DRUG TREATMENTS
DOMAIN PARTICIPANT INFORMATION SHEET

Title:	Better Evidence And Translation for Calciphylaxis (BEAT-Calci)
Investigators:	Prof Meg Jardine (Co-ordinating Principal Investigator) *[Name]* (Principal Investigator) *[Name]* (Associate Investigator) *(if required by institution)*
Study Sponsor:	The University of Sydney
Coordinating Centre:	NHMRC Clinical Trials Centre
Site:	[Site name] (where PI will recruit)

1 Which drug treatments are being tested?

Vitamin K, Sodium Thiosulfate and Magnesium Citrate will be tested in this study. These drug treatments are used in humans for other conditions. We do not know if they will be effective in the treatment of calciphylaxis and that is why this study is being conducted. Your study team may refer to these treatment types as a 'pharmacotherapy domain'.

a) Vitamin K1

Vitamin K plays a role in how the body manages safe levels of certain chemicals in the blood. Vitamin K starts a process that stops the build-up of calcium in the blood. Vitamin K is also used by the body to help blood clot, which is important for wound healing. Low levels of Vitamin K are common in dialysis patients and may result in an increased calciphylaxis risk and a longer time for wound healing.

Vitamin K1 will be taken by mouth. You will take one 10mg capsule following each dialysis session (3 times per week).

b) Sodium Thiosulfate

Sodium Thiosulfate is a treatment that is injected. It is currently used in the management of cyanide poisoning. Sodium Thiosulfate is thought to affect the way the body manages and removes calcium, as it attaches to calcium in the blood.

Sodium Thiosulfate will be given as an injectable solution. You will receive 25g, 3 times per week (usually at the end of a dialysis session).

c) Magnesium Citrate

Magnesium Citrate plays a role in many processes in the body and it may protect against the build-up of calcium in the blood. Treatment with Magnesium Citrate may reduce tissue swelling and improve wound healing in calciphylaxis. It may also reduce pain.

Magnesium Citrate will be taken by mouth. The total required dose is 450mg and will be taken in several doses. You will take three tablets per day. On days where you receive dialysis, the middle daily dose should be taken after your dialysis session.

2 What happens at the beginning of the study and during follow-up?

Vitamin K, Sodium Thiosulfate and Magnesium Citrate will be compared to matched placebo (a lookalike medication, with no active ingredients) and to each other. By comparing these treatments, it will be possible to see if one drug is more effective in reducing wound size.

If you choose to take part, you will be randomly allocated (like a roll of a dice) to receive one of the following treatment options:

1) Vitamin K1, Placebo Sodium Thiosulfate and Placebo Magnesium Citrate
2) Sodium Thiosulfate, Placebo Vitamin K1 and Placebo Magnesium Citrate
3) Magnesium Citrate, Placebo Vitamin K1 and Placebo Sodium Thiosulfate
4) Placebo only

Neither you nor your study team will know which initial treatment option you receive at any point throughout the study.

After commencing (drug) treatment, your safety will be checked throughout the study. Your routine bloods, collected as part of your standard care, will have additional laboratory tests at Weeks 1, 4 and 12. These test results will be reviewed by your study doctor to check it is safe for you to continue treatment. You will not need to provide any additional blood samples for this safety check.

3 What happens if my condition is not improving?

If your calciphylaxis condition does not respond to treatment, your treatment will be intensified at Week 4 and/or Week 12.

At Week 4, this will involve taking an additional active drug. For example, if you receive Vitamin K1 initially, you will also receive Sodium Thiosulfate or Magnesium Citrate (two active drugs in total). If you started with placebo only, you will receive one of Vitamin K1, Sodium Thiosulfate or Magnesium Citrate (one active drug in total).

If there is no response to treatment at Week 12, you will receive all three active drugs for the remainder of the study. From Week 12, study treatments will be given as 'open-label' meaning that you and your study team will know which drugs you are receiving.

This process of adding an additional active drug ('treatment intensification') has been built into the study. This means you are more likely to receive a treatment that works during the study and as early as possible. Treatments that are shown not to work will be removed from the study. This makes it more likely for you to receive a treatment that improves your condition.

4 What if I miss a treatment?

It is very important that you inform your study doctor and the study team if you are unable to attend the hospital to receive treatment. If you are taking study treatment outside of hospital visits, please try and make a note of any doses that you miss. Your study team will ask you this at each visit for the trial and you will be asked to bring any unused tablets and bottle/s to your follow-up visits.

5 Can I have other treatments during this research study?

The following medications and supplements will need to be stopped prior to taking drug treatments in this study, in addition to those already outlined in the General Participant Information Sheet.

- Magnesium
- Vitamin K
- Sodium Thiosulfate
- Proton pump inhibitors
- Statins
- Orlistat

Alternatives to these medications may be possible and your study doctor will discuss your individual treatment if this applies to you.

6 What are the possible side effects?

All medical treatments involve some risk of harm. The most common (but still rare) unwanted side effects associated with the treatments being tested are described below;

a) Vitamin K1

Vitamin K1 can lower blood pressure, which can result in dizziness, nausea and loss of consciousness. In theory, Vitamin K1 can also increase the risk of developing a blood clot. Whilst unlikely, too much Vitamin K1 can affect the way your liver works, which may result in tiredness and nausea.

b) Sodium Thiosulfate

Sodium Thiosulfate can cause a chemical imbalance in your blood, which can result in nausea, headaches and a change in appetite. Some people may also notice a change in their breathing and feel weak and tired.

c) Magnesium Citrate

Magnesium Citrate can cause mild to severe stomach and intestinal issues, which can result in diarrhoea, stomach cramping, vomiting and nausea.

All these side effects are rare, particularly for patients who are already on dialysis. Please tell your study doctor if you experience any of these symptoms, as reducing the dose may help.

7 Could my treatment be stopped unexpectedly?

There are some circumstances where your study doctor may recommend modifying the study treatment, such as changing your treatment dose. Your study doctor will monitor you and check it is safe for you to continue treatment throughout the study. If study treatment is permanently stopped, you can still continue to be a part of the study and will be encouraged to attend follow-up visits.

At any time throughout the study, you can choose to stop the study treatment should you wish but please discuss this more with your study doctor, so they are aware.

At the end of your follow-up in this study, your treating doctor at the time may choose to continue or stop use of Vitamin K1, Sodium Thiosulfate or Magnesium Citrate, however, this will be discussed with you.