Parent/Guardian Participant Information Sheet

NEOLEV3: high dose levetiracetam for neonatal seizures

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INTRODUCTION/ KUPU ARATAKI

You and your baby are invited to take part in a study aiming to find better treatments for neonatal seizures.

Please think about whether you would like your baby to take part. You are encouraged to discuss participation with other people such as family / whānau, or other healthcare providers. There is some urgency to detect and treat seizures; however, it is important that you take the time you need to decide.

Taking part is completely voluntary (your choice) and if you decide you do not wish your baby to take part, it will not affect your baby's current or future healthcare in any way. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

If you agree for your baby to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

Why are we doing this study?

The aim of this study is to find better treatments for newborn (neonatal) seizures. We monitor and treat newborn seizures because we want to reduce the risk of harm to baby's brain from ongoing seizures. Harm to baby's brain can have an impact on learning and development throughout childhood and as an adult.

Currently we use medicines called phenobarbital and phenytoin. These are our most effective medications and stop seizures in 60-80% of babies. While they are effective, they can cause side effects including sedation (making baby sleepy), low blood pressure and respiratory suppression (slowed breathing). Information from animal studies suggests that these medicines may also damage brain cells. In about 25-40% of newborns phenobarbital and phenytoin are not effective in stopping seizures. There is a great need to find better medications for the treatment of newborn seizures.

Levetiracetam (LEV) is a medicine that has been in use for 20 years in older children and adults with seizures with excellent safety and few side effects. We recently conducted the NEOLEV2 study in newborn babies, which compared LEV at a dose of 60mg/kg with phenobarbital at 20 to 40mg/kg. LEV stopped the seizures less often than phenobarbital in NEOLEV2 but had fewer side effects.

Complete seizure control for 24 hours occurred in:

- 28% of babies treated with LEV alone
- 80% of babies treated with phenobarbital

Adverse side effects of sedation, low blood pressure and respiratory suppression leading to the need for breathing support (intubation and ventilation) occurred in:

- 5% of babies treated with LEV alone
- 30% of babies treated with phenobarbital

In this NEOLEV3 study, we want to find out if higher doses of LEV could be more effective at stopping seizures and provide safer care for babies. Your family's participation will help us to do this.

How is the study designed?

All babies taking part in this study will be treated with standard dose LEV (60 mg/kg). If seizures continue, babies will then be randomised to receive either <u>additional LEV</u> or standard seizure medication phenobarbital at 20-40mg/kg. Both LEV and phenobarbital are initially given intravenously, through a line into baby's blood supply. Babies will receive ongoing maintenance treatment, either IV or orally, and if seizures continue or increase at any stage, the baby will receive phenobarbital.

Randomisation is a way of assigning individuals to different treatment groups by chance. In this study, 3 babies will be randomised to the additional LEV group for every 1 baby randomised to phenobarbital. Randomising some babies to LEV and some to phenobarbital allows us to understand the two drugs in terms of how safe they are and how effective they are at stopping seizures.

This is an open-label study which aims to find the most effective, safe dose of LEV. Open-label means that you and the doctors caring for your baby will know which treatment they are receiving; however, you will not be able to choose which group your baby is in.

This study will be carried out in three stages:

- In stages 1 and 2 we will invite babies with mild to moderate seizure severity (at least 30 seconds duration and less than 8 minutes per hour) to take part. In the NEOLEV2 study this group had a better chance of response to LEV alone with 41% of these babies having complete seizure control. Babies with high seizure activity who are more likely to need phenobarbital will not be included in stage 1 and 2.
- In stage 3, if higher doses of LEV have shown to be effective, we will invite babies with more frequent seizures (up to 30 minutes of seizures per hour) to take part.

The additional LEV dosage changes during the study based on what dose has already been proven to be safe, effective, and tolerable. At least 10 babies will receive an extra dose of 30 mg/kg in stage 1 before we study higher doses. The next 10 babies (stage 2) will receive up to 60 extra mg/kg as required. Once safety of that has been established, the next group of babies (stage 3) will receive up to 90 mg/kg additional dose. If any dose is shown to be unsafe or ineffective, we will stop the study, so that we do not give any babies an unsafe or ineffective dose.

Why is my baby being invited to take part?

Your baby has been asked to take part because they are at risk of having seizures or is suspected of having seizures and are suitable for treatment with LEV. In total 133 babies will be asked to take part for this study across New Zealand and the United States.

What participation will involve

If you consent for your baby to take part in this study the following will occur:

1) **Seizure monitoring**: continuous video electroencephalogram (EEG) monitoring will use small needle detectors (electrodes) placed on the scalp to record the electrical activity of the brain. This is standard of care at this hospital. Usually 6 electrodes are used, however, in the study we will use 10 electrodes to improve the sensitivity of the EEG. Often you cannot tell from looking at a baby that a seizure is happening. The EEG helps us to pick up seizures. A paediatric neurologist will be reviewing the EEG frequently. This is an innovative part of this study. It is closer and more detailed monitoring than is available routinely for clinical care. We will keep monitoring with EEG for 24 hours. Longer EEG monitoring may be needed if your baby is treated with hypothermia.

   We are also using computers with specialised Persyst software to read EEG and alert us to seizures. An **optional** part of the study involves providing your baby's deidentified EEG data to external researchers/companies including Persyst. For example, this may be used to help computers better recognize seizures and figure out when changes in the EEG are due to other activity (such as burping the baby or changing nappies).

   If you provide consent for your baby to take part but they do not have seizures, then no study related treatment or further study specific assessments will occur. We will follow your baby's clinical care and collect limited information on how they are doing while being monitored on the EEG. Your signed consent form and this limited information about your baby will retained with the study.

2) **Treatment**:
Initial treatment: if your baby has seizures, they will be enrolled into the study and receive LEV at 60 mg/kg. This is considered a 'new medicine' and it is being used instead of the current standard treatment for seizures, phenobarbital. If there are no further seizures in the first 24 hours of monitoring, your child will continue to receive LEV for 5 days.

Randomised treatment: if more seizures are seen on EEG in the first 24 hours of monitoring after the initial LEV has been given, your child will be randomised to receive either:

- Additional LEV at a higher dose (30 mg/kg, 60 mg/kg, or 90 mg/kg depending on how far through the study we are), OR
- phenobarbital at 20-40 mg/kg.

This treatment will continue for 5 days, either IV or orally, if your baby is able to be fed. If your baby responds well to the LEV, they may continue to receive it after the study is completed. The study doctor will discuss with you whether continuing LEV is suitable for your baby.

LEV discontinuation or addition of phenobarbital: if your baby is doing well on LEV as part of their initial or randomised care, they may continue on this treatment alone. However, sometimes it may be necessary for your baby to stop study treatment with LEV and start phenobarbital treatment, or for phenobarbital to be added as part of their ongoing treatment. This may need to happen if your baby's seizures increase in frequency or duration and changing to phenobarbital/adding phenobarbital is considered to be the safest course of treatment.

3) **General wellbeing**: because your baby is unwell, we are already monitoring their heart rate, blood pressure and breathing rate. This will help monitor for any possible side effects from their treatment. A study doctor or nurse will visit every day while your baby is in hospital to examine your baby and check the chart for possible problems related to their treatment.

4) **Blood tests:** we will check your baby's blood counts, kidneys and liver with blood tests, to ensure that they are not affected by the treatment. This will be done at the start of treatment, at 24 hours and at 5 days. For most babies the first two tests would have been done anyway as part of your baby's care, while the day 5 blood sample is likely to be additional for this research study.

We would like to measure the LEV level in your baby's blood. The purpose of this testing is to check the LEV level so we can be sure we know the right amount of medicine to give to a baby, without it building up in the baby's body. This is important but optional. If you consent to this, up to six blood samples will be collected over approximately one week. The total amount collected for LEV levels is 3mL (half a teaspoon).

To start with we will be able to take blood through your baby's IV line. If the IV line stops working, the blood may be collected by squeezing the baby's heel after a small pinprick. Most of the blood draws will coincide with the regular lab tests that your doctors need for general care. The total amount of blood collected (including for LEV levels) is less than 7mLs (1.5 teaspoons) over 5 days.

5) **Questionnaire:** we will ask you to complete a questionnaire about your experience in the study. This may be done before your baby is discharged from the hospital or up until 6 months from discharge.

Many newborns with seizures need to stay in the hospital for a week or two until they improve. We will visit your baby in the nursery daily to check on all these things during the 5 days of the study and check in again just before your baby is discharged home.

What will happen to my baby's blood samples?
Blood tests for your baby's general wellbeing (blood count, kidney and liver function) will be processed as per standard practice at the local laboratory. We expect these to be part of your baby's routine care.

If you agree, your baby's blood samples to test LEV levels will be frozen and sent overseas to University of Minnesota, MN, USA. This part of the study is **optional**. Your baby's samples will be coded with their unique study number before being sent to the overseas laboratory. This means that no identifiable details will be on the sample. Once we have the results of these blood tests, the blood sample will be destroyed. No karakia will be available during the destruction of the blood samples.

You may hold beliefs about sacred and shared values of any tissue samples removed and data originating from the tissue. The cultural issues associated with sending your baby's tissue samples and data overseas should be discussed with your family/whānau as appropriate. If you need cultural support this can be provided. Please let us know and we will arrange this for you, or you can ring the number at the bottom of the participant information and consent form. Cultural support is different to knowing more about the study treatments. In these cases, we can arrange a Study Doctor to come and talk to you and your whānau.

Follow up in early childhood

We would like to follow up your child's wellbeing in early childhood. Babies who have seizures are at risk of movement and learning problems including doing less well when they reach school. If this is identified early in childhood, neurodevelopmental therapy can help. Most children who experienced seizures as a newborn have follow up through the child development unit as part of their standard care, we will take extra steps to make sure this happens for all children who took part in this study.

The first assessment will happen around 2 years of age, and again around 4 to 5 years of age. We will access your child's medical records to see if the follow up assessment has been done as planned and to collect the results. If your child hasn't been seen at 2 or 4-5 years, we will contact you to arrange an appointment. We may also ask you at that time about participating in additional follow-up as part of this study.

Around the time of your child's 2-year assessment we will also ask you to complete a questionnaire about your experience in the study.

So that we can arrange any follow up we ask that you let the study team know if your contact details change.

What are the risks of the study?

The most common side effects seen with LEV are irritability, lack of energy or sleepiness. In NEOLEV2 the rate of each of the following side effects was 5% (1 in 20): sleepiness, poor feeding, infection, respiratory suppression, abnormal heart rate. Babies treated with phenobarbital showed higher rates of these side effects (ranging from 5-25%). No babies in NEOLEV2 were irritable but this has been seen in larger studies involving older children and adults so it will be monitored. Effects on blood counts or blood chemistries are extremely rare. If your baby has any serious side effect because of the study drug it may be stopped, and other therapy may be started.

Safety information from animal studies and use of higher doses of LEV in pregnancy, children and in adults are reassuring. Information from cases of overdose indicate even much higher doses of LEV remain safe. However, there may be side effects from the use of the study drug at high dose, which are not yet known. This could include serious allergic reaction or even death.

There is a risk of ongoing seizure activity if LEV does not work and leads to a delay in when we give phenobarbital. The risk that your baby will suffer a high seizure burden due to a delay in receiving phenobarbital will be minimised by continuous EEG monitoring and clear study guidelines for starting phenobarbital treatment if seizures get worse.

Most blood samples will be collected from your baby's IV line and will not cause any pain. However, if their IV-line stops working after a few days blood samples may require an additional heel prick and this may cause pain and bruising. This will be carried out by an experienced healthcare professional and all efforts will be made to minimise discomfort such as by warming baby's heel, giving sucrose/glucose and/or offering a feed.

The EEG monitoring in the study may make your baby less mobile, but you will still be able to hold your baby. To record the EEG, it is necessary to place small needle detectors on the scalp. Pain relief will be given during this.

For more information about these risks and side effects, ask your baby's study doctor.

Are there any benefits to taking part in the study?

There may not be any direct benefit to your baby from taking part in this study.

If LEV stops your baby's seizures, they may avoid treatment with phenobarbital, and therefore avoid the side effects of phenobarbital, which include: sedation (making baby sleepy), low blood pressure and respiratory suppression (slowed breathing).

Your baby will be more closely monitored as part of the study. The continuous video EEG monitoring in particular may pick up seizures that might have been missed. This can allow earlier treatment to help stop your baby's seizures.

The main benefit will be to future babies if the optimal dose of LEV is found. Many families who take part in health research express a sense of wellbeing knowing that they have helped to inform the best care for babies in the future.

What are the alternatives to taking part?
You are free to choose not to have your baby participate in this study. This will not affect your baby's current or future healthcare in any way. Your doctors will continue to provide the current standard treatments to your baby and do all they can to stop the seizures. LEV is not currently available as part of standard care.

What are the costs?
There are no costs associated with participation in this study. The study related EEG monitoring and treatment drugs are part of standard of care. Support, such as petrol vouchers, may be provided to ensure you are able to attend the follow up in early childhood.

What if something goes wrong?
If your baby is injured in this study, you would be eligible **to apply** for compensation from ACC for your baby just as you would be if they were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your baby's/child's recovery.
If you have private health or life insurance for your baby, you may wish to check with your insurer that taking part in this study won't affect their cover.

What will happen to information collected for this study?
During this study the study team at Starship (doctors, nurses and coordinators) will record information about your baby and their study participation. This includes the results of any study assessments and information from your baby's/child's hospital records until 5 years of age when the follow up assessments are complete. Your baby cannot take part in this study if you do not consent to the collection of this information.

Data collected from the study procedures will go into your baby's/child's permanent health records. Research data collected from this project will be stored at Starship Child Health, Te Toka Tumai, or a secure archiving facility, for a minimum of 26 years (10 years after the last participant turns 16). Research data (but not your child's permanent health record) will then be destroyed in compliance with Starship Child Health, Te Toka Tumai Governance requirements.

<u>Identifiable Information</u>
Identifiable information is any data that could identify you/your baby (e.g. name, date of birth, or address). The following groups may have access to your/your baby's identifiable information:

- Staff at *Kidz First* involved in the research study.
- Your baby's GP as they will be notified about participation with your consent.
- Study monitors to make sure the study is being run properly and that the data collected is accurate.

Your baby's identifying information may also be accessed by the sponsor, ethics committees, regulatory agencies, or government agencies from New Zealand or overseas, for example if the study is audited. As this is a US Food and Drug administration (FDA) funded study, this may include the FDA and other US or foreign government or regulatory agencies or authorities. Audits are done to make sure that participants are protected, the study is run properly, and the data collected is correct.

De-identified (Coded) Information

Research data will be collected and stored using a secure, password protected web-based data collection system hosted by the University of Minnesota in the US. This will not include any contact or identifying information. Instead, your baby will be identified by a study number. After the study is completed, the de-identified, archived data will be transmitted to and stored at the University of Minnesota Data Repository.

Your baby's video EEG data will be reviewed by neurologists at *Kidz First* and overseas as part of this study as part of their care and in order to improve computerised detection of seizures. The EEG will have identifying information removed and will be securely transferred to a database at the University of Minnesota. After EEG data has been completed, analysed and de-identified, the archived data will be transmitted and stored at the University of Minnesota Data Repository.

An **optional** part of this study includes consenting to de-identified EEG data being shared with researchers and/or companies interested in providing better treatments for babies with seizures. This includes, but is not limited to, the EEG analysis company Persyst. There is potential that Persyst or other companies may profit from this research if they are able to develop better tools for detecting seizures using EEG brainwave data from this study. The ownership rights to these discoveries, inventions or commercial products will belong to Persyst/the researcher/commercial company. You and your family will not receive any financial benefits or compensation from, nor have any rights to, any developments, inventions, or other discoveries arising from this additional analysis.

Coded study information will be kept in secure, cloud-based storage indefinitely. All storage will comply with local and/or international data security guidelines.

The following groups may have access to your coded information (including groups overseas):

- The study organisers for the purposes of this study.
- Regulatory or other government agencies worldwide to support the use of LEV treatment including the Food and Drug Administration (FDA), European Medicines Agency (EMA) and Medsafe in New Zealand.
- Individuals or groups as required or permitted by law, regulation, or order of a court or administrative tribunal.

Publication and future use of study data

The results of the study will be published and/or presented at conferences, but not in a form that would reasonably be expected to identify you/your baby. This study will be registered at clinicaltrials.gov and results of the trial will be published here as well as in peer-reviewed journals. Following publication, de-identified data from this study may be requested by other researchers whose proposed use of the data has been approved by the trial investigators and an independent ethics review committee. No identifying information will be included in any publication.

Risks

Although efforts will be made to protect your baby's privacy, absolute confidentiality cannot be guaranteed. Even with coded information, there is no guarantee that your baby cannot be identified. The risk of people accessing and misusing this information (e.g. making it harder to get or keep a job or health insurance) is currently very small but may increase in the future as people find new ways of tracing information.

Your coded information is being sent overseas. Other countries may have lower levels of data protection than New Zealand. There may be no New Zealand representation on overseas organisations which make decisions about the use of your information. There is a risk that overseas researchers may work with information in a way that is not culturally appropriate for New Zealanders.

Rights to access your baby's/child's information

You have the right to request access to your baby's information held by the research team. You also have the right to request that any information you disagree with is corrected.

Rights to Withdraw Your Information

You may withdraw consent for the collection and use of your baby's/child's information at any time, by informing the Study Doctor. If you withdraw consent, your baby's study participation will end, and the study team will stop collecting information about them. Information collected up until your baby's withdrawal from the study will continue to be used and included in the study. This is to protect the quality of the study.

Māori Data Sovereignty

Māori data sovereignty is about protecting information or knowledge that is about (or comes from) Māori people. We recognise the taonga of the data collected for this study. To help protect this taonga we have consulted with He Kamaka Waiora (Māori Health Team), Te Toka Tumai Auckland about the collection, ownership, and use of study data.

What happens after the study or if I change my mind?

When the study stops your baby/child will be under the care of their primary doctor. If you consent for your baby to take part but change your mind you can withdraw their participation at any time by informing the Study Doctor. No further study assessments or data collection will be carried out, however, any data or blood samples that have been collected until that point will be retained and included in the study.

You and your child will be told if any important new information is found during the course of this study that may affect your wanting to allow your child to continue.

Can I find out the results of the study?

Yes, if you would like to know the study results these will be provided to you. This will occur after the entire study is complete and has been analysed and published. It may be several years before this is available.

Who is organising and funding the study?

This study is being organised and coordinated by a team of study doctors including Principal Investigator Dr Cynthia Sharpe, Starship Child Health, Te Toka Tumai – Auckland, New Zealand, and US based Principal Investigators Sonya Wang, Jeffery Gold and Richard Haas based at University of Minnesota and UC San Diego and Rady Children's Hospital, respectively. The study has been funded by a grant from the US Food and Drug Administration (FDA).

Who has reviewed this study?

This study has been reviewed and approved by the Southern Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards, and the Research Review Committee at Te Toka Tumai – Auckland.

Who should I contact if I have further questions?

If you have any questions you can contact the principal investigator/study doctor Dr Cynthia Sharpe on **09 631 6122**.

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@advocacy.org.nz
Website:	https://www.advocacy.org.nz/

If you require Māori cultural support, talk to your whānau in the first instance. Alternatively, you may contact the administrator for He Kamaka Waiora (Māori Health Team) by telephoning 09 486 8324 ext. 2324.

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone:	0800 400 569 (Ministry of Health general enquiries)
Email:	hdecs@health.govt.nz

Thank you, tēnā koe, for making the time to read about, and for considering taking part in this study.

Parent/Guardian Consent Form

Study title: NEOLEV3: high dose levetiracetam for neonatal seizures
Principal Investigator: Dr Cynthia Sharpe, Starship Hospital, Paediatric Neurology; (09)631 6122

Site Investigator: Dr Chris McKinlay, Neonatologist, Kidz First Neonatal Care
Phone: 0274725099

Please note: if you require an interpreter, one can be provided for you.

Please sign to indicate you consent to the following:

- I have read the participant information sheet for NEOLEV3, or I have had it read to me in a language I understand. I have had the opportunity to discuss this project. I am satisfied with the answers I have been given.
- I have had the opportunity to use family / whānau support or a friend to help me ask questions and understand the project.
- I have had time to consider whether to take part in this project.
- I understand that taking part in this project is voluntary (my choice) and that I can stop my baby taking part at any time and this will in no way affect my baby's continuing or future health care.
- I understand that participation in this project is confidential and no material which could identify my child personally will be used in any reports on this research study.
- I understand the compensation provisions in case of injury during the study.
- I consent to the study team collection and processing information about my baby, including about my baby's health.
- I understand my baby's de-identified information will be sent overseas to secure databases at University of Minnesota.
- I know who to contact if I have questions about the project in general.

Please select yes/no for the following statements:

I wish to receive a summary of the results from this research study once available.	☐ Yes ☐ No
I consent to my child's GP being notified of our participation in this study.	☐ Yes ☐ No
Optional: I consent to my baby's de-identified EEG recording being provided to external companies and researchers, including Persyst. I understand that ownership rights to any discoveries, inventions or commercial products will belong to the external party.	☐ Yes ☐ No
Optional: I consent to my baby's blood sample being sent to University of Minnesota in the US to test levels of LEV. I understand it will be destroyed after the testing.	☐ Yes ☐ No

Declaration by parent/guardian

I hereby consent for my child to take part in this research study.

Name of Child: ______________________________

Parent/Guardian name: ______________________________

Signature: ______________________________ Date: ______________
(DD/MMM/YYYY)

Declaration by member of research team

I have given a verbal explanation of the research study to the parent/guardian and have answered the parent/guardian's questions about it. I believe that the parent/guardian understands the research study and has given informed consent for their child to participate.

Researcher's name: ______________________________

Signature: ______________________________ Date and time: ______________
(DD/MMM/YYYY, HH:MM)

PHONE CONSENT (if applicable)

Complete this section at the time of verbal consent via phone. Participant should confirm verbal consent by signing below.

I verify that Study Investigator [name]___________________ discussed information in the information sheet with the participant and answered any questions they had. At the time of signing, [name]___________________ gave consent for their child to participate in this study.

Name of staff member witnessing the phone consent: ________________________________

Signature: ____________________ Date and time: ____________________
(DD/MMM/YYYY, HH:MM)

Declaration by parent/guardian

I consented by phone for my child to take part in this research study on the date: ____________________

Signature: ____________________________ Date of signature: _________________________

Member of Research Team

I verify that I have now met in person with parent [name]___________________ and confirmed the phone consent.

Name of Study Investigator: ________________________________

Signature: ____________________ Date: ____________________
(DD/MMM/YYYY)