National Research Ethics Committee

NREC-CT A Meeting

09 November 2022

Attendance

Name	Role
Prof. Mary Donnelly	Chairperson, NREC-CT A
Ms. Erica Bennett	Committee Member, NREC-CT A
Prof. Tina Hickey	Committee Member, NREC-CT A
Mr Gerard Daly	Committee Member, NREC-CT A
Prof. Catherine Hayes	Committee Member, NREC-CT A
Ms Muireann O'Briain	Committee Member, NREC-CT A
Prof. David Brayden	Committee Member, NREC-CT A
Prof. Patrick Dillon	Committee Member, NREC-CT A
Dr John O'Loughlin	Committee Member, NREC-CT A
Dr Darren Dahly	Committee Member, NREC-CT A
Prof. Gene Dempsey	Committee Member, NREC-CT A
Prof. Austin Duffy	Committee Member, NREC-CT A
Mr Gerald Eastwood	Committee Member, NREC-CT A
Dr John O'Loughlin	Committee Member, NREC-CT A
Ms Ann Twomey	Committee Member, NREC-CT A
Ms Patricia Kenny	Project Officer, National Office for RECs
Ms Rachel McDermott	Project Administrator, National Office for RECs
Dr Anne Costello	Programme Manager, National Office for RECs
Dr Susan Quinn	Programme Manager, National Office for RECs
Dr Emma Heffernan*	Project Officer, National Office for RECs

*Drafted minutes

Apologies: Dr Heike Felzmann, Prof Alistair Nichol, Ms Evelyn O Shea, Dr Dervla Kelly, Dr Geraldine Foley, Prof Donal Brennan, Prof. John Wells, Dr Jimmy Devins

Quorum for decisions:

Yes

Agenda

- Welcome & Apologies
- 22-NREC-CT-164
- 22-NREC-CT-167
- 22-NREC-CT-168
- 22-NREC-CT-169
- 22-NREC-CT-170
- AOB

- The Chair welcomed the NREC-CT A.
  - The minutes from the previous NREC-CT A meeting on 05 October 2022 were approved.
  - The NREC Business Report was discussed and noted.

Applications

22-NREC-CT-164

Principal Investigator: Dr Patrick Hayden

Study title: A Phase 3, Two-Stage, Randomized, Multicenter, OpenLabel Study Comparing CC-92480, Bortezomib and Dexamethasone (480Vd) Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) in Subjects with Relapsed or Refractory Multiple Myeloma (RRMM)

EudraCT: 2021-001957-30

Lead institution: St James's Hospital

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

- Request for more information

- **Additional Information Required**

- The NREC-CT noted that the proposed start date for the trial is stated in the Application Form as 30 August 2022 and requested confirmation that the trial has not started and will only start following full ethical approval.
- The NREC-CT requested that the 'CTIMP in Combination with Exposure to Radiation Form' is reviewed and signed by both a medical physicist and radiologist/radiation oncologist
- The NREC-CT welcomed the inclusion of a study summary in the PISCF, and requested that details of the potential risks / benefits of trial participation are added to this section
- The NREC-CT noted that pg. 24 of the Application Form states that "*If a subject has a learning disability or is unable to understand the written information and consent forms, the sponsor and the site will provide the necessary assistance…"*. The NREC-CT requested that a description of what arrangements are in place to support participation of adults with learning disabilities / participants unable to understand written information, is described in section E.10-E13 of the Application Form.
    - In response to this point the sponsor should address whether this cohort may lack decision making capacity and whether an evaluation of decision-making capacity to consent to the research will take place. If there are participants who lack decision making capacity, the sponsor should confirm participant assent will be obtained (as well as consent by the participant's legal representative) and that a consent declaration will be sought (see section E note on informed consent in the Application Form)
    - The NREC-CT requested that the box at section D 8 is ticked to indicate that participants with learning disabilities are eligible to take part in the trial.
- The NREC-CT noted the inclusion of an impartial witness in the PISCF and requested clarification as to the role of the impartial witness in the consenting process.
- The NREC-CT commented that, in accordance with Irish data protection legislation no individual can consent for another for the processing of data. For clarity it is requested that the text *'I am not consenting on behalf of participant'* is added to the impartial witness section on pg. 39 of the PISCF

- The NREC-CT noted the inclusion of a QoL questionnaire (EORTC QLQ – MY20 and EORTC QLQ-C30) and requested details of provisions in place to support participants, should the questionnaire indicate a mental health issue.
    - The NREC-CT has requested that the PISCF includes an acknowledgement that undertaking these assessments may cause distress and details of psychological supports available to participants.
    - The NREC-CT noted that participants will be required to complete the QoL questionnaires via an electronic device and requested clarification as to whether participants would have the option to complete a paper version of these questionnaires would they be unable / unwilling to complete the questionnaires via an electronic device.
- The NREC-CT noted that genetic testing is mandatory for inclusion in the trial and requested justification for mandatory genetic testing
    - The NREC-CT further requested that the section on the trial objectives provides a clearer account of the role and impact of genetic testing in the trial.
    - Furthermore, the NREC-CT noted that the section of genetic testing may be confusing for participants and requested that a clear description of genetic testing is provided in the PISCF.
- The Committee noted that the PISCF is seeking blanket consent for future use of samples, including left over left-over samples, for unspecified purposes, without further consent. This type of consent not in line with best practice, the Declaration of Taipei 2016 and not in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), where informed participant consent is a mandatory safeguard. The NREC-CT requests i) that consent for future use of samples is provided on a separate consent form and not bundled ii) is made optional, and iii) sufficient information is provided about possible future use of samples such that participants are able to make an informed decision about this and/or iv) that an option is provided to enable participants to consent to be contacted is provided in a separate consent form
    - The NREC request confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
    - The NREC noted that the Pregnancy / Pregnancy Partner PISCF describing the potential future use of data is also not compliant with the Health Research Regulations 2018 and should reflect the requested changes set out in point 3.7.1.
    - The NREC-CT requested confirmation that further research using participant samples or data from this study will undergo full ethics review.
- The NREC requested that all PI CVs are signed by the relevant PIs
- The NREC noted that the DPIA does not state how long data will be stored for and requested that this is clarified and stated in the DPIA
    - Furthermore, the NREC requested that the DPIA references Irish data protection law.

- The NREC- noted that the study insurance certificate provided does not cover the whole trial duration and requested assurance that the trial will be adequately insured for the whole duration and will cover all sites

22-NREC-CT-167

Principal Investigator: Dr Sarah Curry

Study title: A Phase 3, Randomized, International Multicenter Trial Of DAY101 Monotherapy Versus Standard Of Care Chemotherapy In Patients With Pediatric Low-Grade Glioma Harboring An Activating RAF Alteration Requiring First-Line Systemic Therapy (LOGGIC/FIREFLY-2)

EudraCT: 2022-001363-27

Lead institution: CHI Crumlin

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

- Request for more information

- Additional Information Required RFI

- The NREC-CT noted that section D5 of the NREC-CT Application Form states that 'Identification of potential participants will involve the review of medical records' and requested further details as to how this will be undertaken, and where will it be documented.
- Section E6 of the NREC-CT Application Form suggests that an interpreter may be provided for deaf participants. The NREC-CT requested reassurance that if an interpreter is needed for a deaf participant, one will be provided.
- The NREC-CT noted that while the trial drug related side effects were detailed in the PISCF, there was limited information on the potential side effects from Standard of Care and requested that further detail on the potential side effects of Standard of Care is provided in the PISCF**.**
    - Furthermore, the NREC-CT requested confirmation that the SoC will be explained to participants by the site PI
- The NREC-CT noted that it is unclear as to how many visits participants are required to undertake over the course of the trial and requested that a clear estimate of the projected number of visits is detailed in the PISCF, so participants are fully informed.

- The NREC-CT requested clarification as to whether the Optional Tumour Sample Collection on pg. 6 of the PISCF is part of routine care or part of the research study and requested that a clearer explanation is provided in the PISCF.
    - Furthermore, pg. 8 refers to 'tumour sample'' in the section titled 'Why is a tumour sample being asked of me?' and requested that this is amended to 'Why is an *optional* tumour sample being asked of me?'
- The NREC-CT noted that the pregnancy advice in the 13-15 assent form includes separate advice for girls and boys and requested an overall section titled 'contraception' is included instead.
- The NREC-CT noted that on pg. 9 of the PISCF (What is the procedure, and how long will I be involved?) is limited in detail and requested that a more detailed explanation of the procedure involved is provided.
- Pg. 7 of the Adult PISCF states that the study consists of 3 periods, yet 4 are subsequently listed. The NREC-CT requested that this is corrected.
- The NREC-CT noted that pg17 of the PISCF refers to 'local guidelines' in relation to withdrawal from the study and requested that more details as to these guidelines is provided in the PISCF
- The NREC-CT noted that the language in the assent forms (7 to 12 and 13-15) may be difficult to understand for these age groups and requested it is amened to be more age appropriate and provide better descriptions of terms, such as 'cable', 'needle in your arm' and 'MRI machine'.
- The NREC-CT noted that pg.5 of the assent forms refers to pain associated with the insertion of needles and requested that a description of local anaesthetic is described here to reassure participants about the potential pain from insertion of needles.
- The NREC-CT noted that the consent for data processing is not line with Irish data protection legislation and Health Research Regulations 2018, whereby the age of consent is 18 years of age. It is requested that participants under the age of 18 will need to provide assent for the processing of their data and their parents /guardians will need to provide consent for the processing of data

22-NREC-CT-168

Principal Investigator: Dr Maeve Crowley

Study title: A multicenter, randomized, open-label, blinded endpoint evaluation, phase 3 study comparing the effect of abelacimab relative to apixaban on venous thromboembolism (VTE) recurrence and bleeding in patients with cancer associated VTE (ASTER)

EudraCT: 2021-003076-14

Lead institution: Cork University Hospital

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

  Request for more information

- **Additional Information Required**

- The NREC-CT requested that the GP letter is amended to include the following information:
    - Date when participant starts the trial
    - Details of which arm of the trial the participant has been randomised to
    - Side effects of study medication
    - Addition of prohibited and permitted medications
    - Contraceptive advice
- The NREC-CT requested clarification as to the processes in place for study interruptions, for example should participants be required to stop the IMP for elective medical procedures or ongoing cancer treatment, and this is elucidated in both the protocol and PISCF.
- The NREC-CT noted that the PISCF states *'Blood samples may also be collected and stored for future exploratory testing*' (pg. 3) and '*Your blood samples for exploratory biomarker testing will be stored specifically for future exploratory analysis' (pg5)*.
- Please note, in line with best practice, the Declaration of Taipei 2016 and in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), informed explicit participant consent must be obtained. The NREC-CT requests confirmation that only the only future use of samples and data '*related to the study drug or your medical condition'* as set out in the consent form. Any undefined unknown future use must have informed consent.
    - The NREC-CT requested confirmation that subsequent research ethics review will be sought for all future research set out in the consent form
- The NREC-CT noted the use of technical language in the main PISCF and requested the terms 'pharmacokinetic' and 'pharmacodynamic' are explained in plain language
- The NREC-CT noted the use of technical language in the Optional Genetic ICF and requested that the terms 'proteomics' and 'metabolomics' are explained in plain language.
- The NREC-CT noted that pg.8 of the PICSF in relation to contraceptive advice for female participants, states that 'The following contraception methods are *recommended*' and requested that this is amended to 'The following contraception methods are *accepted*'.

- The NREC-CT requested that any reference to 'The Institutional Review Board or Ethics Committee' being able to review participant's medical records is removed from the PISCF, as NREC-CT do not have access to participant's medical records.
- The NREC-CT noted that participants will be required to undertake QoL questionnaire via smartphone and request the following:
    - Clarification as to the privacy / security risks associated with use of participant's personal smartphone devices.
    - Details for the data security features in place for participants undertaking QoL on their personal smartphones and the potential security risks / exposure of personal data this may pose is added to the PISCF
    - Details of the requirement to download the App to their personal smartphones is added to the PISCF
    - A more detailed description of the training involved in learning how to use the App is added to the PISCF, so participants are fully aware of the level of training required to complete the questionnaires.
    - Clarification as to whether participants who do not have a smart phone will be provided with one
    - Clarification as to whether participants are able to opt out of completing QoL questionnaires via smartphone and are permitted to complete a paper version instead.
- The NREC-CT noted that the CV of the PI was sparse and requested a more detailed account of Dr Crowley's previous clinical trial experience.
    - Furthermore, the NREC-CT requested evidence of an up-to-date ICH GCP certificate for Dr Crowley
- The NREC-CT requested further detail on financial compensation for trial participants and requested details on the following are elucidated in the PISCF
    - Clarification if meals are included
    - Clarification as to the upper limit of compensation participants can claim for each study visit.
    - Requested a more detailed account of the compensation arrangements in place for participants, such as how often participants will be reimbursed, and the process involved in reimbursement and contact details of someone they can contact in Ireland should they require help with claiming compensation

22-NREC-CT-169

Principal Investigator: Dr Maeve Crowley

Study title: A multicenter, randomized, open-label, blinded endpoint evaluation, phase 3 study comparing the effect of abelacimab relative to dalteparin on venous thromboembolism (VTE) recurrence and bleeding in patients with gastrointestinal (GI)/genitourinary (GU) cancer associated VTE (Magnolia)

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

- Request for more information

- **Additional Information Required**

- The NREC-CT requested that the GP letter is amended to include the following information:
    - Date when participant starts the trial
    - Details of which arm of the trial the participant has been randomised to
    - Side effects of study medication
    - Addition of prohibited and permitted medications
    - Contraceptive advice
- The NREC-CT requested clarification as to the processes in place for study interruptions, for example should participants be required to stop the IMP for elective medical procedures or ongoing cancer treatment, and this is elucidated in both the protocol and PISCF
- The NREC-CT noted that the PISCF states *'Blood samples may also be collected and stored for future exploratory testing*' (pg. 3) and '*Your blood samples for exploratory biomarker testing will be stored specifically for future exploratory analysis' (pg5)*.
- Please note line with best practice, the Declaration of Taipei 2016 and in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), informed explicit participant consent must be obtained. The NREC-CT requests confirmation that only the only future use of samples and data '*related to the study drug or your medical condition'* as set out in the consent form. Any undefined unknown future use must have informed consent.
    - The NREC-CT requested confirmation that subsequent research ethics review will be sought for all future research set out in the consent form.
- The NREC-CT noted the use of technical language in the main PISCF and requested the terms 'pharmacokinetic' and 'pharmacodynamic' are explained in plain language
- The NREC-CT noted the use of technical language in the Optional Genetic ICF and requested that the terms 'proteomics' and 'metabolomics' are explained in plain language.

- The NREC-CT noted that pg.8 of the PICSF in relation to contraceptive advice for female participants, states that 'The following contraception methods are *recommended*' and requested that this is amended to 'The following contraception methods are *accepted*'.
- The NREC-CT requested that any reference to 'The Institutional Review Board or Ethics Committee' being able to review participant's medical records is removed from the PISCF, as NREC-CT do not have access to participant's medical records.
- The NREC-CT noted that participants will be required to undertake QoL questionnaire via smartphone and requested the following:
    - Clarification as to the privacy / security risks associated with use of participant's personal smartphone devices.
    - Details for the data security features in place for participants undertaking QoL on their personal smartphones and the potential security risks / exposure of personal data this may pose is added to the PISCF
    - Details of the requirement to download the App to their personal smartphones is added to the PISCF
    - A more detailed description of the training involved in learning how to use the App is added to the PISCF, so participants are fully aware of the level of training required to complete the questionnaires.
    - Clarification as to whether participants who do not have a smart phone will be provided with one.
    - Clarification as to whether participants are able to opt out of completing QoL questionnaires via smartphone and are permitted to complete a paper version instead.
- The NREC-CT noted that the CV of the PI was sparse and requested a more detailed account of Dr Crowley's previous clinical trial experience.
    - Furthermore, the NREC-CT requested evidence of an up-to-date ICH GCP certificate for Dr Crowley.
- The NREC-CT requested further detail on financial compensation for trial participants and requested that details on the following are elucidated in the PISCF:
    - Clarification if meals are included
    - Clarification as to the upper limit of compensation participants can claim for each study visit.
    - Requested a more detailed account of the compensation arrangements in place for participants, such as how often participants will be reimbursed, and the process involved in reimbursement and contact details of someone they can contact in Ireland should they require help with claiming compensation

22-NREC-CT-170

Principal Investigator: Prof Owen Smith

Study title: ALLTogether1 - A Treatment study protocol of the ALLTogether Consortium for children and young adults (0-45 years of age) with newly diagnosed acute lymphoblastic leukaemia (ALL)

EudraCT: 2018-001795-38

Lead institution: CHI Crumlin

- **NREC-CT comments:**

The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

- Request for more information

- **Additional Information Required**

- The NRECT-CT noted that the 5.1.1 ICF sections 7 and 8 'I give permission for my medical information to be used in research projects, approved by the ALLTogether consortium science committee' and requested confirmation that all future research will also undergo full ethics approval by the appropriate REC for the research in question, and this is added to the consent documents
- The NREC-CT noted that participants will be stratified according to risk and requested further detail on how participants are stratified and how risk is assessed
- The NREC-CT requested clarification as to whether all participants will be invited to take part in the Brain Study and the CSF study
- The NREC-CT requested clarification as to when participants will be invited to participate in the maintenance therapy sub-study.
- The NREC-CT requested clarification that participants who refuse to consent to some items listed in the consent form are still permitted to take part in the trial (5.1.1 ICF)
- The NREC-CT noted that participants with Down syndrome are eligible with take part in the trial and the NREC-CT requested that the sponsor should address whether any members of this cohort may lack decision making capacity and how capacity will be assessed in such circumstances (including the provision of appropriate decision-making supports) If there are participants who lack decision making capacity, the sponsor should confirm participant assent will be obtained (together with consent by the participant's legal representative) and that a consent declaration will be sought (see section E note on informed consent in the Application Form).
- The NREC-CT noted that pregnancy avoidance advice is inconsistent throughout the PISCFs and requested that these are aligned across the adult PISCFs and in the 13-15 PISCF with appropriate language.
- The NREC-CT requested confirmation that male participants will also be given advice re pregnancy avoidance, and reminders at site visits

- The NREC-CT noted that the requirement for pregnancy testing is mentioned in the 13-15 PISCF but not the other PISCFs and requested that this is added to relevant PISCFs.
- The NREC-CT noted the large number of drugs that participants may be required to take both as part of SoC and trial involvement and requested that an appendix is added to the PISCF listing the various SoC and trial drugs.
- The NREC-CT noted that the acronym 'ALL' may be confusing to children and read as the word 'all'. The Committee requested that this is written in full in the assent forms
- The NREC-CT noted that the contact details on all PISCFs relate to CHI Crumlin and requested confirmation that all PISCFs will include site specific contact details for adults taking part in the trial, so participants know who to contact for more information or in case of emergency.
- The NREC-CT requested clarification as to the number of PISCFs a participant may receive over the course of the trial.
- The NREC-CT requested clarification as to why only participants with Down syndrome are being tested for HIV at screening
- The NREC-CT noted that the language in the Down Syndrome PISCF was potentially complex for some participants with Down Syndrome and requested that this is amended. The NREC-CT recommend that all of the forms for the DS group in NRI2 do not carry an age category on their front page, but are graded instead by language difficulty, and adapted to be suitable in tone for adults/teenagers, so that the appropriate form can be selected (following consultation with parents/clinician who knows them) according to the language and intellectual capacity of the individual patient.
- The NREC-CT requested that the phrase 'pregnancy test for girls who are sexually active' is amended to 'pregnancy test for participants of childbearing potential' in the relevant PISCFs
- The NREC-CT requested that the parent/guardian PISCF include a reference to the need for parents/ guardians to discuss all aspects of the participation in the trial with their child in an age/understanding appropriate manner, and similarly to discuss any withdrawal from the trial with their child, so that children are involved in decisions that affect them
- The NREC- noted a number of typos across the PISCF documents and requested that all documents are thoroughly proof-read for accuracy
- The NREC noted that information forms are separate from consent forms and is concerned that this may lead to errors. The NREC requested that the appropriate information and consent forms should be amalgamated in each case.
- The NREC-CT requested that CVs are provided for all site investigators.
- he NREC-CT requested further information is provided in relation to renumeration of trial participants and requested the following:
    - Clarification as to what expenses will be covered in Ireland, and what is the maximum amount of compensation provided to participants for travel and refreshments and that this be further elucidated in the relevant PISCF

- Clarification as to what expenses are covered for parents/ guardians of children participating in the trial and this is clearly outlined in the relevant PISCF
- Clarification as to the potential impact trial participation / opting out of SoC will have on participants with private medical insurance and this is explained in the PISCF

- AOB:
- The Committee commented that many members are currently overburdened by the volume of work they are currently being tasked with on NREC-CT A, including ethical review of new studies, substantial amendments, and responses to requests for further information. In addition, the Committee are attending sub-committee and main NREC meetings, adding to the burden of review.
- The Committee noted the requirement for broader discussions across all the NRECs regarding information provided in participant information leaflets regarding pregnancy and sexual activity, where the participants are minors of childbearing potential.