PARTICIPANT INFORMATION SHEET & INFORMED CONSENT FORM

Study Name:	Controlled human infection for penicillin against *Streptococcus pyogenes*: a double blinded, placebo controlled, randomised trial
Protocol No:	1111-1264-9535
Study Sponsor:	Telethon Kids Institute
Study Doctor:	Associate Professor Laurens Manning
Study Site:	Linear Clinical Research

You are being invited to take part in a research study. This is because you are 18 to 40 years of age and in good general health. This Participant Information Sheet and Informed Consent Form (PICF) has information to help you decide if you want to participate.

Please take your time to read this document carefully and ask the study doctor or staff any questions you may have, and to explain any words, terms, or sections that are unclear to you. You should not sign this form until you understand all of the information presented in the following pages and until all of your questions about the research have been answered to your satisfaction.

You will be asked to complete a simple multiple-choice quiz prior to signing the consent form to confirm that you understand all of the information presented to you, if you select an incorrect answer a staff member will explain which is the correct answer and why the answer you chose was incorrect, incorrect answers will not prevent you from joining the study.

Your participation in this study is entirely voluntary and you may withdraw at any time. If you decide to participate in this study, you can then choose to stop taking part in the study at any time for any reason. You are encouraged to discuss the study with your family and friends prior to signing consent. We also recommend discussing your participation with your General Practitioner (GP), should you have one, especially if you are taking any prescription medication.

Linear Clinical Research Ltd will be paid by the Sponsor, Telethon Kids Institute, for conducting this study.

Study Synopsis

We are conducting this study to find out the minimum level of penicillin (an antibiotic) in your blood required to prevent pharyngitis (a sore throat caused by bacteria) due to infection by *Streptococcus pyogenes* (Strep A - a type of bacteria). To achieve this, we will be giving participants different doses of benzylpenicillin (a type of penicillin antibiotic) administered

intravenously (directly into a vein) and then exposing them to the Strep A bacteria to see whether or not the participant gets a sore throat. Although a sore throat is something that is normally easily recovered through treatment by antibiotics, previously untreated Strep A infections can leave patients exposed to further unwanted side effects or more severe diseases if they are re-infected (described below). When this occurs (typically in vulnerable children in areas of socioeconomic disadvantage), patients usually require deep, painful, monthly injections of penicillin for a minimum of 10 years. We would like to identify more effective treatment strategies for these patients, which involve less pain and less frequent interventions. To come up with this solution, it is crucial for us to know what level of penicillin is required to prevent re-infection. This will allow us to calculate the total amount of penicillin required and also the correct release rate to be used in alternate treatment strategies.

Why is this study important and what is involved?

Streptococcus pyogenes or Strep A is a bacterium that commonly causes a sore throat and skin sores in susceptible people. It is usually a mild illness cured with a course of appropriate oral antibiotics. However, when Strep A infections are not properly treated with antibiotics (i.e. in areas of socioeconomic disadvantage), the body's own response to Strep A can lead to a condition known as acute rheumatic fever (ARF). ARF is rare in industrialised settings with access to a high standard of living and sanitation. However, people living in socioeconomic disadvantage with poor access to healthcare (such as children in low- and middle-income countries or Indigenous Australians) remain vulnerable to it. ARF typically develops 2-4 weeks after Strep A infection and symptoms include joint swelling and pain, fever, uncontrolled movements, and skin rash. Untreated and over time, repeated episodes of ARF can lead to damage of the heart valves, also known as rheumatic heart disease (RHD). RHD affects an estimated 33.4 million people worldwide, resulting in the death of approximately 319,400 people each year. In Northern Australia, Indigenous populations are particularly affected due to the socioeconomic disadvantages prevalent in these communities such as inadequate access to healthcare and overcrowding due to inadequate housing.

Benzylpenicillin is marketed in Australia as BENPEN™ and is a penicillin antibiotic that has been approved by the Therapeutic Goods Administration (TGA) for the treatment of other infections such as streptococcal infections, infections of the upper respiratory tract, syphilis, meningitis and some skin diseases.

BENPEN™ is an antibiotic that belongs to a group of medicines called penicillins. Another longer-acting form of penicillin (called Benzathine Penicillin G) is typically given monthly by deep, painful injection into the thigh muscles of patients who have previously been diagnosed with ARF or RHD to prevent further Strep A infection. However, many patients who need this treatment (often young children and teenagers) will fail to attend these injections because of the associated pain and frequency. If we can develop more effective and tolerable treatments (i.e. longer acting and less painful), this may increase patients' willingness to receive this vital

treatment. Therefore, we are investigating the minimum blood penicillin level that offers effective protection against Strep A re-infection by using sore throat caused by Strep A to represent the more serious conditions such as acute rheumatic fever and rheumatic heart disease.

Through this research study, we hope to find out the minimum penicillin concentration in a person's bloodstream that will prevent Strep A pharyngitis. We want to find out what effects it has on you and your health as healthy adult males and females.

The design of this study is a double-blind, randomised and placebo-controlled challenge study.

A double-blind study means that the study doctor and the participants who take part won't know which group is getting Benzylpenicillin and which group is getting placebo. This way, the findings from the two groups will be treated equally. Neither you nor the study doctor will know which group you are in. However, this information can be obtained in case of an emergency.

To be randomised means that a computer will put participants into groups by chance. You are 4 times more likely to receive study drug than placebo. If the number of participants in the total group decreases, then this could mean that your chances of receiving the active study drug are higher. Neither you nor the study doctor can choose what you receive.

This study will compare Benzylpenicillin with placebo. The placebo will be similar to the penicillin treatment, but with no active drug in it. One group of participants will take Benzylpenicillin and another group will take the placebo. The effects of the study drug will be compared to participants who are taking the placebo.

A challenge study means you will be deliberately exposed to an infectious agent to see if the dosage of study drug you receive is capable of preventing symptomatic infection. In this study you will receive a challenge of Strep A bacteria applied to your throat to evaluate whether the dosage of Benzylpenicillin that is received is effective at preventing symptomatic infection.

We will be testing a continuous infusion of the study drug in up to 60 healthy volunteers. The first 45 of the participants will be divided into 5 groups of 9 people each. The dose level received by the final 15 participants will be determined based on the results of the initial groups. The following is the way that the groups are planned to be dosed:

Group	**Number of Participants**	**Dose level** (ng/mL)
A	9	20
B	9	12
C	9	6
D	9	3
E	9	0 (placebo)
F	15	TBC

The dose level may vary based on the safety information that is reviewed by the safety monitoring committee, but you would be informed if this was the case. You will be informed of the actual dose that you will receive, bearing in mind that you may receive placebo.

The study drug will be administered via a continuous infusion for at least 24 hours into your arm. After at least 12 hours of infusion you will be administered the Strep A challenge via oropharyngeal (to the top of your throat) swab. You will not be required to fast prior to your continuous infusion but you will be required to fast from food and water for 90 minutes prior to and following the Strep A challenge.

This study is being conducted by Linear Clinical Research Ltd. The study is being sponsored in Australia by Telethon Kids Institute.

Your GP will be notified of your participation in this study and of any clinically relevant information.

What will I be asked to do?

If you choose to take part in this study and it is determined you are eligible and able to participate, your length of involvement would be up to approximately 61 days.

You would be required to attend a Screening Visit up to 35 days before your scheduled challenge. You will also be required to attend the clinic for the day for a baseline visit up to 21 days prior to the scheduled challenge to determine how quickly your body gets rid of the penicillin to evaluate how much you will receive on dosing day. You will check-in the day before your scheduled challenge to begin your continuous infusion of the study drug and may remain in the clinic for a maximum of 6 days and 6 nights. Your health will be evaluated prior to discharge from the clinic, you may be discharged earlier than expected if you develop pharyngitis. Follow-up visits will be performed 7 and 28 days after starting the oral antibiotics. During your stay at the clinic, all meals and refreshments will be provided for you, so please inform the staff if you have any special dietary requirements.

Additional volunteers will be recruited and admitted to the unit as alternates in order to ensure we are able to dose the required number of participants.

Please note that if you are deemed eligible following the screening and baseline visits, this will not automatically mean you will be included in the study, with additional eligibility checks needing to occur on the day of baseline and Day -1. If you have been admitted to the unit for the baseline visit and are not required for the confinement period, you will be considered an alternate. You will be advised whether or not you will be required by the study team prior to check-in on Day -1.As well as alternates, there may be some participants who are admitted to the unit and are not required for dosing. If you are not required for dosing on Day 1 you will receive a partial payment of $400.

What will happen during the study visits?

Screening Visit – (Day -35 to Day -8; visit should be about 3-4 hours)

This visit will occur up to 34 days before your entry into the study and will involve:

- A discussion with the study doctor to make certain you fully understand the study, its procedures and requirements. Please make sure you ask any questions you may have about the study before or during this visit. After completing a simple quiz to confirm that you understand what will occur during the study, you will need to sign the attached Informed Consent Form to confirm you are willing to participate in this study and follow all instructions provided by the study staff, as well as abide by any study restrictions (these are detailed in the 'What are my responsibilities in this study' section).

  Please note that you will have the opportunity to receive this participant information sheet and consent form prior to coming into the clinic for the screening visit. This will allow you to review the information and discuss your potential involvement in this study with family, friends and/or a medical professional of your choosing (such as your GP). After signing the consent form in the presence of the study doctor you will have the opportunity to leave the clinic and come back at a later time, to complete the screening visit assessments outlined below, should you wish to discuss your involvement further with friends, family or a medical professional of your choosing.

- Following your consent, you will undergo a complete medical examination which will include:
  - Documentation of demography (race, gender, ethnicity);
  - Description of your medical and surgical history. Please ensure you inform the study doctor of any important family history and describe your personal history in full including any periods of hospitalisation, illness, surgery, blood

donations and drug reactions/allergies as these may affect your capacity to safely participate in this study;

- A full physical examination. Your overall health will be assessed which may include assessment of your general appearance, head, neck, ears, eyes, nose, throat, skin, cardiovascular system, respiratory system, gastrointestinal system, and neurological system; height and weight will also be measured. You will not be required to undress for this examination but may be required to move or lift parts of your clothing out of the way to allow examination of the chest, back and abdomen. For your privacy, this will be done behind a closed curtain;
- Electrocardiogram (ECG; a recording of the electrical activity of the heart), which involves placement of painless sticky pads (or electrodes) onto your chest, arms and legs to assess the electrical activity of your heart. You will be required to remove or lift your clothing out of the way to allow placement of the electrodes on your chest area and this will be done behind a closed curtain for your privacy;
- Vital sign measurements (blood pressure, pulse rate, breathing rate and temperature).

- You will be asked about any medications that you have taken in the last 6 months, or any other medications or products that you are currently using (including alcohol and tobacco use), as some medications must not be taken before or during the study (please refer to the 'What are my responsibilities in this study' section for medications to avoid during the study).
- You will be required to give a urine sample that will be used to perform tests to assess your general health, including screening for drugs of abuse. Please note you will not be eligible to participate in this study if you return a positive test result.
- Breathalyser samples for alcohol use will be obtained, please note you will not be allowed to participate in the study if you return a positive result.
- You will be asked how you are feeling. Please make sure you tell study staff as much information as possible.
- A sample of blood (approximately 12 mL, or 3 teaspoons) will be taken from a vein in your arm with a needle and syringe – this will be used to perform tests to assess your general health. If you are female, one of these samples may also be used to perform a pregnancy test or a follicle stimulating hormone (FSH) test to confirm post-menopausal status. Please note you will not be eligible to participate in this study if you return a positive pregnancy result.
- In order to take part in the study, you must agree to have specific serology testing for Hepatitis B, Hepatitis C and Human Immunodeficiency Virus (HIV). Approximately 5 mL, or 1 teaspoon of blood, will be taken for this testing (included in the volume above). You will receive information and counselling before the test. If a positive result

is found as a result of this testing, appropriate counselling services will be arranged by the study doctor to discuss treatment options. You will not be eligible to participate if you return a positive test result. Please note that as per Western Australian Law, Hepatitis B, Hepatitis C and HIV are notifiable diseases, and a positive result will be notified to the Department of Health.

- An additional sample of blood (approximately 4mL, or one teaspoon) will be taken to assess for any pre-existing immunity to Strep A. You will not be eligible to participate if you return a positive test result.
- You will be tested for bacterial infection via 3 throat swabs. To collect the swab sample, you will be asked to tilt your head back prior to the swab being inserted into your mouth towards the back of your throat. The swab will be rotated several times and then removed.
- At the conclusion of screening, provided you are eligible and willing to participate in the study, a study staff member will contact you and explain the details of the study to you, including re-confirming the study dates and restrictions.
- After your screening visit, you will be required to undergo an echocardiogram. An echocardiogram uses ultrasound waves to produce images of your heart. This commonly used test allows the measurement of the size of different parts of your heart and to see how your heart is beating and pumping blood. The study team will assist in booking your echocardiogram for you and provide you with directions on how to get there.
- There may be reasons why you are not allowed to take part in this study. The study doctor or staff will discuss these with you.

Individualised Penicillin Assessment – (Day -21 to Day -8; visit should be about 7-8 hours)

This baseline visit will occur up to 20 days before your entry into the study and will involve a number of assessments to determine how quickly your body gets rid of penicillin. This will allow the study team to determine the exact dose of penicillin required on Day -1.

The following assessments will be performed at various times throughout the day:

- Physical examination
- Measurement of your height and weight
- Measurement of your vital signs
- Blood samples (up to 8 mL or approximately one and a half teaspoons each time) will be taken for tests to assess your general health.
- Additional blood samples (up to approximately 15 mL or three teaspoon each time) will be taken for research purposes. Samples obtained for research purposes will give us better insight into how your body reacts to Strep A infection, how your body gets rid of penicillin and how Strep A reacts to penicillin.
- Additional blood samples (up to approximately 5 mL or one teaspoon each time) will be taken to measure levels of penicillin in your blood (PK sample).

- If you are a female a sample of urine may be collected to perform a pregnancy test (please note you will not be allowed to participate in the study if you return a positive pregnancy result)
- You will be regularly asked how you are feeling and if you had any changes in your health or taken any new medications. It is very important to tell the study staff about anything that has changed so that it can be properly recorded before you have any study medication. These changes won't necessarily keep you from continuing in the study, so please make sure you tell study staff as much information as possible.
- An indwelling cannula (a flexible, small plastic tube) will be inserted into a vein in your arm to allow for the collection of blood before the penicillin is administered and at specific intervals up to 6 hours after administration. If the cannula becomes blocked or stops working, some of the blood samples which were planned to be collected in this way may be collected with a needle and syringe.
- A second indwelling cannula will be inserted into a vein in your arm for the delivery of the penicillin. Penicillin will be administered via infusion over 2 minutes. The study doctors will use the data collected from this procedure to decide on the amount of penicillin to administer on Day -1.
- You will be provided with meals during your inpatient stay.

Treatment Period (Day -1 up to Day 6)

You will check in to the Linear study clinic the day that you will receive the continuous penicillin infusion (i.e. Day -1) and will be assessed to confirm your ongoing eligibility to participate in the study. Please note that in order to protect members of the public from infection you will be confined to a separate ward to our other participants. You will be permitted to leave this ward in emergencies and when you need to use the bathroom. The study team will explain this to you in more detail.

The following assessments will be performed at various times during your stay at the Linear study clinic:

- Physical examination
- Measurement of your vital signs
- Blood samples (up to approximately 8 mL or one and a half teaspoons each time) will be taken for tests to assess your general health.
- Additional blood samples (up to approximately 3 mL or slightly less than one teaspoon each time) will be taken for research purposes.
- Additional blood samples (up to approximately 5 mL or one teaspoons each time) will be taken to measure levels of penicillin in your blood (PK sample).
- A urine sample will be collected to test for drugs-of-abuse. If you are a female this sample may also be used to check for pregnancy (please note you will not be allowed to participate in the study if you return a positive pregnancy or drugs-of-abuse result).

- Breathalyser samples for alcohol use will be obtained at check-in, please note you will not be allowed to participate in the study if you return a positive result.
- You will be tested for bacterial infection via throat swabs. To collect the swab sample, you will be asked to tilt your head back prior to the swab being inserted into your mouth towards the back of your throat. The swab will be rotated several times and then removed.
- Saliva samples will be collected to measure penicillin levels. You will be asked to rinse your mouth with water and then fast for 60 minutes prior to placing a cotton swab in your mouth. You will then be asked to move the cotton swab around in your mouth until it is saturated.
- Nasal lining fluid will be collected via special collection device. An absorbent strip of the device will be inserted into your nostril for approximately 60 seconds.
- Photographs of the back of your throat will be taken. You will be asked to stick out your tongue and say 'ah' in order to capture the best view of your throat for the photo. If required, the investigator will use a wooden tongue depressor to gently push down on your tongue for a better view.
- You will be given a questionnaire to complete at 3 timepoints (Day -1, Day 3 and Day of Discharge) during your confinement, it is estimated that each timepoint will take up to 30 minutes to complete, you are encouraged to complete these questionnaires in your own time. You will also be given a diary to log your feelings to complete during your stay. If you have any questions about the questionnaires or diary you can contact a CHIPS study representative on (08) 6319 1456 or (08) 6319 1254 for assistance.
- On Day -1 a midline intravenous catheter will be inserted into the middle upper arm under guidance via ultrasound. A midline catheter is an 8-12cm catheter that sits in your vein for drug delivery over multiple days. You will be administered an individualized loading dose of penicillin initially for 2 minutes followed by continuous administration for a maximum of 5 days. The study team will inspect the catheter every 12 hours following insertion.
- On Day 1 after at least 12 hours of continuous penicillin administration you will be 'challenged' with Strep A bacteria. This will involve your throat being swabbed to apply the bacteria. You will be required to fast from food and water for 90 minutes prior to and after the challenge. Following challenge you will be assessed by the study doctor every 12 hours to monitor for pharyngitis, if you have a sore throat at all during the study you will be offered pain relief medication (paracetamol) to ease your symptoms.
- If you develop pharyngitis from the Strep A challenge the continuous penicillin will be stopped and you will be administered non-penicillin oral antibiotics (azithromycin). If you do not develop pharyngitis, on Day 5, the continuous penicillin will be stopped and you will be administered non-penicillin oral antibiotics. During your stay you will be able to request paracetamol at any given time to control any symptoms you may be feeling.

- You will be regularly asked how you are feeling and if you had any changes in your health or taken any new medications. It is very important to tell the study staff about anything that has changed so that it can be properly recorded before you have any study medication. These changes won't necessarily keep you from continuing in the study, so please make sure you tell study staff as much information as possible.
- You will be provided with meals during your inpatient stay. You will be required to avoid eating for at least 90 minutes prior to challenge and for 90 minutes after the challenge.
- 24 hours after starting your oral antibiotics (azithromycin), if the study doctor approves, you will be checked out of the clinic and can return home. Please make sure you let the study doctor or study staff know of any symptoms you may be feeling before leaving the clinic, so the study doctor can properly assess you before you leave.

Follow-up Visits (7 and 28 days post oral antibiotics) (Visit should be approx. 2 hours)

You will need to return to the study clinic for a follow-up visit 7 and 28 days after starting your 5 day course of oral antibiotics and may undergo the following procedures:

- Physical examination
- Measurement of your vital signs
- Blood samples (up to approximately 8 mL or one and a half teaspoons each time) will be taken for tests to assess your general health.
- An ECG will be performed
- You will be required to give a urine sample that will be used to perform tests to assess your general health.
- Additional blood samples (up to approximately 3 mL or 0.5 teaspoons each time) will be taken for research purposes.
- Saliva samples will be collected. You will be asked to rinse your mouth with water and then fast for 60 minutes prior to placing a cotton swab in your mouth. You will then be asked to move the cotton swab around in your mouth until it is saturated.
- You will be asked how you are feeling and if you have had any changes in your health since dosing and whether you have taken any other medications.

	Screening	Individualized Penicillin Assessment (Baseline)								Confinement										Outpatient Follow Up	
Day	D(-35) to -8									-1	1				2	3	4	5	6	7 Days post A/B	28 Days post A/B
Hours		0	0.25	0.5	1	2	3	4	6		0	2	12	24							
Review eligibility	x	x								x											
Informed consent	x																				
Survey questions & Diary										▼											
Medical history	x	x																			
BMI	x	x								x											
Vital signs	x	x						x		x	x[1]				x[1]	x[1]	x[1]	x[1]	x[1]	x	x
Physical Examination	x	x								x	x				x	x	x	x	x	x	x
Echocardiogram	x																				
Breathalyser & Urine drug screen	x									x											
Urinalysis	x																				x
ECG	x																				x
Clinical Lab tests	x	x								x											x
Pregnancy test	x	x								x											
Midline insertion										x											
Penicillin Administration		x								x	x[2]										
PK Sample		x	x	x	x	x	x	x	x	x	x		x	x	x	x[2,3]	x[2,3]	x[2,3]			
Research Bloods		x								x		x	x	x	x	x	x	x		x	x
Strep A challenge											x										
Throat swabs	x									x				x	x	x[3,4,7]	x[3,4,7]	x[3,4,7]	x[3,4,7]	x	x
Photo of throat										x			x[5]								
Nasal lining fluid										x		x	x	x	x						
Saliva Sample										x			x[6]							x	x
Oral antibiotic (A/B)													x[5]							If required	
Adverse Events and Symptoms		▼																		x	x
Current Medications	x	▼																		x	x

Study Schedule of Assessments

1: 4 Times a day | **2:** Until diagnosis or Day 5 | **3:** 12 hourly | **4:** Until Discharge | **5:** At diagnosis or Day 5 | **6:** At Start of Oral A/B and at discharge | **7:** At sore throat

What are my responsibilities in this study?

The following things are important during your participation in this study:

- Please inform the study doctor of any medications, including herbal, vitamin, over the counter or prescription you have taken in the month prior to the expected dosing day, as these will need to be recorded and will help to determine your eligibility for study participation.
- You will not be permitted to take any non-study penicillin-based antibiotics from screening through to the end of the study. You will also not be permitted to take probenecid or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs - e.g. ibuprofen) within 14 days prior to penicillin administration. Sporadic ibuprofen use (less than 5 occasions) over the 14 days is permissible.
- You must not have been vaccinated 28 days or used any antibiotic therapy 14 days prior to your challenge, except for seasonal flu or COVID-19 vaccination. Please inform the investigator if you have received these vaccinations recently.
- You must not have had a significant infection within the 14 days prior to the challenge
- You must not smoke or use any tobacco products for the duration of the study.
- You must not use any prescription or non-prescription drugs and herbal supplements within 14 days prior to your challenge until the end of study. 2 grams of paracetamol (equivalent to 4 standard 500mg tablets or 3 sustained release 665mg tablets) per day and hormonal contraceptives are allowed, vitamins are prohibited within 7 days of your first follow up visit.
- You must not be related to anyone directly affiliated with this study.
- You must not use mouthwash from the day of screening until your first follow-up visit.
- You will not be permitted to consume any caffeine containing foods or beverages during your stay at the clinic. Decaffeinated coffee and tea may be provided to you.
- Report any changes in the way you are feeling to the study doctor or study staff at any point throughout the study.
- While you are resident within the study clinic you must maintain a good level of personal hygiene. This includes bathing daily (or when instructed by the study staff), bringing enough appropriate clean clothing with you for the duration of your stay, following staff instructions on cannula care and maintaining good hand hygiene (washing your hands after using the bathroom, before consuming your meals).

What effects could the tests have on me?

Blood Collection:

There is some slight discomfort involved in taking blood by indwelling cannula or with a needle and syringe. The insertion of a cannula is usually safe, but there are potential risks associated with this. There is a risk that a clot will form in the vein, which may take a number of weeks to resolve. There is a small risk of infection, although the use of sterile techniques and antiseptic solutions prior to insertion of the cannula minimises this risk. There is the possibility of bruising and discomfort around the site of an intravenous cannula, although this is generally minor and resolves within a few days. There is a very small risk that a nerve could be damaged during insertion of a cannula, however, the site of cannulation is carefully chosen to minimise this risk. Symptoms of nerve damage include tingling, shooting pain and pins and needles in the area of cannulation. Nerve damage may persist indefinitely, but usually resolves within 6-12 months. There is also the small chance that the cannula becomes dislodged from the vein, which can cause minor bleeding.

Procedures relating to blood collection can also occasionally cause light-headedness or fainting. These reactions are usually mild, of short duration and limited to a feeling of weakness, accompanied by sweating, slowing of heartbeat, and a decrease in blood pressure.

ECG:

As a result of the patches that are put on your skin when performing the ECG, there is the possibility a rash or minor irritation of the skin may result.

Midline Insertion:

Like insertion of a cannula for blood collection, the midline catheter insertion can cause some discomfort. This insertion is usually safe but there are some potential risks involved. Like cannula insertion there is a small risk of infection, although the use of sterile techniques and antiseptic solutions prior to insertion of the catheter minimises this risk. There is the possibility of bruising and discomfort around the insertion site but this normally resolves within days. There is a risk of inflammation of the vein (phlebitis) or swelling and redness in the tissue surrounding the catheter and there is a very small risk of the catheter moving out of place or breaking inside the vein, your midline will be inspected at least every 12 hours to ensure no complications have developed. Rarely a small or sometimes larger clot may form in the vein (thrombosis or deep vein thrombosis), if this is suspected the study doctor may refer you for additional tests or treatment.

There is a very small risk that a nerve could be damaged during insertion of a catheter, however, the site of cannulation is carefully chosen to minimise this risk. Symptoms of nerve

damage include tingling, shooting pain and pins and needles in the area of insertion. Nerve damage may persist indefinitely, but usually resolves within 6-12 months.

Throat Swabs:

You may experience some slight discomfort during the test and may gag a little when the swab is inserted.

Strep A Challenge:

Strep A has previously been used safely in a previous human challenge study conducted by members of this study's research team. 85% of participants in this study developed a sore throat after being exposed to Strep A and there were no serious side effects experienced by any participant over the course of the study.

You may develop symptoms such as a sore throat, fever, muscle aches or painful neck glands due to the administration of Strep A, however, the bacterial strain has been extensively tested and has previous been shown not to be associated with serious complications. This will minimise the risk of the complications, most of which are seen in untreated patients. Also, you will be given antibiotic treatment (azithromycin) as soon as the diagnosis criteria are met and therefore, your risk of developing complications relating to pharyngitis is very low. There is a very slight chance that you may experience a relapse of a sore throat following antibiotic treatment, you will be advised to contact the study doctor if you experience any further symptoms of pharyngitis and a study doctor will refer you for further treatment if confirmed.

If Strep A is left untreated and your immune system is unable to defend your body properly it can result in Invasive Group A Streptococcus infection (Invasive GAS infection). This is where the Strep A bacteria invades other parts of your body (e.g. your blood or lungs) and can cause a number of side effects, these can include a high fever, low blood pressure, vomiting, rashes and infection of the lung, bone or meninges (membranes that cover your brain). In rare cases patients can also develop a skin infection resulting in blisters, fever, fatigue and pain. As described earlier there is also the risk of ARF and RHD from untreated Strep A. There is also a risk of developing kidney inflammation as a result of the infection. As you will be receiving antibiotic treatment prior to discharge the risk of developing these side effects is extremely low, none of these severe side effects were seen in the previous Strep A study challenge in humans.

Sometimes people who experience a sore throat from Strep A become chronic asymptomatic carriers of Strep A, this means that you still have strep A bacteria in your throat but you show no symptoms. There is a small chance that this could happen to you following treatment. The study team will be checking for this by throat swab at each follow up visit but there is no evidence to show that being an asymptomatic carrier causes an increase in discomfort or transmission to others.

Strep A pharyngitis is considered a contagious illness. Due to this, precautions will be taken throughout your stay to prevent transmission to those around you. Strep A pharyngitis is not considered contagious 24 hours after antibiotic treatment, you should not be contagious on discharge.

What are the possible risks of the medication?

Benzylpenicillin has been used since the 1950s and is approved in Australia by the Therapeutic Goods Administration (TGA) as BENPEN™ for the treatment of a number of infections. BENPEN™ and other penicillins are generally well tolerated, side effects from BENPEN™ are very uncommon with 69% of side effects due to hypersensitivity (allergic reaction).

The following information provides a list of potential side effects which have been reported with the use of BENPEN™:

Common Side effects (Between 1 in 10 and 1 in 100 or 1-10% of people affected)

- Infusion site reaction (pain, redness, swelling)
- Abdominal pain
- Nausea
- Diarrhoea and Large Intestine Inflammation
- Allergy

Uncommon Side Effects (Between 1 in 100 and 1 in 1,000 or 0.1-1% of people are affected)

- Vomiting

Rare Side effects (between 1 in 1,000 and 1 in 10,000 or 0.01-0.1% of people are affected)

- Black Tongue
- High/Low levels of electrolytes
- Confusion
- Convulsions or seizures
- Coma Changes in blood test parameters

Side effects with Unknown Frequency

- Rash and Urticaria (hives – itchy, red skin rash)
- Fever
- Oedema (fluid build-up in tissue)
- Trouble breathing
- Hepatitis (liver inflammation) or other liver issues
- Abnormal kidney function

Other side effects which have been reported with the use of penicillin therapies such as BENPEN™ include anaphylaxis - a severe allergic reaction that can cause itchy rash, throat

swelling, a drop-in blood pressure and possibly death; and severe cutaneous adverse reactions (SCAR). SCAR is a rare but potentially fatal adverse drug reaction which may cause rash, fever, tissue death and damage to internal organs if left untreated. You will be closely monitored for any signs of anaphylaxis or SCAR and will not be able to participate in this study if you have a history of sensitivity to penicillin and some other allergens. The study doctor will discuss these in more detail with you.

Additional information related to the use of BENPEN™ will be provided to you in the Consumer Medicines Information (CMI) sheet.

There may be additional adverse effects in humans that are not yet known. If the study doctor has any concerns regarding your health during the study, additional tests may be performed to ensure your safety. These may include physical examinations, measuring your vital signs, performing an ECG and/or collecting blood samples to check your general health.

Linear's clinical facility is fully equipped with a crash cart (an emergency care trolley) and all staff are trained to deal with medical emergencies. In addition to appropriate first aid supportive measures by clinical and medical staff at Linear, your treatment may include the administration of various drugs, which may include adrenaline, anti-histamines or hydrocortisone. The local hospital Emergency Department will also be contacted if required.

Are there risks associated with becoming pregnant while participating in the study?

Previous human experience with penicillins during pregnancy has not shown any evidence of side effects on the foetus. Benzylpenicillin is classed as pregnancy Category A drug in Australia, meaning it has been taken by many pregnant women and women of child-bearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the foetus can be excluded.

It is recommended that participants use a condom for all sexual intercourse even if they or their partner are already on hormonal contraception for the entire duration of the study until completion of the follow-up visit. You should advise your study doctor if you become pregnant or father a child while participating in the research project. In the event you do fall pregnant or father a child within this period, the Sponsor may ask that you or your partner sign a separate consent form to allow monitoring of the pregnancy and the birth and the health of your child up to 1 year of age. Your study doctor will advise on medical attention for your partner should this be necessary.

It is highly recommended that you inform your partner of your participation in the study. You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

You will be told in a timely manner about significant new information that might affect your decision to stay in the study.

What happens to my samples that are collected?

During the study, the estimated total blood volume to be collected will be approximately 160 mL (a little more than ½ a cup). As a reference, a standard blood donation is 470 mL in any 12-week period. You are advised not to donate any additional blood for 12 weeks after completing the study. As with all studies requiring blood donations, adequate rest and good eating habits are also advisable.

Your samples will be stored in either the laboratory of the Sponsor, or the laboratory of a company contracted to work with the Sponsor for a period of up to 7 years following the completion of the study. Access to study samples will be limited to laboratory personnel working for the Sponsor or who are contracted to work for the Sponsor and authorised to perform analyses. Your name will not be present on any samples and the individual performing the testing will not know your identity, solely the participant number that you are assigned will be present.

You have the right to withdraw from this study at any time, however, information and samples that already have been collected from you may continue to be used.

Additional information you need to know

Compensation for Injury

If you are injured as a result of your participation in this trial you may be entitled to compensation. There are two avenues that may be available to you to seek compensation.

1. Sponsors of clinical trials in Australia have agreed that the guidelines developed by their industry body, Medicines Australia, will govern the way in which compensation claims from injured participants are managed by Sponsors.

   However, as guidelines, they do NOT in any way dictate the pathway you should follow to seek compensation. The Sponsor is obliged to follow these guidelines.

   These guidelines are available for your inspection on the Medicines Australia Website (www.medicinesaustralia.com.au) under Policy – Clinical Trials – Indemnity & Compensation Guidelines. Alternatively, your study doctor can provide you with a hard-copy of the guidelines.

2. You may be able to seek compensation through the courts.

It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice before taking any steps towards compensation for injury.

What benefits could there be from taking part in the study?

There will be no clear benefit to you from your participation in this research. Information learned from the study may help other people in the future.

Are there alternatives to participation?

Since this study is intended only to test the effect of the study drug in healthy volunteers, your alternative to being a volunteer in this study is to choose not to participate in the study.

Will I receive a fixed payment per visit to cover any out of pocket expenses?

The payment for participants who participate in and complete this study will be $2,695.

Participant payment is for your time and inconvenience. Your travel expenses and parking costs have been factored into this payment and will not be separately reimbursed.

A member of the study team will discuss with you the timing of the payments, including any interim payments you can expect.

Any payment received may be considered taxable income. Participants are encouraged to seek independent financial advice as to how any payment may affect your personal financial situation.

If you choose to withdraw your consent or in the unlikely scenario you are no longer required to participate in the study, then the level of payment you will receive will be on a pro-rata basis (i.e., you will receive a partial payment). You should also be aware that your study payment may be reduced or forfeited if you fail to follow any of the restrictions specified in this Participant Information Sheet. You will receive partial payment if you are withdrawn from the study due to non-medical reasons. You will receive full payment if you are withdrawn from the study because of medical reasons or a medical event related to the study.

Payment may be withheld entirely in the event that you are withdrawn from the study due to unacceptable behaviour, such as causing distress or behaving aggressively towards study staff or other participants.

Voluntary participation / Withdrawal from the study

Your participation in this study is purely voluntary. You may refuse to take part or withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. You may be withdrawn from the study if the study doctor feels it is best for you or if you do not comply with the requirements of the study. The Sponsor or the study doctor can also stop this study at any time for clinical or administrative reasons without regards to the participant consent.

If you wish to withdraw from the study while staying in the clinical trial unit, please discuss this with the study staff who will assist you in this matter and ensure you are medically fit to

leave. Before you leave the study, the study doctor will want to examine you, measure your vital signs and/or collect blood samples to check your general health.

Any significant new findings developed during the course of the research, which may affect your willingness to continue participation in this study, will be provided to you in a timely manner and may require you to sign an updated informed consent form in order to continue participating in the study.

Termination of the study

The research project may be stopped for a variety of reasons. These may include the following: unacceptable side effects, the drug being shown not to be effective, the drug being shown to work and not need further investigation, and decisions made in the commercial interest of the Sponsor.

How will my privacy be protected?

If you decide to be in this study, the study doctor and research team will use health data about you to conduct this study, as described in this consent form. This may include your name, address, phone number, medical history, photographs, date of birth, and information from your study visits. With your permission, this health data may come from your family doctor or other health care workers.

Please note that Linear does not sell any medications to the public and Linear personnel would never offer to sell any products to you. All medication provided by Linear for the purpose of the trial will always be free of charge to you.

By signing this document, you agree to allow the research team to share health data about you with government agencies and ethics committees that oversee the research, the Sponsor, and those working for the Sponsor, which may include affiliates of the Sponsor located in your country or other countries. An affiliate of the Sponsor includes all companies directly or indirectly owned by Telethon Kids Institute. To make sure the study rules are followed, people who work for the Sponsor will be able to see all health data about you when they visit the study site.

This clinical trial requires study monitors (people working for or on behalf of the trial Sponsor) to visit the study centre to review the clinical trial data so they can verify that study procedures have been followed and the study data have been entered correctly in the study records. This process is called ‘data verification’. An important part of this data verification includes confirming in a timely manner that the parts of the clinical trial that relate to protecting patient safety and wellbeing are properly performed at the study centre. This process typically takes place during regular monitoring visits to Linear Clinical Research’s facilities.

The health data that is sent to the Sponsor and those working for the Sponsor will not identify

you by name. Instead, it may include your initials, date of birth and study visit dates. You will not be identified by name in any published reports about this study or in any other scientific publication or presentation. If you think that you were harmed from being in the study, the study team may also share health data about you with the Sponsor's insurer to resolve your claim.

The Sponsor and those working for the Sponsor, which may include affiliates of the Sponsor, may use the health data sent to them:

- to see if the study drug has any side effects;
- how much of the study drug gets into the bloodstream and how long it takes to get rid of it;
- how much of the study drug is required to prevent infection

For these uses, the Sponsor may share this health data with others involved in these activities, as long as they agree to only use the health data as described here. The Sponsor and those working for the Sponsor, which may include affiliates of the Sponsor, may transfer health data about you from your country to other countries where the privacy laws are not as strict. Once the research team shares health data about you with others, it may no longer be protected by privacy laws. However, in the case of health data that identifies you, or from which your identity may be ascertained, an entity subject to Australian privacy laws that has collected your information must take reasonable steps to ensure that an overseas recipient handles the information in accordance with any relevant Australian privacy principle (unless an exemption applies). If you have any questions about this, direct them to the Principal Investigator.

Your permission to use and share health data about you will not end. You may however take away your permission to use and share any future health data about you at any time by writing to the study doctor. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after that date. However, health data about you that has already been gathered may still be used and given to others as described in this form.

In most cases, you have the right to request access to personal information collected from you in connection with the study and discuss any information that you believe is incorrect.

Your records relating to this study and any other information received will be kept strictly confidential. However, staff participating in your care, the Sponsor and other agencies authorised by law, may inspect the records related to the study. In the event you are admitted to hospital as a result of an adverse event resulting from this study, your treating doctor may require access to your study records. Auditors or inspectors (people who oversee the research to ensure compliance) may access your study record as well as any relevant external medical records, as authorised by law, during the study or in the future. Such access may occur at the study centre or remotely through a Linear Clinical Research secure electronic platform.

Your identity will not be revealed and your confidentiality will be protected in any reviews and reports of this study that may be published. However, results may be suppressed for commercial reasons as the Sponsor of the project retains the rights to the data.

Linear Clinical Research has a privacy policy which can be viewed at https://www.linear.org.au/privacy-policy/clinical-trial-participants/. It contains information about the use and disclosure of personal information relating to participants, and what Linear Clinical Research is required to do to maintain confidentiality of information.

Independence of Linear Clinical Research

Linear Clinical Research is an independent institute and is not part of the North Metropolitan Health Service or its hospitals and health services, or the Government of Western Australia. The health professionals involved in the conduct of this clinical research do so in a private capacity and not as employees of Sir Charles Gairdner Hospital or the State.

Will information about this trial be included in a Registry Databank?

A description of this clinical trial will be available on http://www.anzctr.org.au as required by the Declaration of Helsinki and the Australian National Statement on Ethical Conduct in Human Research. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who do I call if I have questions about…

- **The study or I need to report a medical condition (e.g. injury or illness):** Speak to a study team member at Linear Clinical Research Ltd. at (08) 6382 5100.
- **I need to speak to a doctor urgently:** Doctors at Linear Clinical Research can be contacted 24 hours a day, for urgent advice or emergencies, on (08) 6382 5116.

  If you experience a medical emergency, you should seek medical assistance by contacting 000 or attending your nearest hospital Emergency Department.
- **Your rights as a participant in the study:** The Bellberry Human Research Ethics Committee has reviewed this study in accordance with the National Statement on Ethical Conduct in Human Research (2007) incorporating all updates. This Statement has been developed to protect the interests of people who agree to participate in human research studies. Should you wish to discuss the study or view a copy of their Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Operations Manager, Bellberry Limited on 08 8361 3222.

Informed Consent Quiz

This quiz is designed to review your understanding of the study so that we can be confident that you fully understand what is involved by your agreement to participate. Please make sure you have read the information booklet in full and asked the study team any questions you have. If you don't answer all the questions correctly, don't worry. We will discuss these questions with you to ensure that you fully understand the study before signing consent.

Participant Name: _____

Date __ __ / __ __ __ / __ __ __ __

Please clearly circle one answer for each question;

1. **The study involves volunteers being given bacteria:**
   A. In a drink
   B. Using a throat swab
   C. In a tablet
   D. By injection

2. **If you participate in this study, you are likely to get which of the following:**
   A. Acute Rheumatic Fever
   B. Malaria
   C. Rheumatic Heart Disease
   D. 'Strep throat' (also known as pharyngitis)
   E. All of the above

3. **Screening for this study includes which of the following?**
   A. Urine and blood tests (including an HIV test)
   B. Physical examination
   C. Heart ultrasound (also known as an echocardiogram)
   D. The researchers contacting your GP (should you have one)
   E. All of the above

4. **Participation in the study involves:**
   A. Staying overnight in a research ward for up to 6 nights
   B. Having intravenous lines ('drips') put into your arms
   C. Getting a constant infusion (either medicine or a salty water placebo) through the drip
   D. Not consuming beverages containing caffeine (decaf will be allowed) for the duration of stay at the research facility
   E. All of the above

5. During this study, we will collect what kind of samples from you?:

A. Blood, sweat, tears, urine
B. Blood, stools, urine, saliva, nasal lining fluid
C. Nasal lining fluid, saliva, blood, throat swabs
D. Blood, throat swabs, skin biopsies

6. Which of the following statements is <u>FALSE?</u>:

A. I can withdraw from the study at any time without penalty or any effect on medical care I will receive in the future.
B. If I withdraw from the study after I have been given the Strep A bacteria, I will get a course of antibiotics to take regardless of whether I develop a throat infection or not.
C. Once I give consent to participate in the study, I must complete the confinement period and I cannot withdraw my consent unless there is an emergency or permission from the investigators.
D. I am able to withdraw from the study at any time but I understand the investigators will try to contact me after I leave to check on how I am doing.

7. What strep throat symptoms might you experience during this challenge study?

A. Sore throat
B. Fever
C. Muscles aches
D. Painful neck glands
E. All of the above

8. If I develop a sore throat during the study and experience pain or discomfort:

A. I will have to do my best to put up with it in the interest of medical science and helping others
B. I will be reviewed by a medical doctor and will be offered pain relief medications to help ease my symptoms
C. I will be given medicine to gargle and soothe my throat
D. I will be given pain relief only if it is deemed severe

9. Which of the following statements is <u>TRUE</u>?

A. I am putting myself at significant risk of developing acute rheumatic fever or rheumatic heart disease by taking part in this study.
B. The bacteria used in the study has not been tested in humans before.
C. I am not putting myself at significant risk of developing acute rheumatic fever or rheumatic heart disease because I am healthy and will receive antibiotics to treat my sore throat as soon as infection becomes apparent or before I am discharged.
D. This research is being done because the investigators are not sure if penicillin works for prevention of acute rheumatic fever in people who are at risk.

Score: ___/ 9

Where applicable, the Investigator/Senior Researcher confirms that:

- There has been an opportunity to discuss and clarify any incorrect responses elicited during this pre-consent quiz
- The participant has, after discussion, demonstrated adequate understanding of what is involved in the CHIPS study and the Investigator/Senior Researcher is satisfied that they are able to provide informed consent.

Investigator/Senior Researcher signature _____

Date __ __ / __ __ __ / __ __ __ __

PARTICIPANT INFORMED CONSENT FORM

Sponsor Protocol Number: 1111-1264-9535

Study Name:	Controlled human infection for penicillin against *Streptococcus pyogenes*: a double blinded, placebo controlled, randomised trial
Study Doctor:	Associate Professor Laurens Manning

- I have read and understood this Participant Information Sheet and Informed Consent Form.
- I am between 18 to 40 years of age (inclusive) and have been given enough time to consider my participation and asked for advice if necessary.
- I have been given the opportunity to have a member of my family or another person present while the study is explained to me.
- I have had the opportunity to ask questions and have received satisfactory answers.
- I understand that all information will be kept confidential and that the results will be used for scientific objectives.
- I authorise my research and medical records as they pertain to this study to be reviewed by the Sponsor, authorised representatives and other regulatory agencies as described in this consent form.
- I understand that my participation in this study is voluntary and that I am completely free to withdraw my consent or refuse to participate at any time without changing in any way the quality of care that I receive. If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.
- I understand that if I agree to leave the study for any reason, the study doctor may ask me to do some end-of-study tests.
- The nature and purpose of the research project and potential risks and discomforts associated with it have been explained to me. I understand them and agree to take part.
- I consent to my GP and /or treating specialist being notified of my participation in this study and of any clinically relevant information noted by the study doctor in the conduct of the study, and to be contacted to obtain information regarding my medical history during the study and in the future for the purposes outlined in this information sheet.
- I confirm that I will provide, to the best of my knowledge, a full and accurate medical and surgical history and details of any current medical conditions and medicines I am taking.
- I agree to additional tests being conducted during the study, as requested by a study doctor, if the doctor has any concerns in relation to my health whilst on the study.
- I acknowledge that Linear Clinical Research is an independent institute and is not part of the North Metropolitan Health Service or its hospitals and health services, or the Government of Western Australia. The health professionals involved in the conduct of this clinical research do so in a private capacity and not as employees of Sir Charles Gairdner Hospital or the State.
- I have been given a copy of the Participant Information Sheet. I am aware that I will receive a copy of this fully signed and dated Informed Consent Form.
- As a healthy volunteer, I freely consent to participate in this study.

Participant's Name (printed):					
Signature:		**Date:**	__ __ / __ __ __ /__ __ __ __	**Time*:**	____ : ____

Please document any questions that the participant raised below and how they were answered.

Declaration by Investigator/Senior Researcher: I have given a verbal explanation of the study, its procedures and risks, have addressed any questions asked by the participant, and I believe that the participant has understood my explanations.

Investigator/Senior Researcher's Name (printed):					
Signature:		**Date:**	__ __ / __ __ __ / __ __ __ __	**Time*:**	____ : ____

**** Participant must sign the consent form first, prior to the Investigator/Senior Researcher.***
Note: All parties signing the Consent Form must date their own signature.