National Research Ethics Committee

NREC-CT B Meeting

12 April 2023

Attendance

Name	Role
Dr Cliona McGovern	Chairperson, NREC-CT B
Dr Jean Saunders	Deputy Chairperson, NREC CT-B
Ms Serena Bennett	Committee Member, NREC-CT B
Mr Philip Berman	Committee Member, NREC-CT B
Dr Enda Dooley	Committee Member, NREC-CT B
Dr John Hayden	Committee Member, NREC-CT B
Dr Mary McDonnell Naughton	Committee Member, NREC-CT B
Mr Gavin Lawler	Committee Member, NREC-CT B
Ms Paula Prendeville	Committee Member, NREC-CT B
Prof. Colm O'Donnell	Committee Member, NREC-CT B
Ms Mandy Daly	Committee Member, NREC-CT B
Prof Andrew Green	Committee Member, NREC-CT B
Ms Susan Kelly	Committee Member, NREC-CT B
Ms Deirdre MacLoughlin	Committee Member, NREC-CT B
Prof Seamus O'Reilly	Committee Member, NREC-CT B
Dr Christina Skourou	Committee Member, NREC-CT B
Prof Abhay Pandit	Committee Member, NREC-CT B
Dr Emily Vereker	Acting Head, National Office for RECs
Ms Patricia Kenny	Project Officer, National Office for RECs

Dr Emma Heffernan*	Project Officer, National Office for RECs
Dr Anne Costello	Programme Manager, National Office for RECs
Ayesha Carrim	Project Officer, National Office for RECs
Rachel McDermott	Project Administrator, National Office for RECs
Bryony Milner	Administration Assistant, National Office for RECs

*Drafted minutes

Apologies: Dr Mark Robinson, Prof David Smith, Dr Eimear McGlinchey, Prof John Faul, Dr Lorna Fanning, & Ms Caoimhe Gleeson

Quorum for decisions: Yes

Agenda

- Welcome & Apologies
- 2022-501352-28-00
- 22-NREC-CT-100_Mod-2
- 21-NREC-CT-049_Mod-4
- 21-NREC-CT-154_Mod-5
- 22-NREC-CT-046_Mod-2
- 21-NREC-CT-179_Mod-4
- 22-NREC-CT-112_Mod-3
- AOB

- The Chair welcomed the NREC-CT B.
  - The minutes from the previous NREC-CT B meeting on 15 March 2023 were approved.
  - The NREC Business Report was discussed and noted.

Applications

2022-501352-28-00

Principal Investigator: Dr Laffey

Study title: A randomized, placebo-controlled, double-blind, multi-center, phase III trial to assess the efficacy and safety of trimodulin (BT588) in adult hospitalized subjects with severe community-acquired pneumonia (sCAP)

EudraCT: 2022-501352-28-00

Lead institution: University Hospital Galway

- **NREC-CT comments:**

- The NREC-CT B 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**

Part 2 Considerations

- The Sponsor is requested to clarify if a consent declaration for data processing for of personal data of individuals who lack decision-making capacity, will be necessary (Ref: DATA PROTECTION ACT 2018 (SECTION 36(2)) (HEALTH RESEARCH) REGULATIONS 2018)
- Poster design not submitted – text only is approved.
- The wording in the Continued Participation Information Sheet and Informed Consent Form should be edited to ensure all wording reflects that the participant has already been included in the trial. This form should not refer to consent to initial participation. For example: Page two "*to help you decide if you want to take part in this study,"* should be edited to "…if you want to *continue* to take part…". Any reference to 'taking part' or 'take part'. should be edited to refer to '*continue*' or '*continuing*' to take part as relevant.
- The main Patient Information Sheet and Informed Consent and Continued Participation Information Sheet and Informed Consent Form: All abbreviations 'PK' and 'PD' should be replaced with the full words; Pharmacokinetics and Pharmacodynamics respectively.
- Patient Visit Guide: Regarding the D29 and D91 quality of life questionnaire, the guide should provide an indication of the length of time this will take to complete.
- The 'Continued Participation Information Sheet and Informed Consent Form' should remove the term "next of kin/NOK" as this term has no lawful meaning in Ireland. The definition of 'legally designated representative' should be used instead - as defined under

Irish legislation S.I. No. 40/2022 - European Union (Clinical Trials on Medicinal Products for Human Use) Regulations 2022

- In the 'Continued Participation Information Sheet and Informed Consent Form' (pg. 21) it is not clear whether participants have, or have not already been enrolled in the *Optional Future Research Part* and/or *Optional PK Research Part* of the study. An additional tick box e.g. 'Not-Applicable, N/A' to indicate that they have not been enrolled in the *Optional Future Research Part and/*or *Optional PK Research Part* might be useful

22-NREC-CT-100_Mod-2

Principal Investigator: Dr Rachel Crowley

Study title: Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid (TOPaZ)

EudraCT: 2016-003228-22

Lead institution: St Vincent's University Hospital

- NREC-CT comments:

- Based on the above, the NREC-CT A Committee agreed that this substantial amendment application be designated as favourable with conditions

- NREC-CT Decision:

- Favourable with conditions

- Conditions of Approval

- The Committee were unclear why the update to the protocol to include potential contraindications for paediatric population has been added to this research if the trial is already over. Please clarify.

21-NREC-CT-049_Mod-4

Principal Investigator: Dr Raymond McDermott

Study title: A Randomized Phase 3 Study of MRTX849 in Combination with Cetuximab Versus Chemotherapy in Patients with Advanced Colorectal Cancer with KRAS G12C Mutation with Disease Progression On or After Standard First-Line Therapy

EudraCT: 2020-004048-27

Lead institution: St. Vincent's University Hospital

- NREC-CT comments:

- The NREC-CT Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision on this Substantial Amendment

- NREC-CT Decision:

- Request for more information

- Additional Information Required

  - The Committee requested justification/clarification on the relevance of the new wording in the Main PISCF (pg 11) regarding collection of race and ethnicity data. The Committee also requested that the PIL be updated to provide information to the participant about the reasoning for this to ensure it is clearly communicated to the participant. Please note that data on ethnicity is considered as equality data which is more sensitive than other personal data and legal basis for using this should be clearly stated and justified.

  - The Committee were unclear if after signing the Main ICF and following the screening, the participant is then not eligible to take part in the trial why is their data (pg 12) and samples (pg 52) still being kept for future research. The Committee commented that if the sponsor wishes to create a biobank of tissues samples with the associated data then this must be done under separate clinical trial application and not as an add on to this trial.

  - The Committee commented on the apparent ambivalence and contradictory nature of the Consent process. They noted that the PISCF (p.23) contains a section 'Optional Tumour and Blood Sample Collection for Correlative/Exploratory Studies' and Main Consent (p.51, box 6) versus Optional Consent (p.52). The Committee felt the associated consent process was unclear as there is the potential to agree Main Consent but refuse consent for Optional however they were unclear which takes precedence? Please clarify.

21-NREC-CT-154_Mod-5

Principal Investigator: Prof Ray McDermott

Study title: A Phase 3 Double-blinded, Two-arm Study to Evaluate the Safety and Efficacy of Pembrolizumab (MK-3475) versus Placebo as Adjuvant Therapy in participants with Hepatocellular Carcinoma and Complete Radiological Response after Surgical Resection or Local Ablation (KEYNOTE-937)

EudraCT: 2018-004800-20

- Lead institution: St Vincent's University Hospital

- NREC-CT comments:

- Based on the above, the NREC-CT A Committee agreed that this substantial amendment application be designated as favourable with conditions

- NREC-CT Decision:

- Favourable with conditions

- Conditions of Approval

- The Committed advised that the PIL needs to be updated to clarify PD-L1 (programmed cell death ligand 1.

22-NREC-CT-046_Mod-2

Principal Investigator: Dr Declan O'Rourke

Study title: A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients With Duchenne Muscular Dystrophy

EudraCT: 2015-002069-52

Lead institution: The Children's University Hospital

- NREC-CT comments:

- Based on the above, the NREC-CT A Committee agreed that this substantial amendment application be designated as favourable with conditions

- NREC-CT Decision:

- Favourable with conditions

- Conditions of Approval

8-12 assent

- The Committee noted the wording “We will keep your information in secret” and suggested that it would be better to communicate that the information will be kept private to you and to those who are gathering and studying this information. The Committee noted that the use of the word “secret” is problematic and that this suggested change is in line with “Stay Safe” programme taught in Irish schools
- The Committee commented that the small amendment to boxes in assent document need to be aligned to relevant assent statements. Please update.

21-NREC-CT-179_Mod-4

Principal Investigator: Prof. Gerry McElvaney

Study title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study Investigating Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Two Dose Levels of Belcesiran in Patients with Alpha-1 Antitrypsin Deficiency-Associated Liver Disease

- NREC-CT comments:

- The NREC-CT A Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision on this Substantial Amendment

- NREC-CT Decision:

- Request for more information

- NREC-CT Decision:

- Request for more information

- Additional Information Required

- The Committee requested confirmation that these duration, dosing & procedure changes will not impact existing participants? If they will, the Committee stated that the PISCF should be updated, and existing participants be reconsented.
- The Committee requested the brochure and PISCF be updated to provide more explanation for the changes to “What will happen if I join the study” regarding the “Optional Biopsy” and “additional optional dosing.
- The Committee were unclear what the justification was for updates to for the Inclusion Criteria, Duration, Dosing & Procedure (biopsy) changes in the Screening, Study therapy & follow-up periods as these changes are not consistent across the documentation provided.
- The Committee commented that it was not immediately clear as to how many doses of the study drug or placebo that a participant will receive IM. A variety of figures are presented across the materials. The Committee requested that these be standardised across every document for better patient understanding.
    - ICF Flipchart and Patient Brochure state that a patient will receive 6 to 16 doses of the study drug or placebo after the first injections, depending on whether the patient opts in for extra dosing.
    - Participant Journey Cohort materials state that the patient will receive 13 injections over the course of the study and does not mention the extra doses.
    - Study Advocacy Factsheet states that participants will receive 7 to 17 doses at least one month apart over the duration of the study depending on enrolment group.

Brochure

- The Committee requested clarification around the changes to “Who can participate in the study” as they are too general. For example, the exclusion of women of childbearing age is no longer referenced, does this mean that women of childbearing age can now join the study? If so, please supply evidence of HPRA / EMA approval for the use of the study drug with this cohort of women. The Committee noted that the front page of the Trifold Brochure has an image of a woman who is of childbearing age. Please update the brochure with any changes.
- The Committee noted the study references a video about the Estrella study with a QR link (QR code not provided however) however this was not made available for review by the committee. Please clarify if the video has already been approved. If not, please supply for the committee to review. Please update to include the QR Code.
- The Committee stated that the font on the brochure is very small and so the brochure is not accessible. Please update to make the brochure accessible to all.
- The Committed noted that pg 2 Brochure (Who can participate in the study?) specifies that other study requirements will apply, but these are not outlined. The Committed advised that these need to be outlined. If there is an extensive list then at least one or two should be listed.

ICF Flipchart:

- The Committee noted the addition of new goal re. the “comparison of two different dose levels” The Committee were unclear if this was reflected in the Protocol and IB? Please clarify and point to the sections of both documents where this new goal has been added. Please clarify if the HPRA have had input regarding the two dosing levels and which dosing level have they already approved?
- The Committee were unsure how the flipchart is used/introduced to each participant. Is it introduced on an individual basis to a potential participant or in a group setting? Please clarify.
- The Committed noted the wording on Talking point 3- “Emphasize that clinical research studies test whether a drug is safe, improves people’s health and does not cause severe side effects”, The Committee would advise replacing “emphasize” with “inform” as it gives more balance in the narrative required here including the risk/benefit.
- The Committee noted that Talking point 7 explains the role of placebos however the Committee advised that this should be explained at an earlier stage as they are referenced on page 4 but no explanation given at that time.

Study Advocacy Factsheet

- The Committee noted that the website is not live (Version 3- Jan 10,, 2023) and advised that they would like to view the information that participants will access.
- The Committee commented that the print on information for participants is very inaccessible and suggested that it be updated to be more accessible.
- The Committee noted that the language used in this document is directive for example Box 1: “you will need to read and sign the ICF...”. The Committee’s

alternative suggestion would be “you will be invited to ...and to consider participation in”...

- The Committee also noted the narrow representation on the poster. The Committee advises that any advertisements/website images, etc for this study considers greater equity in representation across gender, age, cultural background etc in any materials presented to participants.

22-NREC-CT-112_Mod-3

Principal Investigator: Dr Catherine Flynn

Study title: A phase III, randomized, open-label, active-controlled, multicenter study evaluating the efficacy and safety of Crovalimab versus Eculizumab in patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) currently treated with complement inhibitors.

EudraCT: 2020-000597-26

Lead institution: St. James’s Hospital

- NREC-CT comments:

- The NREC-CT A Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision on this Substantial Amendment

- NREC-CT Decision:

- Request for more information

- Additional Information Required

- The Committee were unsure what has happened around the half life of Crovalimab that has been discovered at Phase 3 of a study that brings about these changes. Please provide some more background/information around this change.
- The Committee also queried if there is Paediatric Haematologist on the research team.

Substantial modification Form:

- The Committee noted inconsistencies in the substantial modification form and the Main ICF. Substantial Modification Form Pg.6 states “Arm C …. Will additionally be opened to adult patients ” however the Crovalimab Main ICF Pg.6 states “you will be assigned to Arm C if under 18 years old” Please clarify and update as necessary.

Assent Form 12-15

- The Committee noted the wording on pg.3. " If you are a girl that could become pregnant... your parent or guardian might find out" The Committee advised that the latter statement be removed and rephrased as these participants are under 16 and are minors. The Committee advises that this section be updated to provide reference to additional supports that are available should such an incidence arise. There are safeguards under National Child Protection Guidelines and the Committee advises that these are consulted prior to any revisions been made.
- The Committee noted the wording on pg.5: "if you have started your periods, discuss birth control with your study doctor" and advised that there are regulations regarding the dissemination of this information to minors. The Committee advised that this section requires attention and that information around national regulations and the appropriate safeguards that will be put in place should be mentioned.
- The Committee advised that more information is included in the assent form to obtain layered consent for this age group including indicating their understanding of what is asked, confidentiality,, discussion with parents/guardian, the risks involved, etc.

Crovalimab Main ICF:

- The Committee commented that pg.12 states "side effects associated with Crovalimab are listed below" but they cannot find the list of side effects. They noted that on pg.14 the side effects associated with Eculizumab are listed. Please update to include list of side effects associated with Crovalimab.
- The Committee requested that pg 17 be updated to explain what IRR's refers to.
- The Committee noted that pg.25 "Exploratory biomarker test results will not be shared with patients". The Committee requested clarification on what would happened if something of note is discovered. The Committee would expect that it should be shared with the patient. Please clarify.
- The Committee advised that pg.29 Reference to 'leftover samples' is disingenuous. Please update.
- The Committee advised that Consent form is too generalised needs to be layered to seek specific consent for
    - Sharing of personal data with Courier Company, Home Visit Nurse (from Study site) and Home Visit Service
    - Storage duration of samples for whole genome sequencing
    - Exploratory biomarker testing (Pg.25)

Addendum ICF V2.0

- The Committee were unclear if this is still required and relevant now as the Covid 19 pandemic has passed? Please comment.
- It was unclear to the Committee from this document if a participant could consent to one procedure and not the others (telemedicine, home visits, home treatment). Please update to clarify.

Infant Authorisation Form:

- The Committed advised that pg.2 “The people and groups of people may receive and use your infant’s health information for the purposes stated in this form...The IRB or Ethics committee responsible for protecting the right and safety of people who take part in research” is incorrect. Please note that the NREC will not receive or seek identifiable information for participants or infants. Please remove reference to this from the PISCF’s.
- Pg.4 The committee advises that this ICF include statements and tick box for each statement to structure explicitly what is being consented to there.
- Pg.5 The sponsor should ensure that any involvement of a representative of proxy individual in the consent protocol, is an accordance with all applicable legislative frameworks. Specifically, under Irish data protection law, a legally authorised representative cannot lawfully consent on behalf of another individual for the processing/use of personal data for health research but can provide assent as a safeguard.”
- The Committee noted that the consent form is for female participants that become pregnant during the trial and were unclear what would happen in the following situations, please advise:
    - What about female participants that become pregnant during the elongated Safety Follow-up period?
    - What about female partners of male participants that become pregnant during the trial or the Safety Follow-up period

ICF Mobile Nursing

- The Committee advised that pg 5 needs to be updated. Boxes need to be added after each consent statement to support participants with this consent.
- Pg 6. The sponsor should ensure that any involvement of a representative of proxy individual in the consent protocol, is an accordance with all applicable legislative frameworks. Specifically, under Irish data protection law, a legally authorised representative cannot lawfully consent on behalf of another individual for the processing/use of personal data for health research but can provide assent as a safeguard.

Commodore Story Board

- The Committed advised that the wording on Images 33/45 “Throw away the transfer needle/used syringe.” be changed to “dispose of syringe safely...”

- AOB: