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| **Committee:** | Northern A Health and Disability Ethics Committee |
| **Meeting date:** | 19 June 2018 |
| **Meeting venue:** | Novotel Ellerslie, 72-112 Greenlane Rd East, Ellerslie, Auckland |

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| **Time** | **Item of business** |
| 1:00pm | Welcome |
| 1:05pm | Confirmation of minutes of meeting of 15 May 2018 |
|  | New applications (see over for details) |
|  | i 18/NTA/82  ii 18/NTA/83  iii 18/NTA/85  iv 18/NTA/88  v 18/NTA/89  vi 18/NTA/92  vii 18/NTA/93  viii 18/NTA/94  ix 18/NTA/95 |
| 5:15pm | Substantial amendments (see over for details) |
|  | i 17/NTA/51/AM03 |
| 5:30pm | General business:   * Noting section of agenda |
| 5:45pm | Meeting ends |

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| **Member Name** | **Member Category** | **Appointed** | **Term Expires** | **Apologies?** |
| Dr Brian Fergus | Lay (consumer/community perspectives) | 11/11/2015 | 11/11/2018 | Present |
| Dr Karen Bartholomew | Non-lay (intervention studies) | 13/05/2016 | 13/05/2019 | Present |
| Dr Christine Crooks | Non-lay (intervention studies) | 11/11/2015 | 11/11/2018 | Present |
| Dr Kate Parker | Non-lay (observational studies) | 11/11/2015 | 11/11/2018 | Present |
| Dr Catherine Jackson | Non-lay (health/disability service provision) | 11/11/2016 | 11/11/2019 | Present |
| Ms Toni Millar | Lay (consumer/community perspectives) | 11/11/2016 | 11/11/2019 | Present |
| Ms Rochelle Style | Lay (ethical/moral reasoning) | 14/06/2017 | 14/06/2020 | Present |
| Dr Melissa Cragg | Non-lay (observational studies) | CEN Co-opt | CEN Co-opt | Present |

## Welcome

The Chair opened the meeting at 1:00pm and welcomed Committee members.

The Chair noted that it would be necessary to co-opt members of other HDECs in accordance with the Standard Operating Procedures for part of the meeting. Dr Melissa Cragg confirmed their eligibility, and were co-opted by the Chair as members of the Committee for the duration of the meeting.

The Chair noted that the meeting was quorate.

The Committee noted and agreed the agenda for the meeting.

## Confirmation of previous minutes

The minutes of the meeting of 15 May 2018 were confirmed, noting the meeting did not start at 8am rather 1:00pm

## New applications

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| **1** | **Ethics ref:** | **18/NTA/82** |
|  | Title: | ZEST EU |
|  | Principal Investigator: | Professor Peter Gilling |
|  | Sponsor: | Zenflow, Inc. |
|  | Clock Start Date: | 07 June 2018 |

Rachael Hamill and Deborah Bell were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The objectives of the trial are to demonstrate the safety and performance of the Zenflow Spring System in relieving the symptoms of obstructive Benign Prostatic Hyperplasia (BPH) in men aged 50 and above.
2. The study is a multi-centre, prospective, single arm safety and performance trial. Patients enrolled in the study will have a procedure, implanting the device into the prostatic urethra to assist in alleviating the narrowing of the urethra due to the enlarged prostate.
3. All participants will require six follow up visits over the course of 24 months. The evaluations will include medical and surgical history and physical examination, including a Digital Rectal examination.
4. A maximum of 10 clinical sites will be used to enrol up to 50 participants across United Kingdom, New Zealand and Australia.
5. The Committee noted that this research appears to have the potential to offer a very good alternative for men in relieving symptoms of urinary obstruction secondary to BHP.
6. The Committee noted that the burden involved in screening is high.
7. There is no payment for participation.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee queried whether modifications have been made to the study or device as a result of the peer review. The Researcher(s) confirmed the sizes have been modified, (now two sizes) and the delivery system was also modified to allow for clearer visualisation and better placement of the device.
2. The Committee stated adequate training of investigators is key and requested assurance it will be undertaken. The Researcher(s) explained the training that has occurred. The Committee accepted this response.
3. The Committee queried the reference to Medsafe. The Researcher(s) noted this relates to device registries.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. For the questionnaires, only the unique code should be used, not the initials and full name, and claims to anonymity cannot be made. Please amend documents to reflect this.
2. The insurance is inadequate and only covers 10 participants in New Zealand. Please update this to cover the full 20 participants. Please have the Sponsor address this.
3. Please confirm the inclusion criteria age range. The Researcher(s) stated it was 45 years old. Please make sure this is consistent across study documentation.
4. The Committee asked whether the implant could mask any other diseases, or delay the identification of prostate cancer. The Researcher(s) explained as part of the follow up procedures the participants will have an ultrasound to ensure the device has not migrated. The Researcher(s) added that these patients are advised to have regular PSA screening, stating this is a continuous part of standard of care. The Researcher(s) stated this occurs for 2 years in the study but expected it would continue after (as standard of care). The Committee noted that continued scanning and PSA testing is not standard of care in New Zealand. The Researcher(s) explained that the stent will not impact the PSA testing. The Researcher(s) explained that based on historical evidence, incidence of migration generally occurs within first 6 months. The purpose of the ultrasound is to ascertain whether or not it has migrated. Historical evidence, and from prior studies, there was no evidence to suggest that devices migrated any time after 2 years.
5. The Committee remained concerned about the potential of the stent device to mask the symptoms of prostate cancer after the study procedures, and do not consider the advice to patients to regularly check PSA to be sufficient. The Committee requested that the Researcher(s) confer with the Sponsor to consider this longer term risk and provide the Committee with their assessment of this risk and a plan to mitigate the risk.The Researcher(s) explained that the device is designed as a permanent implant. The Committee asked if the participant wanted the device removed after 10 years, would this be at the participants cost? The Researcher(s) confirmed it would be. The Committee requested that more information about long term removal of the device is added to the participant information sheet.
6. The Committee asked if there is any plan for long term monitoring or follow up. The Researcher(s) explained that it is likely that they will extend the study. The Committee requested that participants are informed that there is no long term follow up plan, and that benefits that are experienced may not be long term.
7. Please have the sponsor confirm only participants that can provide their own informed consent are recruited.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. The participant information sheet requires amendment, particularly regarding the statement of risks which do not currently include all of the risks identified in the protocol (incontinence, perforation).
2. Improved explanation of some of the procedures is required (e.g. Cystourethroscopy is also rectal exam and void is to urinate).
3. Improved explanation of rights to withdraw is required, for example does that mean they will take out the device, and who pays for that, or is it only data related. The Researcher(s) explained that if it causes no issue the device will be left in, but it would be removed if the patient requested removal, noting the use of the retrieval tool. The Committee requested that this is made clearer in the PIS. The Researcher(s) confirmed this would occur at the sponsor’s expense.
4. The Committee asked whether samples go overseas. The Researcher(s) explained that de-identified data will be sent to the Sponsor, but no biological samples. Please remove the bullet point that refers to samples going overseas from the consent form.
5. Patients should be advised to abstain from sexual intercourse and sexual activities for at least four weeks following insertion of the Spring implant (this is not currently mentioned in the PIS but it is noted in the instruction sheet).
6. Include the following from the instruction sheet: Post-void dribbling may occur in the weeks following Spring implant insertion. Methods for managing post-void dribbling should be discussed with the participant.
7. Patients should be informed of actions to take in case of an emergency, i.e., when to consult a physician following insertion of the Spring Implant. Patients should be informed of the importance of always carrying their Implant Card.
8. Page 2 – states the device is not currently registered in New Zealand. The Committee asked whether it was registered anywhere in the world. The Researcher(s) stated it was not. Please make it clear it is in fact not registered anywhere in the world.
9. Please revise the benefits statement and ensure that the benefits stated are commensurate with the small sample size of the pilot”
10. Remove the last sentence under ‘benefits’ of the study (relation to tissue).
11. Add or remove general anaesthetic, currently only lists local. If general is an option please add risks of general anaesthetic.
12. Add what other options are available (alternative treatment options).
13. Remove yes/no questions on the consent form if they are not truly optional.
14. Review HDEC wording for compensation. <https://ethics.health.govt.nz/guides-templates-forms-0>

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Provide information on sponsor insurance. *(Ethical Guidelines for Intervention Studies para 8.4).*
* Provide further information on the study design, *in particular the ongoing screening* (*Ethical Guidelines for Intervention Studies para* 5.4)
* Address outstanding ethical concerns in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Kate Parker and Dr Brian Fergus

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| **2** | **Ethics ref:** | **18/NTA/83** |
|  | Title: | The gut microbiome in autism spectrum disorder (ASD) |
|  | Principal Investigator: | Associate Professor Mike Taylor |
|  | Sponsor: | University of Auckland |
|  | Clock Start Date: | 07 June 2018 |

Associate Professor Mike Taylor, Dr Pratima Giri and Dr Johanna Martin were present in person for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. Disorders of the autism spectrum are life-long, and estimated to affect approximately 1% of New Zealanders. This high prevalence, combined with the associated demands on social and educational care, represents a major issue in human health.
2. The underlying cause(s) of autism spectrum disorder (ASD) is currently uncertain, although there is evidence that microorganisms in the gut (the "gut microbiome") may play a role. This is consistent with published observations of a high prevalence of gut problems among people with ASD.
3. The Researcher(s) will use DNA sequencing technologies to identify gut microbes which may play a role in the disease process, and also to gain insights into the potential function of these microbes. Faecal (stool) samples will be used to provide a non-invasive proxy of the gut microbiome.
4. The Researcher(s) also plan to analyse metabolites of microbial origin in collected urine samples. The results of our study will contribute to the international effort to understand the causes of ASD, and ultimately translate to targeted treatments and a more specific health and educational support system for patients and family members.
5. The gut microbiome can be manipulated by, for example, diet, probiotics or other interventions, and although we will not be doing any interventions in this study, our findings should help inform future such endeavours. Finding a microbial "signature" of ASD in children (compared with non-affected controls) may also facilitate earlier diagnosis of this disorder in the future.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Researcher(s) explained the data management with regards to identifiability, noting that data would be stored in a coded form.
2. The Committee asked about the public (unrelated individuals) control recruitment. The Researcher(s) explained that there is the ‘Minds for Minds’ network that has a newsletter. This will be one avenue of recruitment.
3. The Committee asked if unrelated individuals are matched. The Researcher(s) confirmed as much as possible, adding that unrelated can mean inclusion of relatives that are not first degree.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee discussed capacity issues for participants who are over 16 years and noted that welfare guardians are not allowed to consent to a person taking part in any “medical experiment” other than to save the person’s life or to prevent serious damage to the person’s health (Protection of Personal and Property Rights Act). Whether the current study is a ‘medical experiment’ is a legal issue and, while the Committee does not provide legal advice, the Research(s) may seek their own legal advice.
2. The Researcher(s) confirmed for this study there will not be participants who are over 16. Please amend protocol to ensure this is reflected.
3. The Committee asked about the questionnaires, would they actually be able to provide appropriate ‘meta-data’ on diet to link with microbiome findings as they appear to be short and with non-standard dietary questions. The Researcher(s) explained that they were trying to balance level of information sought with feasibility of completion (and participant comfort). The Committee suggested that there were established dietary questionnaires for children and they may wish to further consider ensuring that they collect the information that will answer their research questions.
4. The Committee asked whether any clinically relevant results be identified in the study analyses (incidental findings) eg infections. The Researcher(s) stated it was not impossible. The Researcher(s) noted identification of incidental findings may not be clinically relevant. The Committee requested information on the process around incidental findings was detailed in the protocol and participant information sheet.
5. Please upload any advertisements that will be used.
6. The Committee asked whether the samples going overseas or not for analysis.
7. The Committee accepted the Researcher(s) proposal for not routinely returning results as they are not clinically meaningful at this point. However it noted that participants have the right to request results under the Code of Rights if they wish to.
8. Add detail on data management (I.e where it is stored, for how long etc), to the protocol.
9. Please note that health data derived from the study must be stored for a minimum of 10 years after the child turns 16 according to the [Health (Retention of Health Information) Regulations 1996](http://legislation.govt.nz/regulation/public/1996/0343/latest/DLM225650.html).
10. The Committee noted that this amendment was to split the genetic and microbiome study. The Committee understands that the recruitment for the genetic study is going well. When the next amendment comes in to update the existing approval regarding the genetic study the Committee requested that all study documentation (PISCF and Protocol) is uploaded at that time as there were some concerns around process for consent and PIS in this study that require re-examination for the main study.
11. The Committee noted that at 2 pages the protocol was very light and did not contain all the information usually required, particularly in a study with children. In particular, there is no clear rationale for the inclusion of 500 participants – no statistical justification. Please provide biostatistician review and justification for the proposed sample size, how many in the ASD group and the number of controls in each of the two control groups.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please add more detail to the participant information sheet from the protocol, for example analyses may detect small amounts of human DNA (which will be removed). Just a few sentences – i.e. it is sequencing the bugs. Make it clear that no identifiable data will go overseas, it will be deidentified and include a statement to the effect that in some countries data protection may be different or less restrictive than in NZ.  However, reasonable measures will be taken to keep participants personal health information confidential.  If the results of the study are published they will not be published in a form that could reasonably be expected to identify participants
2. The participant information sheet require amendment for both the parents/guardians and the under 16s, including advice that participants’ data will be included in public databases located in other countries
3. Please have multiple participant information sheets and consent forms for different audiences, including healthy controls and for neurotypical siblings – tailored to them and why you are seeking their participation.
4. Ethnicity data collection – should be conducted using Ministry collection examples.
5. The Committee noted that once a child reaches the age of 16, there should be a re-consent process. A suitable PIS should be used for that reconsent appropriate for the circumstances of the person having regard to differing levels of competence and supported decision making. The Committee noted that if a child turns 16 during the study and cannot provide their own consent they should be withdrawn.
6. Please also use the HDEC template for participant information sheets, particularly for compensation information, return of results etc

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, and assent forms, taking into account the suggestions made by the Committee (*Ethical Guidelines for Observation Studies* *para 6.11*).
* Please provide age appropriate assent form for non-consenting (children) participants to sign (*Ethical Guidelines for Observation Studies 6.21)*
* The Committee stated that it is not possible for HDECs to approve an application unless it is consistent with New Zealand law. As the researchers have not demonstrated that recruiting adults who cannot consent is lawful the HDEC has required that population is excluded from the study.
* Address outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Catherine Jackson and Mrs Toni Millar.

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| **3** | **Ethics ref:** | **18/NTA/85** |
|  | Title: | (duplicate) E Oho Rangatahi |
|  | Principal Investigator: | Dr Kahu McClintock |
|  | Sponsor: |  |
|  | Clock Start Date: | 07 June 2018 |

Dr Kahu McClintock and Eugene Davis were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. This implementation-focused research will pursue the E Oho Rangatahi (youth) programme whose aim is to enable the application of an indigenous Māori approach to increase mental health resilience among young Māori, their families and communities.
2. The research objectives are focussed on prevention and designed to increase the capacity of Māori to prevent and respond early to mental health problems, as well as develop more culturally responsive practices for service providers.
3. The aim is to ensure young people and people throughout the life course, have access to culturally responsive prevention and early intervention mental health support.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee noted the HRC proposal which stated that the intervention had been used for two years and had some evaluation undertaken already which showed improved cultural understanding. The Committee asked whether this study is more about implementing the programme in wider settings. The Researcher(s) explained that this phase is a more robust approach to evidence in a marae setting (the other similar intervention is in a school setting), noting that there was a need for more evidence to support the interventions.
2. The Committee asked whether any health benefits will arise from the study. The Researcher(s) stated identity and culture being raised and developed can have beneficial health impacts.
3. The Committee asked whether this study is about mental health. The Researcher(s) explained it is identity, environmental connections – in relation to educational and kinaesthetic learning. The Researcher(s) juggle mediums of learning. The Researcher(s) noted mental health is a narrow view. This programme is about health and wellbeing that is wider – cultural context, environment and relationship in family.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee noted the HRC letter refers to Pacific focus of the funding. The Researcher(s) explained the funding arrangements. The Committee noted it would be good to have an overview diagram/table to show how the projects fit together e.g. could include proposed cohorts and numbers, duration of programme, the main aim of each project to show how the design/aim differs. This would give the Committee a better overview of the project and its subprojects
2. The researchers did not address many of the issues outlined in the Southern HDEC decline letter, including in the application form they have again given no information on study risks, study outcomes or analyses to be conducted (also missing from the protocol). In terms of outcome measures the Researcher(s) explained that they would submit pre and post outcome measures. The Committee needs to see all relevant information related to this application and requested that outcome measures/instruments to measure these be supplied.
3. The Committee is particularly concerned to ensure that parents and participants are aware of the potential risks, the mitigation and the potential limitations of confidentiality (e.g. disclosure to parent/health provider). Risks should include any relevant risks for overnight marae stay and horse riding component of the intervention. The Committee also noted that further information on psychological distress (a risk identified in the information sheets), if noted during the study, is needed. Researcher(s) explained those with clinical background scan provide referrals or assist when rangatahi are distressed. Assistance will be provided when needed. The Researcher(s) noted this has never happened before. The Researcher(s) confirmed Eugene’s team will lead this component. The Committee asked more information is added here, about assessment and referral, whatever the process is, so the parents and participants understand what might happen if there is a clinical need identified. The observer who is a clinician role seems confusing, please explain further.
4. The Committee noted the STH Decline requested outcome measures, however these are not in the protocol.
5. There is also no information on how participants are identified and consented, and how they are supervised at the sessions.
6. The inclusion of a protocol was helpful, however, between the application form, protocol and various different participant information sheet and consent forms there still seems to be inconsistency and therefore confusion. The HRC application doesn’t have all the components expected in a Protocol.
7. The Committee noted that within the application the Study's CI is identified as Dr Kahu McClintock, however, within the participant information sheet forms it is Eugene Davis who is identified as the key contact and no mention of Dr McClintock. Eugene's CV is also not included as an attachment to the application. The Researcher(s) responded that they are the named investigator, particularly through the HRC funding, however Eugene will be the lead investigator. Please amend study documents to include both names and roles, and upload a CV for Eugene.
8. There is no ACC statement in any of the participant information sheet. Please view and include wording from the HDEC template for guidance <https://ethics.health.govt.nz/guides-templates-forms-0>
9. It is not stated how long time commitment is required for participants at the focus group hui
10. The consistency between participant information sheet forms is poor - they should all essentially provide the same information but just aimed at the specific audience. All PISCF need to explain the aim of the study and the components of the intervention.
11. The Peer Review does not provide a clear indication that the study is robust and this is reflected in the application, protocol and associated forms. Please seek independent peer review using the HDEC template peer review form.
12. The Researcher(s) confirmed the research will be conducted at Marae. The research will be conducted during weekend and holidays, however some mahi days will be during school times. The Researcher(s) explained that there are discussions about missing some school through a waiver in order to attend the research as it will impact school positively. The Researcher(s) stated they believe schools will welcome it. Parent consent will be sought specifically for participation in school hours. This should be made clear on the PIS.
13. The Committee noted that tracked changes should be provided, as well as a letter addressing each point raised – the HDEC found it difficult to compare between what had changed between the application submissions.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Remove any reference to the parallel study Mana Rangatahi from study documentation
2. The Committee asked when the focus groups are planned and whether focus groups are recorded. The Researcher(s) stated they will record it and take notes, but they will seek consent for this. The Researcher(s) stated they will store recordings securely and did not plan to destroy them following transcription. The Committee noted that for other studies the Committee ask that recordings are destroyed after transcription to help protect confidentiality. Unless there is a justifiable reason to store recordings they should be destroyed. Please amend PIS and confirm approach to recordings.
3. The Committee queried whether 20 young Maori at risk males will be recruited. The Researcher(s) confirmed this was correct. The Committee noted that the aims of the projects were in conflict across different documents submitted. The Researcher(s) clarified the aim of the study. The Committee noted that the study aims, outcomes and procedures needed to be clearly explained in the protocol and in each participant information sheet.
4. Add Intervention components (all components) and their timeline, and then includes tailored information regarding the study components (e.g. focus groups).
5. Add Timing for the intervention or activity need to be included
6. Appropriate consents need to be included for <16>16 and parent for the intervention, student focus groups, parent focus groups
7. Add Further information on risks
8. State that school time might be required
9. Include ACC statement
10. Please add time commitments for Whanau etc.
11. Consent for under 16s has the 6 components. This should be in the other participant information sheets. The HRC grant talks to additional components – weekends for example. Please add a table or a paragraph to add this detail.
12. Please view outstanding ethical issues for changes to the participant information sheet.

Decision

This application was *provisionally approved* by vote, with 6 for and 2 against, subject to the following information being received.

* Please amend the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Please provide age appropriate information sheets and assent forms for younger participants and amend the existing information sheets and assent/consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Provide further information on the study design, *in particular by improving the protocol with tracked changes* (*Ethical Guidelines for Intervention Studies para* 5.4)
* Please see (*Ethical Guidelines for Intervention Studies para* 7.2) for more information on levels of data confidentiality.
* Submit CVs for researchers. (*Ethical Guidelines for Intervention Studies para* 5.36)
* Provide further information on the recruitment process (*Ethical Guidelines for Intervention Studies para 6.2)*
* Address outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Brian Fergus, Dr Christine Crooks and Dr Melissa Cragg.

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| **4** | **Ethics ref:** | **18/NTA/88** |
|  | Title: | Prolonged mechanical ventilation following adult cardiac surgery |
|  | Principal Investigator: | Dr Paul Young |
|  | Sponsor: |  |
|  | Clock Start Date: | 07 June 2018 |

Dr Paul Young was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. This retrospective cohort study seeks to describe the characteristics and outcomes of adults who require >48 hours of mechanical ventilation following cardiac surgery.
2. The study will compare patients who underwent cardiac surgery between June 1 2015 and May 31st 2017 (inclusive) and were ventilated for less than or equal to 48 hours, with patients who underwent cardiac surgery during that period and were ventilated in ICU for more than 48 hours.
3. The study comprises three retrospective cohort studies undertaken in parallel, as the information they will provide is anticipated to be complementary. The first will use data from the NZ Ministry of Health database. The second and third will employ data from the Australian and NZ Cardiothoracic Surgical Databases.
4. A range of outcomes will be assessed for the two groups using data from the NZ Ministry of Health. These will include (i) total ICU hours during the index hospital admission; (ii) in-hospital mortality; (iii) day 30 mortality; (iv) day 180 mortality; (v) proportion of patients readmitted to hospital within 180 days of surgery (vi) days alive and out of hospital up to six months following cardiac surgery. A number of baseline variables will also be documented.
5. Using data sought from the Australian and NZ Cardiothoracic Surgical Databases, the following outcomes will be compared for the two groups: in-hospital mortality; day 30 mortality; hours in ICU; highest post-operative serum creatinine; proportion of patients with each of the following complications: (i) stroke; (ii) pneumonia; (iii) deep sternal wound infection; (iv) superficial sternal wound infection; (v) septicaemia; (vi) new renal insufficiency; and (vi) multi-organ failure. A number of other variables pertaining to pre-operative risk factors and to the operation undertaken will also be compared between the groups.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee noted this research has been justified in accordance with guideline 6.43 Observational Guidelines to enable the use of the health data without consent (refer to p.1.4 of the app), namely, given the quantity of the data sought, it is impossible in practice to obtain consent; (b) there would be no disadvantage to the participants or their relatives or to any collectivities involved because, amongst other things, the information seen by the researchers is de-identified and is not considered otherwise to be sensitive; and (c) the public interest in the study outweighs the public interest in privacy.
2. The Committee and The Researcher(s) discussed the NZ Cardiothoracic Surgical Database. The Researcher(s) agreed to update the Committee on the current status of the database, governance and process for access to data for research.
3. The Committee asked what the New Zealand figures were, noting that the totals were not separated from Australia in the application. The Researcher(s) explained initially 1000 will be randomly selected, and then the entire database. New Zealand has around 10,000 total.
4. The Committee asked whether it was intentional for the NZ Cardiothoracic Surgical database not to include NHIs because it seemed like a missed opportunity for potential future research. The Researcher(s) stated he was not involved in the establishment of the NZ database.
5. The Committee noted that the investigators had not been listed in the protocol. The Researcher(s) clarified who was involved, including the statistician and would provide this in writing.
6. The Researcher(s) confirmed that investigation of other international databases is not proceeding at this stage.
7. The Researcher(s) noted the intended use of the Australian data is to define population in different ways, not to compare countries. The main focus was to assemble a group of publications to create impetus that this is a public health issue. A separate application is being made to the Australian Cardiothoracic Surgical database.
8. Ethnicity data in New Zealand research should be collected in accordance with the Ministry of Health Ethnicity Data Protocols (link). The Researcher(s) would confirm how this was collected in the NZ Database, however the Ministry of Health database would use the appropriate classifications and analyses.

Decision

This application was *approved* by consensus.

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| **5** | **Ethics ref:** | **18/NTA/89** |
|  | Title: | Residential Aged Care Facilities and antibiotic resistance: A feasibility study |
|  | Principal Investigator: | Dr Patricia Priest |
|  | Sponsor: | University of Otago |
|  | Clock Start Date: | 07 June 2018 |

Dr Patricia Priest was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

Dr Catherine Jackson declared a potential conflict of interest, and the Committee decided it was not relevant and for her to stay in the room and participate in the meeting.

Summary of Study

1. Antimicrobial resistance (AMR) is of increasing concern both inside and outside hospitals, but little is known about how AMR is transmitted into and within the community.
2. Residents of Residential Aged Care Facilities live in close contact and are high users of antimicrobials, putting them at higher risk of carrying and transmitting resistant organisms.
3. This application is for a study to assess the feasibility of carrying out a large prospective study of the carriage of AMR organisms, to inform policies to reduce the risk of transmission of AMR organisms within these facilities, between hospitals and the facilities, and between the facilities and the community.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee discussed capacity issues for some of the people who may be recruited into this study and noted that welfare guardians are not allowed to consent to a person taking part in any “medical experiment” other than to save the person’s life or to prevent serious damage to the person’s health (Protection of Personal and Property Rights Act). Whether the current study is a ‘medical experiment’ is a legal issue and, while the Committee does not provide legal advice, the Research(s) may seek their own legal advice.
2. The Committee asked about determining capacity to consent. The Researcher(s) explained facilities would assist in this determination. Please add how this determination occurs on the participant information sheet, to ensure only those who can consent participate at this stage.
3. The Committee noted families should be involved but not necessarily seeking their consent (supported decision making).
4. The Researcher(s) confirmed that until legal advice is sought the study will proceed with only participants who can provide their own informed consent.
5. The researchers confirmed the staff involvement was just the focus group. The Committee noted researchers can’t guarantee anonymity of staff input in a focus group setting and that there were potential employment issues like hierarchies and conflict of interest issues involved. The Researcher(s) explained it was only to find out how staff would feel about a similar study running a lot longer. The Committee noted participant information sheet for staff and requested that all references to anonymity should be removed.
6. The Committee noted that staff would need to provide their own consent when giving their feedback, and the researchers cannot claim anonymity for staff participants.
7. The Researcher(s) explained the main feasibility issues were related to residents.
8. The Researcher(s) stated aims of larger study (page 5 protocol).
9. The Committee noted participants need to be informed about data being released by the facility on the participants. Please add how the data is collected to the participant information sheet and protocol.
10. The Committee asked why self-report of health data from participants was proposed, rather than accessing NHI data e.g. on hospitalisations and medications. There was concern that this may be poor quality and lead to incorrect conclusions The Researcher(s) explained that this study was more about collecting samples and consent, not the data collection, adding they wanted to reduce identifiable data access. The Committee noted that there would then be no reason for questionnaires – if that is really the study aim. The Committee also noted that identifiable data was not specifically problematic if it was needed to answer the research question and was consented to, although confidentiality provisions would need further attention.
11. Amend the documentation (advertising) to be for consenting participants.
12. Please explain testing plans. The Researcher(s) noted not likely to identify incidental notifiable results, and that they planned to make the samples anonymised (i.e. all identifier removed) before submission to the lab so that no return of results was possible (to avoid potential participant stigmatisation). The Researcher(s) confirmed microbial culturing in the first instance. If larger study proceeds researchers would sequence to look at relatedness and therefore transition of disease, but that is not part of the present study.
13. For larger study, could raise incidence of VTEC, for example.
14. Please explain reasons for rectal swabs, and the concern about the invasiveness of this testing. The Researcher(s) stated they do not anticipate using this method often but it is a way to collect faecal specimens. Please confirm that the rectal swabs are scientifically adequate for sample collection and whether the participant could do this themselves or not.
15. Please strengthen data storage details in the protocol.
16. Please use Ministry of Health ethnicity classifications when collecting ethnicity data <https://www.health.govt.nz/publication/hiso-100012017-ethnicity-data-protocols>
17. The Committee asked about symptoms – what are other risk factors for this kind of bacteria. The Researcher(s) stated not collecting information on risk factors at this time.
18. The Researcher(s) confirmed the focus groups are not recorded.
19. Please note that health data derived from the study must be stored for a minimum of 10 years according to the [Health (Retention of Health Information) Regulations 1996](http://legislation.govt.nz/regulation/public/1996/0343/latest/DLM225650.html).
20. Please submit any planned advertising.
21. Please submit the remaining pages of the peer review – some pages were missing.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Make the information on rights to results (i.e. can’t get or could if coded) need to be explained in PIS
2. Please remove the witness signature section from the participant information sheet consent form.
3. Please view HDEC template participant information sheet and amend accordingly, including tracked changes <https://ethics.health.govt.nz/guides-templates-forms-0>
4. Self-sample - please make it clear this is an option. Be clear what options are available.
5. Under benefit – make it clear there is no individual benefit to participating in this study.

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, and assent forms, taking into account the suggestions made by the Committee (*Ethical Guidelines for Observation Studies* *para 6.11*).
* The Committee stated that it is not possible for HDECs to approve an application unless it is consistent with New Zealand law. As the researchers have not demonstrated that recruiting adults who cannot consent is lawful the HDEC has required that population is excluded from the study.
* Address outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Catherine Jackson and Dr Brian Fergus.

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| **6** | **Ethics ref:** | **18/NTA/92** |
|  | Title: | A Phase 2, Placebo-Controlled, Double-Masked Study to Assess Safety and Efficacy of ISIS 696844, an Antisense Inhibitor of Complement Factor B, in Patients with Geographic Atrophy Secondary to Age-Rel |
|  | Principal Investigator: | Dr Philip Polkinghorne |
|  | Sponsor: | INC Research New Zealand Limited, a Syneos HealthT |
|  | Clock Start Date: | 07 June 2018 |

Dr Philip Polkinghorne and research co-ordinator were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The purpose of this Phase II study is to evaluate the safety and effectiveness of the experimental drug, ISIS 696844 in patients with Geographic Atrophy, Secondary to Age-Related Macular Degeneration (AMD). The study lasts approximately 22 months and includes up to 37 clinic visits.
2. Following written informed consent, participants will have tests and physical exams for up to 8 weeks (referred to as the screening period), to see if they are eligible to enter the treatment period.
3. Participants who meet the entry criteria will be randomised in a 1:1 ratio to receive either ISIS 696844 or a placebo (a substance that looks like ISIS 696844 but is inactive).
4. However, neither the study doctor nor participant will know which study drug (active ISIS 696844 or placebo) the participant is receiving. Participants will receive study drug by injection under the skin weekly for the first 3 weeks, and then every 2 weeks or monthly for the next 66 weeks (up to 70 weeks in total), receiving up to 36 injections.
5. Safety and clinical laboratory evaluations, ophthalmic exams and imaging, as well as blood sampling for PK analysis, will be performed periodically throughout the Treatment Period.
6. Following the treatment period, participants will be followed for safety assessments for 16 weeks after the last dose of Study Drug and will return to the Study Centre for 3 outpatient visits for safety and clinical laboratory evaluations, ophthalmic exams and imaging, and for blood sampling for PK.
7. Adverse events and concomitant medications will be recorded.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee asked about recruitment. The Researcher(s) stated there is a list of potentially eligible patients from Auckland Eye. The Researcher(s) acknowledged that it is a long study with a lot of visits, but nurses are available to try and reduce clinic visits.
2. The Committee noted the Investigators Brochure refers to previous studies over a period of only 6 weeks, yet this study takes place over70 weeks. The Committee asked if the Researcher(s) were satisfied that the safety profile is appropriate for that length of time. The Researcher(s) confirmed they were.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee asked whether samples are stored in a biobank. If so, where and what are governance arrangements? For example, how will the differing consents be recorded and respected? Please have the sponsor address use and storage of tissue in relation to governance and consent for the main study, for the optional genetic sub-study and for the optional future unspecified research study.
2. For recording participant information please use year of birth not date of birth.
3. The Committee would like more information about the nurses who will conduct the home visits in terms of their qualification and experience and data governance and management issues. The Researcher(s) agreed to provide the Committee with further information.
4. The Committee discussed safety issues relating to the storage of the study medicine in household refrigerators and accidental ingestion by children. The Researcher(s) will consider using a locking mechanism on the medicine container.
5. The Committee noted that data management details are sparse in the protocol in terms of the use of things such as locked filing cabinets for paper based records with limited and auditable access to the same, encrypted electronic communications, password protected data, confidentiality undertakings of staff etc. Patient initials should not be used (refer protocol)
6. The insurance certificate states “Ded: ea Occ: $25,000. Agg: $125,000”. Please confirm that this statement does not impact on the level of compensation available to NZ participants.
7. The Committee asked whether the Researcher(s) intended to recruit participants who may not be capable of giving informed consent. The Researcher(s) advised that they intend to recruit only participants who have full capacity. Hence, the amendments made to the protocol in that regard are not relevant in the NZ context.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please ensure that participants understand the arrangements for reimbursement of travel expenses.
2. Review HDEC wording for compensation. <https://ethics.health.govt.nz/guides-templates-forms-0>
3. p2 of the main PIS states that ”You will receive your routine medical care whether or not you take part” The Committee was not sure that’s correct – if they participate they will receive the trial care instead of standard care. Please address this.
4. Remove withdrawal in writing, participants can withdraw verbally. There can be a written form but it must not be mandatory.
5. Include statements in all relevant PISs that data protection in overseas countries may be different or less restrictive than in New Zealand and
6. The Committee queried the lack of a Māori tissue statement in the Participant Information Sheet. The committee recommended the following statement in **all** relevant PISs: “*You may hold beliefs about a sacred and shared value of all or any tissue samples removed. The cultural issues associated with sending your samples overseas and/or storing your tissue should be discussed with your family/whanau as appropriate. There are a range of views held by Māori around these issues; some iwi disagree with storage of samples citing whakapapa and advise their people to consult prior to participation in research where this occurs. However, it is acknowledged that individuals have the right to choose.”*
7. Page 20 participant information sheet – section 15 notes the study could stop unexpectedly. The National Ethics Advisory Committee guidelines state studies should not be terminated simply for reasons of commercial interest. Please remove this from the PIS.
8. Remove reference to IRB – and American language generally.
9. On page 5 of the PIS reference is made to Vaccinations – please include a statement at that point that further information about the vaccinations is contained in section 9 of the PIS. Likewise, for hep b first mention on page 7, please refer to page 19 that has fuller information.
10. The Committee noted that some genetic testing is mandatory but there are two optional sub-studies. Page 7 of the main PIS should be clearer which one is mandatory genetic testing, by way of a subheading. The Researcher(s) will highlight this. The Committee noted the reasons why this testing is mandatory.
11. The Committee asked if it is possible to withdraw samples from overseas. Please clarify this for participants and to the Committee in a cover letter.
12. Please check with sponsor about payments for side effect treatments. This will also impact the detail which must be included in the participant information sheet.
13. Use pregnancy template wording for males.
14. Any data collected after birth must be re-consented after the child is born. Please amend the relevant PISs accordingly and the consent forms.
15. State where the labs are located and also the labs which read the photographs.
16. Please suggested amending the wording in **all** the PISs from : “If the results of the study are published your identity will remain confidential” to the following wording: “will not be published in a form that could reasonably be expected to identify participants”;
17. Please delete, in **all** PISs, the sentence: “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.” Include statements about the need to be very careful with drug storage.
18. Patients must be made aware of the risks of the vaccines (this is also required by the protocol).
19. Best practice is for a participant’s GP to be advised that s/he is taking part in a clinical trial rather than this being an optional matter. Please amend the consent form accordingly.
20. The return of any significant abnormal results obtained during the study may be optional.
21. There is no information in the participant information sheet about abnormal findings. Please add some process around what will occur in the event of abnormal findings.
22. Include, in the consent form, acknowledgement that images and data, as well as bio specimens, are being sent overseas. Consider the following statement: “I agree to my blood and urine samples and my data, including digital images, being sent overseas and I am aware that my samples will be disposed of using established guidelines for discarding biohazard waste. I understand data protection in other countries may be different or less restrictive than in New Zealand.”
23. Please use Ministry of Health ethnicity classifications when collecting ethnicity data to ensure the options available are suitable for New Zealand participants.
24. The Committee noted that there is no licence for meningococcal vaccine – it will be off licence use, and it does not confer lifelong immunity. Please make it clear in the PIS that participants may still get sick even if they have been vaccinated, and that it does not protect against other forms of meningitis.
25. The Committee asked whether there had been any consideration given to whether participants should be vaccinated against influenza type B because of an increased risk for that type of infection. The researchers are to consider and advise the Committee
26. The Committee discussed the order in which vaccinations should be given.
27. Screening TB – confirmed using quantiferon. The Committee asked for the process and assurance around screening.

Participant information sheet for optional genetic study

1. The Committee noted there are several paragraphs in this PIS about genetic counselling, but the study will not return results. Please remove the counselling paragraphs because they are unnecessary and therefore confusing.
2. State the location of Emory Genetics Lab and the laboratory where the frozen samples will be stored.
3. The committee asked about the nature and extent of the data which will be sent with the genetic samples The Researcher(s) explained that clinical data relating to participants’ eyes will be sent with the samples, participant codes will be used and the sponsor will have no access to confidential information. Please make these matters clear in the PIS
4. Include as a risk in this participant information sheet – that there is a risk of loss of confidentiality of your information (this has been included in the FUR PIS but it does not appear in the genetic optional sub-study PIS).
5. Please check for typos (e.g., on page 6 ‘your sample **will** be stored in such a way that your identity could reasonably be ascertained”)
6. Please be very clear in the PIS what kind of projects might be “closely related further research projects” as mentioned in the consent form. Participants must understand what such projects are before they can consent to them and there is no explanation of them in the PIS. The PIS should clearly distinguish between what the current research project involves and what ‘closely related future projects’ involve.
7. Please remove the double up in the consent form for the different research projects.

Participant information sheet for optional future unspecified research study

1. Please carefully explain and define in the PIS what kinds of research is for ‘future research closely related to this research project’ as referred to in the consent form as compared to any future research. Participants must understand what they are consenting to and there is currently no explanation in the PIS.
2. Delete from the consent form the section about consenting to the GP being informed about the participant’s participation in the study and the return of abnormal results – it is not relevant for this sub-study.

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Provide detail on payments to participants (*Ethical Guidelines for Intervention Studies* *para 6.34*).
* Address storage of tissue and bio banking. (*Ethical Guidelines for Intervention Studies* *para 2.14*).
* Respond to outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Mrs Rochelle Style and Dr Karen Bartholomew.

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| **7** | **Ethics ref:** | **18/NTA/93** |
|  | Title: | Titan |
|  | Principal Investigator: | Dr. Dean Corbett |
|  | Sponsor: | AMO Australia Pty Ltd |
|  | Clock Start Date: | 07 June 2018 |

Dr Dean Corbett was present in person for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The purpose of this study is to allow surgeons experienced in small-incision cataract surgery to evaluate the clinical ‘handleability’ and acceptability of the TITAN Modular Cartridge Delivery System for use in implanting TECNIS® 1-piece IOL Model ZCB00 during routine cataract surgery.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee asked how it is better than standard of care. The Researcher(s) noted it was a faster operation.
2. The Committee asked about the sponsor. The Researcher(s) stated they have a good working relationship due to the site’s good data, good enrolment.
3. The Committee asked how researchers will identify participants. The Researcher(s) stated that patients were already receiving the lens as part of routine care part of study, and would be asked to participate but would have had the decision about the appropriate lens made prior to recruitment.
4. The Committee and the Researcher(s) discussed inducement, financing, insurance and compensation.
5. The Researcher(s) noted exclusion criteria for the trial to minimise risk or AE.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. Please use Ministry of Health ethnicity classifications when collecting ethnicity data to ensure the options available are suitable for New Zealand participants.
2. The insurance certificate expires on 28 September 2018 and must be updated if the study has not been completed by that time by the provision of a new certificate to the Committee. Please clarify what policy territory is.
3. The Researcher(s) stated they would talk to the sponsor and insurers to ensure participants are not excluded from any on-going care resulting from the research. The Committee noted this was important as the involvement in the research still requires participants to pay for the treatment, and to be excluded from ACC equivalent insurance for injuries resulting from a minor part of the treatment would be unfair to participants.
4. Remove English speaking requirement inclusion criteria.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. The Committee queried whether this was a first in human device. The Researcher(s) confirmed it was. Please make this clear in the participant information sheet.
2. The Committee suggested the researcher use the HDEC template <https://ethics.health.govt.nz/guides-templates-forms-0> which will help to reduce the current repetition and use New Zealand language.
3. Add information about personal data that is collected, for example length of eye, name, address, refraction.
4. Please ensure a participant number is used and avoid using any patient identifiers.
5. The Committee queried how confidentiality was maintained when the research involved taking photographs and video. The Researcher(s) noted that the photographs and video are of the eye only, explaining that the Sponsor is providing a high resolution camera. Please add to participant information sheet under study procedures that their eye will be videoed.
6. The ‘what if something goes wrong’ section can be reduced, please review the HDEC template participant information sheet.
7. The Committee and the Researcher(s) discussed the pregnancy information, determining that while it was unlikely to be relevant it could stay in if the Researcher(s) felt it was necessary.
8. Consider increasing spacing between words or use bigger fonts – noting patient population will have poor vision.
9. Note the additional research visit over usual care in the participant information sheet – and make it clear it is at no additional cost. The Researcher(s) noted it is in schedule of payments.
10. Please include in the PIS the risks of the device – currently the PIS just refers to the risk of the cataract surgery
11. Please remove the statement about risk to family members – it is irrelevant
12. Please include a benefit section explaining that there will likely be no benefit from the study for the individual participants but the study may help others in the future. Please note that while participants will have the benefit of better vision that would occur anyway.
13. Make it clear that if a participant withdraws from the study whether the implant is or is not removed.
14. Please remove the Maori tissue statement because no tissue will be taken during the study.
15. Page 8 privacy clause - remove.
16. Provide greater clarity in the PIS about the collection and use of patient data, whether identifiable or deidentified, and what privacy and confidentiality protections will be taken. The current explanations in the PIS are lengthy, repetitive and confusing Please also provide, for the Committee, clear data management and governance plans. .
17. Please amend the consent form so it is consistent with the amendments sought to the PIS

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Please submit evidence of sponsor insurance, and address compensation concerns of the Committee. *(Ethical Guidelines for Intervention Studies para 8.4).*
* Address outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Christine Crooks and Ms Toni Millar.

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| **8** | **Ethics ref:** | **18/NTA/94** |
|  | Title: | CLEAR Outcomes Study |
|  | Principal Investigator: | Dr. Raewyn Ann Fisher |
|  | Sponsor: | Esperion Therapeutics, Inc |
|  | Clock Start Date: | 07 June 2018 |

Mr Chris Taylor was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The main purpose of the study is to see if the study drug [Bempedoic acid (ETC-1002)] reduces the risk of major cardiovascular (heart and blood vessel-related) events in patients with, or at high risk for, heart disease who have had complications related to taking statins. Statins are medications used to lower cholesterol levels in the blood. The study will compare the study drug to a placebo, and will look to see how often cardiovascular events such as heart attacks, strokes, heart-related surgeries, hospitalizations, and also death occur for participants in the study. The study will also look at how the study drug may affect the level of cholesterol and certain proteins in the body and how safe the study drug is.
2. Study consists of a screening period, a run-in period, a treatment period, and a follow-up period.
3. Approximately 12,604 eligible participants will be randomised in ratio of 1:1 to receive 1 of the 2 following treatments in a double-blind fashion (neither doctor or participant would know which drug of the 2 is given):
   * + Bempedoic acid 180 mg tablet once daily (n = 6,302)
     + Matching placebo tablet once daily (n = 6,302)
4. Treatment will begin at Visit T1 and continue daily. Participants will visit at Month 1 (Visit T2), Month 3 (Visit T3), and Month 6 (Visit T4). Following Month 6, participants will be contacted every 3 months (alternating phone and clinic visits) for remainder of study.
5. It is estimated the mean treatment duration will be approximately 45 months (3.75 years).
6. This study will include several independent and expert committees.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee discussed the use of placebo as a control in this study, particularly for high risk participants, noting that it was for statin-intolerant participants only, and was satisfied that it was appropriate.
2. The Researcher(s) confirmed that they collect ethnicity. Please use Ministry of Health ethnicity classifications when collecting ethnicity data to ensure the options available are suitable for New Zealand participants
3. The Committee asked about returning results. The Researcher(s) stated participants are given clinically relevant results as they go through the study.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee queried what was meant by ‘checking state of mind’ of participants. The Researcher(s) stated there was no specific test, but it related to how they are tolerating their involvement in the study. The Committee asked about process if someone discloses concerning information, for example depression. The Researcher(s) stated the researchers would make a determination to refer for assessment and treatment, adding some are GPs, but if the researcher in question does not have the training they will need to refer. The Committee requested detail for those circumstances is added to the protocol.
2. Please ask the Sponsor what they were using for follow up and or questionnaires.
3. Please explain recruitment. The Researcher(s) explained that others sites recruiting are private research units and some public hospitals. Initially they will recruit from existing databases. It is also possible that doctors will go through their GP database and find patients that meet eligibility criteria, and offer it as a treatment option.
4. The Committee requested that the Sponsor addresses locality authorisation, in relation to the sites allowing doctors review health information to screen for recruitment.
5. The Committee noted some documents appeared to only be relevant to the US, such as ‘health insurance not required’. Please ask the Sponsor to clarify that all supporting documents are for New Zealand.
6. Page 7 of participant information sheet – study drug - no post study access. The Committee noted this patient group has no other option. The Researcher(s) noted it is a standard statement, adding that continued access depends on outcome of the study. The Committee noted the restriction on participation in further studies, and asked for a justification of this restriction by the Sponsor. If there is not an adequate justification, take this out.
7. The Committee noted the death on page 9 of the participant information sheet was potentially link to drug. Further information on this was requested, the Researcher(s) agreed to discuss this further with the Sponsor and respond.
8. The Committee noted the Maori responses in application were not up to standard, given the importance of cardiovascular disease to Maori health. See <https://ethics.health.govt.nz/guides-templates-forms-0> for guidance in future.
9. The Committee asked for the Sponsor to confirm that the statin intolerance screening is sufficient to determine intolerance and queried whether independent verification of intolerance could be obtained from participants’ GPs
10. Please have the Sponsor address what the special conditions are on insurance certificate, and provide clarification on impact on ACC equivalent compensation.
11. Please view HDEC template wording for compensation.
12. The Committee noted there should be no requirement to withdraw in writing. Participants can withdraw verbally. A written form can still be used but it must not be mandatory.
13. Advertisement – remove the statement: ‘ Health insurance is not required to participate

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. The Committee requested that follow up by email and text is outlined in the participant information sheet. The Researcher(s) also confirmed it was not done by a third party.
2. The Researcher(s) explained that there is screening for Hepatitis B and C. The Committee noted these are notifiable diseases and positive result need to be referred to public health as a legal requirement. Please make this clear to participants.
3. The Committee asked about samples going overseas, in particular to the US (Top page 8 participant information sheet). The Committee noted if samples are going offshore the name of lab, how long stored etc. is required. The Committee added testing must be study specific tests, not unspecified ‘further analyses’ as currently stated on page 9 – please remove.
4. The National Ethics Advisory Committee guidelines state studies should not be terminated simply for reasons of commercial interest. Please remove wording to that effect from the participant information sheet.
5. Page 7 – biomarker analyses. This is not mentioned elsewhere. The Researcher(s) stated it is not biomarker development, acknowledging this is misleading and would remove.
6. Sponsor not mentioned until page 8. This is unusual – please amend.
7. Data management – provide greater assurance around security around information, include in participant information sheet that data is going overseas, and in some countries will be less protection for that data than exists in New Zealand. Please confirm data is de-identified.
8. The Committee noted there is a pregnancy information template at <https://ethics.health.govt.nz/guides-templates-forms-0> and asked the researchers to review it and add information that is missing from the current version.
9. Add more detail on withdrawing and specific information about specimens use in a case of withdrawing.
10. Please include information in the PIS which explains to participants about the return of abnormal results, particularly given this is an option provided for in the consent form. Please also make it clear in the PIS that a participant’s GP will be notified of his/her participation in the study
11. Please amend the consent form to be consistent with the changes requested for the PIS.
12. Review HDEC wording for compensation. <https://ethics.health.govt.nz/guides-templates-forms-0>

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Please submit evidence of sponsor insurance, and address compensation concerns of the Committee. *(Ethical Guidelines for Intervention Studies para 8.4).*
* Provide further information on the recruitment process (*Ethical Guidelines for Intervention Studies para 6.2)*
* Address outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Catherine Jackson and Dr Brian Fergus.

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| **9** | **Ethics ref:** | **18/NTA/95** |
|  | Title: | OOC-ACM-303: Study of the Efficacy and Safety of Octreotide Capsules in Patients who Previously Tolerated and Responded to Injectable Octreotide or Lanreotide Treatment |
|  | Principal Investigator: | Dr Patrick Manning |
|  | Sponsor: | Chiasma Inc. |
|  | Clock Start Date: | 08 June 2018 |

Dr Patrick Manning was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The study investigates Pharmacologic treatment of acromegaly includes chronic therapy with parenteral somatostatin receptor Ligands (SRLs), including octreotide (commercially-available world-wide). Octreotide capsules is a new formulation that enables the oral delivery of octreotide and may offer advantages to parenteral therapy. Studies to-date demonstrated that it appears to be a safe and effective therapy for acromegaly patients previously managed on injectable SRLs and may fulfil an important unmet need in this patient population.
2. This will be a phase 3, randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy and safety of octreotide capsules in acromegaly in approximately 50 adult patients who previously tolerated and demonstrated biochemical control on injectable Somatostatin Receptor Ligand (SRL) treatment (octreotide or lanreotide).
3. Following an up to 8-week Screening period, eligible patients who are biochemically controlled on SRL injections will be randomized in a 1:1 ratio to octreotide capsules or matching placebo for a 36-week double-blind, placebo-controlled, (DPC) period. During this period, the effective dose for each patient will be determined by dose titration through to and including Week 24 and maintained through to completion of the DPC period.
4. To maintain the blind, patients on matching placebo will undergo mock titrations increasing capsule numbers from 1 capsule twice daily to 2 capsules in the morning and 1 capsule in the evening/night to 2 capsules twice daily.
5. Following completion of the 36-week core study (either on study medication or upon meeting pre-defined withdrawal criteria and being followed per protocol through to week 36), patients will be offered to enter the Open-Label Extension (OLE) period and receive octreotide capsules until the last patient enrolled into the OLE completes one year or until product marketing or study termination by the sponsor.

Summary of ethical issues (resolved)

1. The Researcher(s) confirmed that data will be aggregated and care taken with any sub-set analyses – given the small number of patients in NZ with acromegaly, care will be taken in the publication of any results with any breakdown of data by country which could have the potential to be stigmatising or cause data harm.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee queried whether there are safety issues being off treatment (placebo), noting the design was an FDA requirement.
2. The Researcher(s) explained that these patients are treated with surgery but it does not often result in full cure. The next line of treatment is by way of SLR injections, once a month. Patients can be on this treatment course for many years to control their condition. This study involves an oral formulation of octreotide which has been used in patients with acromegaly, this is a Phase 3 trial.
3. The Researcher(s) acknowledged that stable patients on injections will need to come off their treatment. The Researcher(s) stated it is reasonable to do so due to slow tumour growth. In most cases some tumour remains following surgery, but the Researcher(s) doubt it will increase significantly over 1 year. The Researcher(s) explained that growth hormone is a good marker for the size of the legion, and there is a rescue therapy plan in place. The Researcher(s) stated this would be discussed clearly with participants and it is clearly stated in the PIS.
4. The Committee asked about the statement in the participant information sheet that a brief stoppage of treatment is normal practice. The Researcher(s) explained that there are particular circumstances when treatment might be stopped but standard practice would be to maintain patients on treatment long term. The Committee asked for the PIS to be amended to reflect this.
5. The Committee noted the safety issue that currently, in order to need rescue, patients are required to show symptoms. The Committee would prefer to remove this requirement for symptoms. If blood tests become significantly abnormal the Researcher(s) should be able to rescue the patient prior to symptoms developing. Please amend to provide stronger safety considerations, in relation to rescue therapy. Pg. 3of the participant information sheet currently has 3 bullet points for requirement for rescue therapy. The Committee had safety concerns about this requirement and have asked the Researcher(s) with the Sponsor to consider whether the requirement could be an ‘or’ rather than an ‘and ‘for these three features.
6. Make the need to stop regular medicines earlier, clearer, and length of time being off medicines clearer.
7. Please seek Sponsor clarification on calculation of reimbursement, for example ‘up to 200’ reimbursed could mean 20. Please make the reimbursement calculations clear in the PIS.
8. Please clarify the poster which says “Eligible patients may receive financial compensation for study visits. Why “may”?
9. The Committee noted informing the GP informing should be mandatory in this study. Please confirm this and remove the option on the consent form.
10. Please clarify if there are alternative methods for reimbursement than Greenfire. Some participants may not wish to have their details known by people outside the study.
11. The Committee asked about the extension study – The Researcher(s) noted this is a potential benefit of study participation. The Committee noted they were comfortable about this.
12. The Committee noted the Sponsor cannot require withdrawn participants to come to study visits, but can ask them to attend.
13. Please confirm that the stated conditions in the Insurance certificate regarding: (1) extended incident reporting and (2) legal liability extension will not impact on the compensation available to NZ participants.
14. Please consider ways in which to ensure the safe storage of the medicines in participants’ homes to guard against accidental ingestion by children.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Clarify the three different options for CT scans as study procedures in the PIS.
2. Add in risk section something along the lines of ‘you are currently controlled’ … a risk is that they may become uncontrolled, but will not have any treatment for X period of time’.
3. Page 10 – minimal if any treatment impact – please revise this, it is misleading.
4. Add detail on how difficult it is to re-gain control of disease again.
5. The Committee noted a separate participant information sheet will be required if data is to be collected on a pregnancy or on any child that is born.
6. Storing samples for 4 years, any future unspecified research? The Researcher(s) stated all samples will only be related to the study and no future unspecified research will take place. Please confirm and provide address for storage. The Committee queried why samples need to be stored for 4 years.
7. The Committee noted that blood samples for routine tests will be sent to Singapore for analysis and the blood samples testing for IGF-1 and growth hormone will be sent to a German laboratory. Please confirm appropriate governance procedures are in place for the protection of participants’ privacy and confidentiality.
8. Include an explanation in the PIS that samples and data are going offshore and other counties may have different and less restrictive privacy protections
9. Review HDEC wording for compensation. <https://ethics.health.govt.nz/guides-templates-forms-0>
10. Please use Ministry of Health ethnicity classifications when collecting ethnicity data to ensure the options available are suitable for New Zealand participants <https://www.health.govt.nz/publication/hiso-100012017-ethnicity-data-protocols> .
11. Please remove the clause that states that the study can be terminated for commercial reasons, as per National Ethics Advisory Committee guidelines.
12. Incidental findings – please contain details for participant information sheet so participants are aware of what they might be, including how they will be dealt with and that it is at no additional charge (if that is the case).
13. Storing study drug at home in the fridge. Add a sentence about mitigating this risk.
14. Remove mention of Novotech – they are not the sponsor.
15. Amend the consent forms to be consistent with the amendments sought to the PISs.

Decision

This application was *provisionally approved* by consensus, subject to the following information being received.

* Please amend the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Intervention Studies* *para 6.22*).
* Justify use of Placebo *(Ethical Guidelines for Intervention Studies para 5.22)*
* Please compensation concerns of the Committee. *(Ethical Guidelines for Intervention Studies para 8.4).*
* Update the HDEC on the extension study
* Respond to outstanding ethical issues in a cover letter.

This following information will be reviewed, and a final decision made on the application, by Dr Kate Parker and Ms Rochelle Style

## Substantial amendments

|  |  |  |
| --- | --- | --- |
| **1** | **Ethics ref:** | **17/NTA/51/AM03** |
|  | Title: | rTMS for Treatment-Resistant Depression |
|  | Principal Investigator: | Dr Suresh Mathukumaraswarmy |
|  | Sponsor: |  |
|  | Clock Start Date: | 21 May 2018 |

Dr Suresh Mathukumaraswarmy was present in person for discussion of this amendment.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of amendment

1. Recently the research group has been contacted by a major New Zealand Television production company who would like to feature the research being conducted in the current study 17/NTA/51 “rTMS for Treatment Resistant Depression”. This is potentially an opportunity to advocate for improving access to new mental health treatments for New Zealanders – in particular depression. However, in order to make such a programme, the producers would need to feature one or two of the participants including interviews with the participant and footage of them receiving the treatment. They would also want to interview members of the research team.
2. The Committee observed that whether this was happening as a study amendment or whether it was contingent to the study was not clear, and HDECs role was more of an advisory role to minimise risks in this context, as participation in the interview was not a study procedure.

Summary of ethical issues (resolved)

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee queried what the risks are. The Researcher(s) noted featuring a potentially vulnerable patient like this raises a number of ethical issues, including, but not limited to, loss of privacy and the giving of fully informed consent balanced against allowing participants to make autonomous decisions, avoid paternalism and participate in advocacy if they wish to. The enduring nature of the footage was also a consideration, for example in potential future employment opportunities for participants it may be raised.
2. The Researcher(s) noted they had suggested masking participants’ faces and voices – the media did not want to use this option.
3. The Committee noted there were a range of mitigation of risk options available.
4. The Committee noted that selecting the participants for this matter was critical. The Researcher(s) noted they would take all steps to approach the least vulnerable participants and would seek input from multiple professionals in that determination including participants’ own psychiatrists.
5. The Researcher(s) explained there is not much media on advocacy for new methods to treat depression, unlike cancer treatments which receive high media attention.
6. The Committee noted there is potential public value in raising awareness of alternative forms of treatment for depression but questioned the extent of any benefit for individual participants who bear the most risk.
7. The Committee noted there is not only present risk, but also future occupational risks and younger people may go on TV without thinking those long term risks through. Discussions should be had with the potential participant and ensure they have had time to reflect on the decision.

Summary of ethical issues (outstanding)

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee asked how much control researchers have over the media process. The Researcher(s) noted that they think TV are interested in the treatment options. Such discussions have not developed yet, as the Researcher(s) wanted to seek HDEC views first. The Committee noted a consent form would be important.
2. The Committee also discussed mitigations of coercion to make sure people don’t do it if they feel like they have to, if approached by their clinician or the researchers. Steps would need to be taken to ensure that free and informed choice can be given.
3. The Committee requested a consent form (or perhaps am augmented film consent) is created and the process to identify potential participants is developed and submitted for review. This process should outline how risks have been identified and mitigated, or managed. This includes all stages of the process, selection, informed consent and follow up support after the interview.

Decision

This amendment was *provisionally approved* by consensus, subject to the following information being received.

* Provide the information sheet and consent form, taking into account the suggestions made by the Committee (*Ethical Guidelines for Observation Studies* *para 6.11*).
* The study design must minimise risk of harm Provide an end to end process plan for the interview (*Ethical Guidelines for Observation Studies* *para 5.5*).

This following information will be reviewed, and a final decision made on the amendment, by Dr Christine Crooks and Dr Brian Fergus.

## General business

1. The Committee noted the content of the “noting section” of the agenda.
2. The Chair reminded the Committee of the date and time of its next scheduled meeting, namely:

|  |  |
| --- | --- |
| **Meeting date:** | 17 July 2018, 08:00 AM |
| **Meeting venue:** | Novotel Ellerslie, 72-112 Greenlane Rd East, Ellerslie, Auckland |

The following members tendered apologies for this meeting.

* Mrs Rochelle Style

1. **Problem with Last Minutes**

The minutes of the previous meeting were agreed and signed by the Chair and Co-ordinator as a true record.

The meeting closed at 5.45pm