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Participant Information Sheet/Consent Form (Enrol)

Interventional Study - Adult providing own consent to enrol

| | |
|-------------------------------------|---|
| Title | High-dose Zinc as Adjunctive therapy in COVID positive Critically Ill Patients: A Pilot Randomized Controlled Trial |
| Short Title | ZINC COVID |
| Protocol Number | Version 3, 4th April 2020 |
| Local Principal Investigator | Associate Professor Joseph Ischia |
| Associate Investigator(s) | Dr Oneel Patel, Professor Rinaldo Bellomo, Dr Daryl Jones, Professor Damien Bolton, Dr Glenn Eastwood, Prof Paul Johnson, Prof Christine McDonald |
| Location | Austin Hospital |

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have been admitted to the Austin hospital with severe coronavirus infection. During your hospital stay, you may be at high risk of developing difficulty with your breathing and getting enough oxygen. Soon, you may need a machine to help you breath (mechanical ventilation). Currently, there are no standard drugs for preventing the respiratory failure associated with COVID-19 infection. It is possible that zinc may be useful in reducing the severity of the coronavirus infection. However, we really do not know if it is beneficial or not and therefore we are performing this trial.

This Participant Information and Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part. You are also eligible for new treatments that may arise or other studies that may be suitable for you during your stay.

If you decide you want to take part in the research project, you will be asked to sign this consent form. By signing the consent section, you are telling us that you:

- Understand what you have read
- Consent to take part in the research project



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- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

A pandemic of a novel coronavirus (COVID-19 or 2019-CoV) infection has posed significant threats to international health and the economy. In the absence of any vaccine for this virus, there is an urgent need to find a treatment that can stop the growth of the virus in the body and the complications it can cause.

In more severe cases, coronavirus enters the lungs. As the virus multiplies, it can cause problems with your breathing like bronchitis and pneumonia. Development of pneumonia leads to a reduced ability of the lungs to absorb oxygen. In a small number of severe cases, COVID-19 infections lead to the development of respiratory failure and acute respiratory distress syndrome (ARDS). Respiratory failure and ARDS are medical terms that define a condition where one can find it increasingly difficult to breathe. In such cases, the patient requires a ventilator which helps them to breathe and maintains oxygen levels in the blood. However, if lungs are damaged beyond a certain level and not enough oxygen is provided to the rest of the body, respiratory failure could lead to failure of other major organs, including the liver, kidney and brain.

Zinc is an essential nutrient which performs various vital functions in the body. Zinc is essential for the maintenance and development of the immune system, which helps fight infections. Zinc is required for wound healing and tissue repair. Zinc protects organs against injury instigated by reduced oxygen supply. Zinc has also been shown to protect against pneumonia.

Numerous research studies have shown the potential of zinc to prevent the growth of a number of other viruses (such as those that cause the common cold) that are similar to coronavirus that causes the COVID-19 illness. Furthermore, intravenous zinc has been shown to protect various organs, including the heart, kidneys and liver against the damage caused by the reduced availability of oxygen.

The amount of zinc that we plan to give is thought to be very safe with minimal side effects. This is based on earlier studies where humans with severe burns were injected with nearly double the amount of zinc that we plan to give, and it did not produce any side effects. Furthermore, in a recent study critically ill children were given a 3-times higher amount of zinc compared to what we plan to give in the current study. Again, it did not produce any adverse effects. Based on these human studies, we are confident that the dose of zinc that we plan to use in this study is very safe and well-tolerated.

In summary, we really do not know if zinc is beneficial in people infected with the coronavirus. Therefore, the goal of this study is to test if zinc given as a daily intravenous injection through your drip in participants with coronavirus infection can reduce the severity of the disease and improve patient outcomes. A positive result of our proposed study will have an enormous impact on the health outcomes of patients who have developed coronavirus infections for which there are currently no treatments.

This research has been initiated by the study doctor, Associate Professor Joseph Ischia.

3 What does participation in this research involve?





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If you agree to participate in this study, you will be asked to sign the Participant Consent Form.

This study will be conducted over the time you are admitted to the Austin Hospital in the ward or in the intensive care unit.

In the ward or in the intensive care unit

You are participating in a randomized controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try and make sure the groups are the same; each participant is put into a group by chance (random).

While you are admitted to the Austin hospital, you will be randomly assigned (like tossing a coin) to receive intravenous zinc or placebo. **A placebo is a medication with no active ingredients. It looks like the real thing but is not.** This means that you will have an equal (50/50) chance of receiving either zinc or placebo. Neither the doctor nor you can decide which treatment you receive.

This trial is a 'double-blind trial'. This means that following randomization, your treating doctors and other staff caring for you in the hospital and intensive care unit will not know which intravenous medicine is being given. The zinc chloride is a colourless fluid in the 250ml saline bag. Therefore, it will be impossible to tell which treatment you are receiving.

After you have been enrolled and randomized, the treating doctor will prescribe the amount (dose and frequency) of the study treatment, as they usually do for either of the study medicines: zinc chloride 0.5 mg/kg or Placebo (normal saline) administered daily around 9 am, but it is safe to give the treatment starting anywhere between 8 am to 12 pm. You will receive the zinc chloride through an exclusive lumen of the central venous catheter or peripheral catheter inserted in your vein, which is part of the standard of care. You will receive the treatment (with zinc or placebo) for 7 days, and then the treatments will stop. The treatment will be given in a 250ml bag of saline solution which will contain zinc chloride or placebo (i.e. not have zinc in it). The saline bag will be given over about a 3-6 hour period depending on what your treating doctors think is best for you.

Apart from this once daily drip, you will receive the usual medical and nursing care by the ward team or intensive care unit team. This study does involve the collection of blood samples (approximately 5-15 ml, size of a tablespoon each time). These will be collected daily as per your usual care. Some of this blood will be sent to Prof Jose Villadangos at the University of Melbourne, Parkville, Melbourne for analysis of inflammatory markers. After analysis, these samples will be destroyed as per normal Melbourne University blood product disposal protocols.

Your general hospital care will not be affected in any way by the study.

There will be no formal follow-up, but we will collect data on how you recover from the infection for the time you are in the hospital recovering for up to 28 days. We request access to your medical record to collect research related data such as blood pressure, heart rate changes and the dates you are discharged from the intensive care unit and from the hospital.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.





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4 What do I have to do?

Your involvement in this study will not have any effect on the standard of care you receive. There will be no restriction on your daily activities, or will there be any dietary restrictions. You can take your regular medication; however, we will take a note of the name of the medicine and the amount you take.

5 Other relevant information about the research project

This study will involve only those participants who are admitted to Austin Hospital. For this study, we will seek the participation of 160 people. Eighty will be randomly assigned (like tossing a coin) to receive intravenous zinc, and another 80 will receive a placebo. This project involves researchers from Austin Hospital, University of Melbourne and Monash University.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this participant Information and Consent Form to sign, and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the Austin Hospital.

7 What are the alternatives to participation?

If you decide not to participate in this study, you will continue to receive standard care, and your treatment will be unaffected by your decision not to participate.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research. This study aims to further medical knowledge and improve the understanding of whether zinc is beneficial in critically ill patients suffering from COVID-19 infection.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects or are worried about them, talk with your study doctor. Your study doctors will also be looking out for the side effects.

Choosing to take part in this study should not pose any additional risk to you above the risks associated with your usual treatment in the hospital. Zinc is an accepted treatment for nutritional deficiency states. Although this medicine has been given to many patients over many years and is in regular current use, there may be additional unforeseen or unknown risks.

Uncommon side effects include:

The ZINC COVID Study

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- Mild and short-lasting - Nausea and vomiting, stomach pain and diarrhoea, flu-like symptoms: fever, chills, cough, headache, a decrease in the good cholesterol (HDL) levels in your blood which is thought to be the protective cholesterol against heart disease, changes in taste perceptions (metallic taste), copper deficiency, mental confusion (**less than 5%**)
- Severe and possibly permanent- acute kidney injury and possible chronic kidney disease or need for dialysis or renal transplant (**unknown or thought to be very low- less than 1%**)

As you will be in the hospital when the study medication is given, you will be closely monitored and treated immediately if any effects were to occur.

If at any point during the study, your study doctor feels it is in your best interests not to continue receiving the study medicine; or if during the study, there is evidence to suggest beyond a reasonable doubt that the study medicine is not beneficial then your involvement in the study may be stopped.

10 What will happen to my test samples?

Some of the blood samples that you provide will be transferred to Austin Pathology for routine analysis for your standard care. Some of the blood will be sent for analysis at a laboratory that measures the levels of zinc and other metals to see if treating with zinc causes major changes in these metals. After these tests, any remaining blood samples will be destroyed.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If during the course of the study, a superior treatment becomes available for COVID-19, you have the right to withdraw from the study. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you choose to continue in the research project, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you are able to take all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

13 What if I withdraw from this research project?



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If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with the law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.



14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment is shown not to be effective
- The treatment is shown to work or not need further testing
- Decisions made by local regulatory/health authorities.
- A superior treatment for COVID-19 is discovered.

15 What happens when the research project ends?

After recruiting the planned 160 participants and following up for 28 days, the study will be closed, and the analysis of results will begin. The results will be reviewed by the study team and a statistician to determine if zinc chloride improves outcomes in patients with COVID-19 infection. We will then publish these results in research papers for the medical and global community. No follow-up is required of the study participants.

Zinc chloride is intended as a treatment for COVID-19. Therefore, once the participants have recovered or discharged from the hospital there is no need to take Zinc chloride, and it will not be available to participants.

You are welcome to receive information about the results of the study after they have been analysed and made public. Please provide a written request to the clinical contact person (Assoc Prof Joseph Ischia) noted at the end of this consent and a copy of the research results papers will be provided to you free of charge.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Data will remain confidentially stored in research offices at the Austin Hospital. The offices will be securely locked and only accessible by the research team. Electronic data will be kept securely on a password-protected database. Only



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the ZINC COVID study team at the Austin Hospital will have the list that can link your identity to the study code. Your information will only be used for the purpose of this research project, and it will only be disclosed with your permission, except as required by law. Data collected for this study will be stored for 15 years. After this time, electronic data will be destroyed by confidential erasing and paper records will be destroyed confidential shredding.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research will be published and presented in a variety of forums. In any publication and/or presentation, the information will be provided in such a way that you cannot be identified, except with your permission. Identifiable information will not be made public in any form so that confidentiality is maintained. The study database will contain information from all study participants, but not anything that can identify you as an individual. This information may be made available to other researchers. If this happens, your identity will be protected, and you will not be identified or contacted by other researchers who request access to the study database.

Information about participation in this research may be recorded in your health records. In accordance with relevant Australian state and federal privacy laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible, and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In the event of loss or injury, the parties involved in this research project have agreed to a compensation agreement. Compensation may be available if your injury or complication is caused by the study medicines or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

18 Who is organizing and funding the research?

The Principal Investigator for this study is Associate Professor Joseph Ischia. This research has received funding from the Australian Urologic Cancer Research Trust. All monies will be administered through Austin Health and are directed to run the study at the Austin Hospital. This money pays the Austin Hospital for the work done by its staff in this study. No money is paid directly to individual researchers.

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Austin Health Human Research Ethics Committee.





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This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this study or if you have any medical problems which may be related to your involvement in the study (for example, any side effects), you can contact the following people:

Clinical contact person

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|-----------|--------------------------|
| Name | Assoc Prof Joseph Ischia |
| Position | Principal Investigator |
| Telephone | (03) 9496 3676 |

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

| | |
|-----------|----------------------------------|
| Position | Complaints Officer |
| Telephone | (03) 9496 4035 or (03) 9496 4090 |
| Email | ethics@austin.org.au |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

| | |
|------------------------|---|
| Reviewing HREC name | Austin Health Human Research Ethics Committee |
| HREC Executive Officer | Mrs Lisa Pedro |
| Telephone | (03) 9496 4035 |
| Email | ethics@austin.org.au |



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| | |
|-------------------------------------|---|
| Title | High-dose Zinc as Adjunctive therapy in COVID positive Critically Ill Patients: A Pilot Randomized Controlled Trial |
| Short Title | ZINC COVID |
| Protocol Number | Version 2, 1st April 2020 |
| Local Principal Investigator | Associate Professor Joseph Ischia |
| Associate Investigator(s) | Dr Oneel Patel, Professor Rinaldo Bellomo, Dr Daryl Jones, Professor Damien Bolton, Dr Glenn Eastwood, Prof Paul Johnson, Prof Christine McDonald |
| Location | Austin Hospital |

Declaration by Participant

- I have read the Participant Information Sheet or someone has read it to me in a language that I understand.
- I understand the purposes, procedures and risks of the research described in the project.
- I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Austin Health concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.
- I understand that I will be given a signed copy of this document to keep.

| | |
|------------------------------------|------|
| Name of Participant (please print) | |
| Signature | Date |

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

| | |
|--|------|
| Name of Study Doctor/Senior Researcher [†] (please print) | |
| Signature | Date |

[†] A senior member of the research team must provide the explanation of, and information concerning, the research project. Note: All parties signing the consent section must date their own signature. I understand that, if I decide to discontinue the study treatment, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.



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Form for Withdrawal of Participation - Adult providing own consent to enrol



| | |
|-------------------------------------|---|
| Title | High-dose Zinc as Adjunctive therapy in COVID positive Critically Ill Patients: A Pilot Randomized Controlled Trial |
| Short Title | ZINC COVID |
| Protocol Number | Version 2, 1st April 2020 |
| Local Principal Investigator | Associate Professor Joseph Ischia |
| Associate Investigator(s) | Dr Oneel Patel, Professor Rinaldo Bellomo, Dr Daryl Jones, Professor Damien Bolton, Dr Glenn Eastwood, Prof Paul Johnson, Prof Christine McDonald |
| Location | Austin Hospital |

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Austin Health.

| | |
|------------------------------------|------|
| Name of Participant (please print) | |
| Signature | Date |

Consent provided to use data collected up to the date of withdrawal: Yes No
 Consent provided to access your medical record to obtain information of health status: Yes No

In the event, the participant decided to withdraw verbally, study doctor/senior researcher to give a description of the circumstances below:

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Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

| | |
|--|------|
| Name of Study Doctor/Senior Researcher [†] (please print) | |
| Signature | Date |

[†] A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.