough Symptom Score

DAYTIME COUGH

0 No cough during the day

1 Symptom for one short period

2 Cough for more than two short periods

3 Frequent coughing, which did not interfere with usual daytime activities

4 Frequent coughing, which did interfere with usual daytime activities

5 Distressing coughs most of the day

NIGHT TIME COUGH

0 No cough during the night

1 Cough on waking only

2 Wake once or early due to cough

3 Frequent waking due to choughs

4 Frequent coughs most of the night

5 Distressing coughs preventing any sleep

Subjective Well-Being (SWB)

Overall, how satisfied are you with your life nowadays?

0 1 2 3 4 5 6 7 8 9 10

Not at all **Completely**

Overall, to what extent do you feel that the things you do in your life are worthwhile?

0 1 2 3 4 5 6 7 8 9 10

Not at all **Completely**

Overall, how happy did you feel yesterday?

0 1 2 3 4 5 6 7 8 9 10

Not at all **Completely**

Overall, how anxious did you feel yesterday?

0 1 2 3 4 5 6 7 8 9 10

Not at all **Completely**