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| **Committee:** | Northern B Health and Disability Ethics Committee |
| **Meeting date:** | 03 July 2018 |
| **Meeting venue:** | Novotel Ellerslie, 72-112 Greenlane Road East, Ellerslie, Auckland |

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| **Time** | **Item of business** |
| 12:00pm | Welcome |
| 12:05pm | Confirmation of minutes of meeting of 05 June 2018 |
| 12:30pm | New applications (see over for details) |
| 12:30-1:00  1:00-1:30  1:30-2:00  2:00-2:30  2:30-3:00 | i 18/NTB/103  ii 18/NTB/105  iii 18/NTB/107  iv 18/NTB/109  v 18/NTB/112 |
| 3:00pm | General business:   * Noting section of agenda |
| 3:15pm | Meeting ends |

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| **Member Name** | **Member Category** | **Appointed** | **Term Expires** | **Apologies?** |
| Mrs Maliaga Erick | Lay (consumer/community perspectives) | 01/07/2015 | 01/07/2018 | Present |
| Mrs Stephanie Pollard | Non-lay (intervention studies) | 01/07/2015 | 01/12/2018 | Apologies |
| Miss Tangihaere Macfarlane | Lay (consumer/community perspectives) | 20/05/2017 | 20/05/2020 | Present |
| Mrs Kate O'Connor | Lay (ethical/moral reasoning) | 14/12/2015 | 14/12/2018 | Present |
| Dr Nora Lynch | Non-lay (health/disability service provision) | 24/07/2015 | 24/07/2018 | Present |
| Mrs Leesa Russell | Non-lay (intervention studies), Non-lay (observational studies) | 14/12/2015 | 14/12/2018 | Present |
| Mr John Hancock | Lay (the law) | 14/12/2015 | 14/12/2018 | Present |
| Mrs Jane Wylie | Non-lay (intervention studies) | 20/05/2017 | 20/05/2020 | Apologies |

## Welcome

The Chair opened the meeting at 12:00pm and welcomed Committee members, noting that apologies had been received from Mrs Jane Wylie and Mrs Stephanie Pollard.

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 5 June 2018 were confirmed.

## New applications

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| **1** | **Ethics ref:** | **18/NTB/103** |
|  | Title: | ILUMIEN IV Clinical Study |
|  | Principal Investigator: | Prof Scott Harding |
|  | Sponsor: | Abbott |
|  | Clock Start Date: | 21 June 2018 |

No member 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 is a randomised intervention study comparing the results of coronary stent placement and function when it is inserting using Optical Coherence Tomography (OCT) guidance versus coronary angiographic guidance. It is uncertain from the documentation whether both processes are currently used interchangeably in Wellington. The participant information sheet implies they are but comments in the HDEC form challenge this assumption.
2. The researchers aim to recruit 125 participants to the study. Initial participants will be allocated to the OCT to enable documentation of the lead investigator expertise. Subsequent participants will be randomised to one of the two active treatment arms. Participants will be those who are needing a coronary stent or up to four and who are either "high risk" from Diabetes or who have a "high risk coronary obstruction" by virtue of the lesion characteristics. Previous studies have defined this as the optimal target group.
3. Primary outcomes will be the stent area as measured by post placement OCT measurement (Both arms get this OCT), and time to first cardiac event between 1-2 years post placement. Secondary outcomes are a myriad of clinical and procedural measurements such as patient reported outcomes via Euro Qol 5D.

Summary of outstanding ethical issues

1. The committee noted that it is uncertain from the documentation whether both processes (OCT and angiographic guidance), are currently used interchangeably in Wellington. The participant information sheet implies they are but comments in the application form submitted challenge this assumption. The committee would like to ask the researchers whether either or both procedures are used as standard of care in Wellington.
2. If the answer is yes, the Committee asks whether there are clinical features which lead the researchers to choose one over the other and also whether all study investigators are equally competent in both methods.
3. If the answer is no, the Committee would like to see evidence of the research team’s processes. The Committee also notes that if this is the case the participant information sheet will need significant adjustments so that participants can be informed of how OCT differs from standard care in Wellington and why it is not the go to procedure. For example: is the procedure longer?
4. The Committee noted that the peer review from the FDA assessment could be accepted if it was able to see the redacted portion which offered commentary on the design of the trial. The Committee queried what the information has been redacted and noted that it would want to know what the researchers have done to address any issues raised in that review. The Committee would like to see the commentary given that it also has questions about whether the surgeons are familiar or not with both procedures and is seeking reassurance about whether they are being provided as standard of care. In the event that the commentary cannot be provided the Committee would ask that additional peer review using the HDEC template is submitted. The research team can view and download a copy of the HDEC template at: <https://ethics.health.govt.nz/>
5. The committee noted that the insurance certificate provided is inadequate; it does not refer to this study specifically and provides one million dollars annually for *all* the sponsor’s clinical trials outside of North America. This is not enough to cover for ACC equivalent in a high risk procedure and the Committee would like to see further evidence that there is adequate insurance available in the event that a participant is injured and pursues a claim.
6. The Committee noted that a copy of the EuroQol5D questionnaire was not submitted with this application and, that it would like to see a copy. The Committee will provisionally approve this application and asks that the researchers submit a copy of the questionnaire with your response to the Committee’s provisional approval decision.
7. The Committee noted that the researchers had stated at p.4.3.1 in the application form that they are consulting with their local research advisory group and, that they had stated at p.4.2 that there are no cultural issues that they can identify with the study. The Committee noted that cultural issues include the taking, transporting, storing and disposal of tissue. The Committee would like to see an update on where the researchers are in the consultation process and also would like the researchers to address how the study may benefit Māori and how cultural issues that may arise for Māori participants in the study will be managed.

The Committee requested the following changes to the participant information sheet and consent forms:

1. Please add a lay title to the participant information sheet.
2. The Committee noted that the small risks of OCT disclosed in the application form at question r.1.1 related to catheter injury and extra contrast and kidney injury and asked that these be included in the participant information sheet on page 5 under the heading ‘What are the possible benefits and risks of this study?’ In addition the Committee would also like to see information included about the risks of roll in. It noted that one of the main risks of percutaneous coronary intervention is that people can end up with a large haematoma – and the participants should be informed about the associated risks.
3. The Committee asked the researcher to confirm that all three follow up visits are standard of care. If not, the committee notes that the sponsor should be paying participants’ transport costs.
4. The Committee asked the researchers to advise what additional procedures/tests are to happen for participants in this study. For example, a post insertion OCT for both arms to measure stent area.
5. Page 5, under the heading: ‘What are the risks for women of childbearing age?’ This committee noted that this section contains the following statement which needs clarification in the light of earlier statements about both procedures being approved: *"If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a foetus to a potentially dangerous agent with unknown risk"*
6. The Committee asked that the researchers revisit this section and rewrite as there is duplication and some contradiction in the information provided.
7. Page 7, second paragraph: the committee noted that there is a move from classifying whole groups as 'vulnerable' to regarding individuals in certain circumstances as being vulnerable. It is broad and describes people who have restricted capability to make independent decisions about their participation in the study. It also encompasses people who may lack the ability to consent freely or may be particularly susceptible to harm either because of their health status, physical or mental capacity or employment status. The committee noted that it is important to remember that even if a group is identified as likely to be vulnerable, the label may not apply to all individuals in such groups, and even where it does apply, it may do so only intermittently. The committee asked that the researchers revisit and rewrite the statement on page 7 to align with this current ethical thinking.
8. Page 7, the Committee noted the comment that “the sponsor may stop the study at any time”. The sponsor cannot stop the study without good reason and that studies should not be stopped simply for reasons of commercial interest or public relations.
9. Page 7, under the heading ‘How will your information be kept confidential?’: The Committee asked that the researchers include where the data will be kept and for how long.
10. The Committee queried the lack of a Māori tissue statement in the Participant Information Sheet. The committee recommended the following statement: “*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.”*
11. The Committee asked whether the option of interpreters for participants whose first language is not English will be provided and if it will, please include this information in the information sheet and consent form.
12. Please revise the document and make consistent use of word “study doctor” throughout the information sheet and consent forms.
13. Please ensure that the contact details for an independent Maori health contact are included on page 8 under the heading ‘Who do I contact for more information or if I have concerns?’

Decision

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

* Please provide clarification on whether either or both processes are used as standard of care in New Zealand.
* Please submit evidence of adequate insurance, the EuroQo15D questionnaire, and clarification regarding the redacted portion of peer review.
* Please address how the study may benefit Māori and how cultural issues that may arise for Māori participants in the study will be managed (*Ethical Guidelines for Intervention Studies* *para 4.7*).
* 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*).

This information will be reviewed, and a final decision made on the application, by Mrs Leesa Russell and Mrs Maliaga Erick.

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| **2** | **Ethics ref:** | **18/NTB/105** |
|  | Title: | THE AFR-PROPHET TRIAL |
|  | Principal Investigator: | Assoc Prof Gerard Wilkins |
|  | Sponsor: | Occlutech International AB |
|  | Clock Start Date: | 21 June 2018 |

A/Prof Gerard Wilkins 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 is a first-in-human single arm intervention trial of an intra-cardiac device to hold open and regulate the size of a hole created between the two upper heart chambers (atria) as a therapeutic procedure in patients with severe pulmonary arterial hypertension. The current standard of care is to just make the hole between the two chambers. The size of the hole is difficult to control and it may heal up after a short while necessitating a re-bore. The trial device aims to address both issues.
2. The trial is being conducted worldwide including five centres in New Zealand.
3. Prior use has included use in animal trials and in three compassionate cases in humans: two adults and one child and all did well.
4. The primary outcomes will be: safety at three months, judged by the frequency of occurrence of serious adverse events. Secondary outcomes will be: safety at 6 and 12 months and efficacy at 3, 6 and 12 months as judged by improvement in the number of fainting episodes.

Summary of resolved ethical issues

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

1. The Committee thanked the lead investigator for a detailed cover letter which explains the technical aspects of the disease and treatment very clearly.
2. The Committee noted that it was pleased with the peer review provided and to see that the peer reviewer’s suggestions now appear in the protocol.
3. The Committee noted that the first 15 participants worldwide will be 18 years of age or older and, thereafter that children may be recruited once the interim analysis of the first 15 has been done when the last of the adult participants reaches 3 months, and once "competent authorities” have approved moving to this stage. It was unclear who these authorities are. Both phases appear to be part of the New Zealand application although there is no discussion around the involvement of minors, nor age-appropriate participant information sheets and consent/assent forms provided with the application.
4. The researcher explained that it is not their intention in relation to this protocol to move to including children. The Committee subsequently made clear that it is considering this application in relation to an adult population only. The Committee advised that if the researchers decide to include children in future that this would require a new application being made to the HDEC and that any application in this regard would need to come through with solid safety evidence and justify the need to recruit children to a study.

Summary of outstanding ethical issues

1. It was noted that the participants in this trial will be gravely ill, have a poor prognosis and will have been escalated to highest level of drug therapy available in New Zealand. Being able to move to using this device on compassionate grounds will be more helpful in New Zealand. The Committee noted that it is unclear whether some may be waiting for lung transplantation and asked the researcher whether participation in this research could delay access to this treatment. The researcher confirmed that some participants may be waiting for a lung transplantation and that in general the use of this device in this trial setting will be used as a bridge for those participants. The Committee asked that the researchers make clear to participants in the information sheet that the trial device is a facilitating rather than competing intervention in this small subset of participants and, that if the option of a lung transplantation became available for them while they are on this trial that the researchers will have no hesitation in withdrawing them from the trial to have a lung transplantation.
2. The Committee noted that a Nickel allergy is an exclusion criterion for this study and asked the researcher how they will check for this, noting that a Nickel allergy can be common especially among women who have worn pierced earrings and can induce it by exposure to junk metal. The Committee noted that the brochure also suggests a Nickel allergy can be induced by the trial device. The researcher advised that surface testing is an unreliable way to test for Nickel allergy and that there was no reliable method for testing.. While there appears to be little evidence that these devices cause a problem it is a theoretical risk and should be outlined in the participant information sheet to allow participants to decide whether or not to be in the study even if they have a known nickel allergy.
3. In relation to compensation for injury for participants the Committee noted that the researcher argued that this study is being done primarily for participants’ benefit at question r.1.8 of the application form. This is not the case given that there are significant potential risks being borne by participants in this trial and, the trial sponsor takes benefits in relation to getting data and applying for licensing among other things. When cover under the Accident Compensation Act 2001 will be excluded for the intervention study, investigators and study sponsors have responsibilities to ensure alternative compensation cover for study participants to at least ACC-equivalent standard. This may include earnings-related compensation. As the trial will be done for the benefit of the sponsor the committee requested the compensation wording is updated for accuracy, they suggested the following statement: *“If you were injured as a result of treatment given as part of this study, which is unlikely, you* ***won’t*** *be eligible for compensation from ACC. However, compensation would be available from the study’s sponsor, [x], in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won’t affect your cover.”*
4. The Committee noted that the researchers had answered ‘no’ at question p.4.3 in the application form that formal consultation with Maori is not required on the grounds that it is a small group study looking at compassionate use of a new device and there is no evidence that the condition is more common in Maori. The Committee advised that under the Health Research Council guidelines unless Maori are excluded from a study then formal consultation is required and, that this can be done in parallel with locality authorisation processes.
5. Although it was indicated at question p.4.6 in the application form that ethnicity data would not be gathered, the researcher confirmed that they will be gathering ethnicity data.

The Committee requested the following changes be made to the participant information sheet and consent forms:

1. Please review the document and use the term “GP” in place of “physician”.
2. Please state where participant data will be stored and for how long.
3. The Committee noted that the form as it is currently written reflects the translation from German to English and doesn’t always read well. For example "The clinical study we are presenting, has been evaluated by an independent ethical commission and confirmed by the competent authority as legally required". "The study is induced, organized and financed by the following sponsor," "...check options that contradict you participating in the study”, "The extent of radiation exposure and physical burden during this examination corresponds with the usual amount for this patient group”. The Committee asked that the researchers thoroughly review the document with reference to the HDEC pro-forma (<https://ethics.health.govt.nz/>) to cover all points needed and in a way that is accessible to a New Zealand audience.
4. Page 2: The Committee noted that content under the heading 'Background Information' is a technical and includes the following rather grim statement: "In the course of this disease right heart insufficiency develops with high venous pressure and blood accumulation on the right heart side, eventually leading to right heart failure and death." The Committee noted it reads too much like a medical textbook and asked that the researchers revisit this and rewrite.
5. Page 4, ‘Blood Samples’: the Committee noted that 30 ml blood is noted as being equivalent to one teaspoon when it is more equivalent to two tablespoons. Please replace one teaspoon with the words two tablespoons.
6. Page 5 under the heading ‘Foreseeable Risks and Side Effects’: please clearly state that this is a first-in-human trial with trials having been conducted in animals (7 pigs) in addition to 3 compassionate cases. The Committee would like to see more space given to the risks of the device and expounded on them. For example embolisation includes dropping the device off prematurely and having it block up a vessel somewhere. The Committed noted that the side effects of transoesophageal ECHO (TOE) are described but this procedure is not included in the "What's Involved" section above. It needs to be as it is somewhat invasive and different from a transthoracic ECHO which is what is described under 'ECHO'.
7. The Committee asked that the researchers explain what 'endocarditis prophylaxis' involves. In relation to this the Committee asked whether providing participants with antibiotics for six months after runs the risk of developing resistance. The researcher advised that the participants are compromised and unwell, which is why the antibiotics are required.
8. The Committee asked the researchers to consider including advice on ensuring that if MRI was needed by a device recipient in the future, scanning protocols do not involve excessive time or intensity as per the investigator brochure.
9. The Committee noted that follow up visits involve 6 visits over a year and that the protocol states transport AND accommodation costs will be covered. The Committee noted that this is important for New Zealand where some participants may travel from the provinces to their nearest main hospital. The Committee asked that the researchers make clear in the participant information sheet that that payment for follow up visits includes accommodation as well as transportation.
10. Please include contact details for a Maori support person who is independent of this study and who Maori participants can contact should they have any questions.

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*).

This information will be reviewed, and a final decision made on the application, by Dr Nora Lynch and Miss Tangihaere Macfarlane.

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| **3** | **Ethics ref:** | **18/NTB/107** |
|  | Title: | Two Trials for Treatment of Anxiety |
|  | Principal Investigator: | Professor Bruce Arroll |
|  | Sponsor: | The University of Auckland |
|  | Clock Start Date: | 21 June 2018 |

Prof Bruce Arroll 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. This study aims to test two psychologically-based therapies for anxiety - Rapid Symptom Shift and mBraining.
2. The protocol describes two consecutive RCTs, one with each therapy which follow on one after the other in a single session. Each has its own comparator and set of primary and secondary outcomes.

Summary of outstanding ethical issues

1. The Committee noted the conduct and design of the trials is not clear from the documentation provided to date as the protocol, application form and participant information seem to state different things.
2. The Committee queried the outcome measures and the timing of the study –two therapies are being trialled sequentially, all participants receive Rapid Symptom Shift therapy and only half of the participants receiving the mBraining. The Committee queried how the researchers can be sure that they are measuring the effects of mBraining and that there is not a carryover effect from Rapid Symptom Shift? The researcher stated that RSS makes people feel relaxed but there is currently no data on how long this lasts. It was noted that participants will be re-randomised and half of participants will have meditation and half will have the mBraining which involves a breathing technique followed by meditation. The Committee asked that the descriptions of the study design in the protocol, HDEC form and PIS be reviewed for consistency. The interventions and outcome measures should be made clearer for participants in the information sheets.
3. The Committee noted that the HDEC application mentions monitoring of adverse events and asked whether the researchers will do an interim analysis. The Committee asked that the adverse events plan mentioned in the application form also needs to be clarified in the protocol.
4. The Committee noted that the recruitment materials have not been submitted with the application and asked that the researcher submit these to the Committee. The researcher advised that they intend to recruit participants to the study in a number of ways including through print and radio advertisements and he will submit the documentation to the committee.
5. The Committee noted that there may be a conflict of interest if one of the lead investigators is recruiting patients. The researcher advised that the investigator won’t be recruiting from her private practice. The Committee asked the researchers to acknowledge in the study protocol that vested interest is a risk and to outline how they will manage this.
6. The Committee noted that the peer review documentation provided from 2015 does not cover the scope of this application as it was based only on the Rapid Symptom Shift trial. The Researcher advised that the team have peer review from Australia and that they can provide this for the Committee.

The Committee requested the following changes be made to the participant information sheet and consent forms:

1. The Committee asked that the researchers address the confused messages about the interventions as outlined above, add page numbers, version number and address typos and grammar. The Committee also requested that the resubmitted document has changes tracked so that the Committee can check it against the original document.
2. In addition to reframing and simplifying language, the Committee asked that the researchers use tables and visuals to more readily reflect what is in the protocol.
3. The Committee noted that the information under the headings ‘What is the purpose of the study?’ and ‘What will my participation in the study involve?’ needs revisiting and rewriting in the interest of clarity. For example, it needs to state the reason that the researchers are doing the study, the test that will be used and outline the methods, make clear that they will be asked questions, be randomised, some may get a placebo and how much time is involved.
4. The Committee noted that the information under the heading ‘What are the possible risks and benefits of this study?’ needs to clarify whether there is a chance that participants will have placebo in the mBraining RCT, i.e. that they will potentially not receive active treatment. The committee also noted that the opening sentence assumes that there will be a positive effect: "The benefits for you will be that you have a technique that can make you feel less stressed in a few minutes." Please rewrite this sentence.
5. The Committee asked the researchers to state the involvement of a sponsor under the heading ‘Who pays for the study?’
6. The Committee noted that health information must be retained for 10 years in line with the Health Information Privacy Code. Please state that data will be stored for 10 years (not 6 years as currently stated), under the heading ‘What happens after the study or if I change my mind?’ The Committee sought clarification on what plans the researchers have for secure data storage and noted that it is lawful to digitise health information and store it that way.
7. Consent Form: please revise the statements and only include Yes/No tick boxes for statements that are truly optional.

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 provide evidence of favourable independent peer review of the study protocol (*Ethical Guidelines for Intervention Studies* Appendix 1).
* Please provide print and radio advertisements/recruitment methods.
* Please provide a plan for managing conflicts of interest.
* Please include a plan for managing adverse events in the study protocol.

This information will be reviewed, and a final decision made on the application, by Mrs Leesa Russell and Mr John Hancock.

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| **4** | **Ethics ref:** | **18/NTB/109** |
|  | Title: | The RiCoDIFy study: A Phase 3, randomized, double-blind, active controlled study to compare the efficacy and safety of ridinilazole (200 mg, bid) for 10 days with vancomycin (125 mg, qid) for 10 days |
|  | Principal Investigator: | Dr Nicholas Gow |
|  | Sponsor: | INC Research New Zealand Limited |
|  | Clock Start Date: | 21 June 2018 |

Dr Hasan Bhally 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 is a Phase 3, double-blinded, randomised controlled trial of a new antibiotic for C.difficile induced diarrhoea (CDI), compared against Vancomycin as the standard of care. The study is needed because CDI, which develops from bacterial imbalance in the gut caused by exposure to broad spectrum antibiotics, paradoxically requires another antibiotic to control it. Such treatment may further disrupt the bowel flora allowing C. difficile to flare up again sometime after treatment has finished. This is reported to happen in 30-60% of patients with the standard of care. The new drug-ridnilazole- has a very narrow spectrum of action.
2. Phase 2 studies (64 patients with C.difficile illness exposed to ridnilazole), looking at the microbiota after its use showed less disruption of the bowel flora compared with vancomycin. There was also less frequent relapse (33% cfed 58%) and a slightly greater cure rate at end of treatment (78% cfed 70%).
3. The new drug is also very minimally absorbed out of the gut so systemic toxicity is potentially minimised. This study seeks to confirm these results.

Summary of outstanding ethical issues

1. The Committee asked the researcher to clarify recruitment methods for this study including whether they intend to go through lab results before approaching C.difficile positive patients, whether they will contact patients directly or via their clinician and whether the study will recruit mainly inpatients or also outpatients.
2. The researcher explained that the lead investigators are at Waitemata DHB where recruitment will be limited to North Shore hospital. CDI infections cases identified promptly are patients in the hospital usually with a health care infection; at Waitemata DHB testing done on site is fast and they will recruit only patients who have diagnosis of CDI. At Waitemata DHB all positive results are notified to the infection control team which the investigators are part of.. They have improved processes to find out about cases within 24 hours because this is an entry issue and once they know of a patient has CDI they can take action. If CDI is identified in hospital then they will screen records and an investigator will approach the patient to give them information about the study and to ask whether they consent to take part.
3. The Committee noted the that 2-stage consent process described in application (consent to test stool for toxin using a specific kit then consent to join trial) first appears to be for identification of CDI however, the researcher has just explained that the test for the toxin happens as part of standard of care. It appears that the first stage consent may be an extra consent stage that is not needed. The lead investigator will look into this and confirm that the same standard of care diagnostic procedures apply to the other NZ centres involved in which case a single consent to enter the trial after CDI diagnosis has been made clinically, will be all that is required..
4. Next step is when researchers approach patients for research and to talk about study protocol and randomisation to the study. The Committee asked where the participant’s primary hospital clinician fits in to the loop here. The researcher explained that an infection control consultant will review patient records and approach the hospital clinical team with the details of eligible participants. The researcher noted that he is happy to take advice from the Committee about whether it is better that the primary hospital clinician approach potential participants. The Committee noted that this is the right way round as there needs to be a gate-keeping role with the hospital physician. Who has overall responsibility for the potential participants care.
5. The Committee noted the participant information sheet (page 1) states people are being approached because "you *may* have CDI..." The Committee queried whether this is not already established from a toxin test before the researchers seek consent to the trial itself and asked why consent is being sought unless the researchers wish to extend it to another study population? The researcher explained that the information sheet is a general one from the sponsor and that some of the sites do two separate testing – one for the antigen test and if toxin positive then a second ELIZA test is done. At WDHB they test simultaneously so that they know about diagnosis readily. The Committee again queried the need to consent to test for the toxin and asked whether other centres will recruit outpatients. The researcher agreed to go back to the team to discuss and to come back with a response for the Committee.
6. The Committee sought to clarify the action required when the screen on a participant’s e-diary reads: " You have recorded > 3 unformed bowel motions in the last 24 hours. Please contact the study doctor". What is the time frame if, for example, it is the middle of the night when the message pops up? The Committee also queried whether bowel motions are to be recorded every day until day 90 or every day to day 14 then only if loose to day 90? (That is how the protocol reads and, if so, it needs clarifying in PIS too). The Committee asked that the researchers clarify that contacting the doctor after day 14 be on an as needs basis and that they clarify timeframe in the e-diary (if third runny poo happens within X number of hours contact study doctor).
7. The Committee noted that within the main participant information sheet consent is sought (page 10) to collect data on any pregnancy which occurs during the study within a participant. The Committee noted its preference would be to move this out of the Main PIS and to modify the 'Pregnant Partner' PIS to be a 'Pregnant Participant or Pregnant Partner PIS'. The Committee noted that is because it is not reasonable to assume that the decision made when you are not pregnant would necessarily be the same as you would make once you find yourself pregnant. The Committee asked that the researchers seek consent at the time not beforehand and that they state in the information for participants that they will be asking for permission at the time a participant becomes pregnant.
8. Page 13, second paragraph: the Committee queried why the researchers are retaining the link to the database for 25 years and not 10 years in line with New Zealand privacy law (the query applies to pregnant partner PIS also). The Committee noted the wording which this sponsor has used on data access during and after the trial is acceptable as it allows for the possibility that some record access is possible and some is not depending on the consequence for blinding. The researcher advised that he would ask the sponsor about the 25 year time frame and clarify for the Committee.

The Committee requested the following changes be made to the participant information sheets and consent forms:

1. Please add a lay title and increase the font size if possible.
2. Consent to Test for Toxin: if there is a reason to retain this PISC, please add to main information sheet that you will seek consent to notify a participant’s GP of any incidental findings. Currently this pops up only in the consent form.
3. The Committee noted that p.4.2 on page 27 of the application form covers the main cultural issues that may arise for Maori well and asked that the researchers include this information in the participant information sheet.
4. Page 5, under the heading ‘Reimbursement’: please replace the word “may” with “will” be reimbursed, after providing receipts, for study associated costs. The Committee also asked the requirement for a receipt to get petrol costs reimbursed be removed and

Decision

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

* Please provide clarification about recruitment and the first stage consent process.
* Please provide clarification about why retaining a 25 year link to database is needed.
* 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*).

This following information will be reviewed, and a final decision made on the application, by Dr Nora Lynch and Mrs Kate O’Connor.

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| **5** | **Ethics ref:** | **18/NTB/112** |
|  | Title: | DERBY |
|  | Principal Investigator: | Dr Phillip Polkinghorne |
|  | Sponsor: | Apellis Pharmaceuticals Pty Ltd |
|  | Clock Start Date: | 21 June 2018 |

Dr Phillip Polkinghorne 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 is a randomised controlled trial of APL2 injected into the eye for 'dry' macular degeneration. There is no current therapy for this condition which is progressive and causes a lot of blindness.
2. Active treatment in this study is compared against a 'sham' injection in which nothing is injected into the eyeball. The researcher doing the procedure is unmasked, that is, knows what is being given to each participant, but the participants and outcome assessors are both blinded.

Summary of resolved ethical issues

1. The Committee asked the researcher to describe more clearly the process of recruitment and consent. The researcher explained that participants will be patients who come into the clinic who have slowly progressing age-related dry macular degeneration where there is no agent at present shown to be effective. The Committee noted that participants enter this study on which a good proportion of them will be administered a sham injection for 30 months and noted that this is a long time to be on the control arm. The researcher advised that only those with slow progression will be on the study and that they will be monitored and have referral for any other services as needed.

Summary of outstanding ethical issues

The main ethical issues discussed at the meeting that require addressing by the researcher are as follows.

1. The Committee noted that an interim analysis when 50% (or however many a statistician advises), of participants reach 12 months (the time when the primary outcome will be assessed) would allow a "look see" at the data to make sure that there is not a strong signal in favour of monthly injections over 2nd monthly injections. There was a signal in the Phase 2 study that monthly injections were better than both control and 2nd monthly injections. This is important so as to reduce the possibility that the 2nd monthly injection group might receive another 6 injections between 12-24 months with all the risks and none of the benefits. Further, this is a long study with many visits for those in the control group who may be progressively losing vision during this time. Consider how they will be feeling if the treatment proves effective and they learn this 3 years later. This is another reason to consider an interim analysis. The researcher agreed to take the above to the sponsor and ask them to consider this as an option and to report back to the Committee.

The Committee requested the following changes to the participant information sheets and consent forms:

Main PIS/CF

1. The Committee noted that the main PIS is visually dense and noted that given participants are visually impaired a less dense layout might be best for them to digest this complex information. Although the research team will typically also talk the participants through the information sheet the Committee asked that the more white space be included and also bigger font.
2. The Committee sought clarification on what is meant by a “sham” injection. The researcher advised that the needle doesn’t go into the eye and all other steps in the process are the same so that the patient doesn’t know whether they are getting the injection or not. They get a local anaesthetic as well as a speculum. The Committee asked that be made clearer that an external procedure constitutes the sham injection.
3. The Committee queried why is there is a focus made of female contraception given the participants all have to be 60 or older and asked whether it would be easier to add the words “receiving or intending to receive in vitro fertilisation” to the exclusions to cover the remote possibility of a woman in her 60s going to some medical outpost for a late-life pregnancy.
4. Page 4: Please express randomisation rates in absolute numbers: 2 out of 3 chance of receiving the drug rather than 67% chance. Research has shown the latter percentage method is more commonly misinterpreted.
5. Page 8: Please remove reference to taking a blood sample for genotyping as this is not part of the Main study in New Zealand.
6. Page 9: Reimbursement of parking and travel should be at cost, other incidental expenses such as meals could be at a fixed rate. This is to ensure fairness as participants may travel vastly different distances.
7. Page16: please advise where blood will be stored/analysed in both participant information sheets when documents come back for final approval.
8. Page 17: the Committee queried whether the following statement means that if wet macular degeneration develops and requires VEGF (which can be a complication of the drug APL2), that patients have to fund it themselves? " It may also be necessary for you to take medication during or after the research project to address side effects or symptoms that you may have. You may need to pay for these medications and so it is important that you ask your doctor about this possibility." The researcher advised that the patient is entitled to have the medication and he Committee asked the researchers to assure patients that they would get it at no cost.
9. In relation to compensation the Committee asked that patients be advised that in the event that wet MD occurred that it would be covered as a matter of course and any complication over and above this would go to insurance. Please reflect this in the participant information sheet.
10. Page 18: Please remove from the text, reference to the sponsor stopping the trial for 'decisions made in the commercial interest' or 'administrative reasons'.
11. Page19: Please refer to NZ ethics committee as HDEC or NTB not HREC which is Australian.
12. Page 20: The following paragraph which is currently located under "Complaints" seems lost and more appropriately would belong under' 9. Risks and Disadvantages' where it is currently discussed anyway. "APL-2 has been generally well tolerated. The most frequently reported adverse events have been related to the injection procedure which are commonly found in this type of study. It was noticed that subjects receiving APL-2 are at an increased risk of developing the wet form of AMD, which can be treated with the standard of care with anti-VEGF injections. "-
13. provide a space on the consent form to offer a lay summary. 'Asking the researcher' is not a substitute for a printed summary (p.2.8)
14. Page 24, please refer to the HDEC pro-forma consent form and revise your consent form with this in mind. <https://ethics.health.govt.nz/>

Genetic and Future Research PIS/CF

1. Page 2, under "What is genetic research?" please include a brief definition of 'genome' which appears subsequently. Para 7 says the link between participant and blood sample will be removed before analysis *“The results of this research project will not provide you with any direct benefit because the link between you and your blood sample will be removed before your blood sample is analysed.”* Para 12 says blood samples will be stored as re-identifiable specimens *“Your blood samples will be stored at [Name of bank]. It will be stored as a re-identifiable sample. This means that your sample will be identifiable by a code; it can be identified as yours even though the bank does not know your identity.”* Which one is correct?
2. Page10: The committee noted the sentence “I can withdraw my consent to participate in this research project by completing a “Withdrawal of Consent” form” and asked that reference to written advice of withdrawal be removed. The Committee noted that the main participant information sheet correctly states that withdrawal from the study can be done at any time without the requirement to complete a written request and asked that the researchers review all participant information sheets and request forms to be consistent with this approach. The onus is on the researchers to record verbal rather than a requirement on participants to provide it in writing.

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 provide a plan for interim analysis information.

This following information will be reviewed, and a final decision made on the application, by Dr Nora Lynch and Mr John Hancock.

## 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:

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| --- | --- |
| **Meeting date:** | 07 August 2018, 12:00 PM |
| **Meeting venue:** | Novotel Ellerslie, 72-112 Greenlane Road East, Ellerslie, Auckland |

The following members tendered apologies for this meeting.

* Dr Nora Lynch

The meeting closed at 3.30pm.