**Background and Rationale**

- **Recently published evidence related to the proposed work has not been cited.**
- The applicant does not indicate that key evidence supporting their proposed project is still considered inconclusive/controversial by the research community.
- The novelty is unclear as the applicant’s previously published papers seem to indicate the majority of the proposed work has already been completed.
  - It is hard to distinguish between the preliminary data and the proposed experiments.
- The level of experimental validation provided for the proof of principle was weak. Only a weak effect was demonstrated by the preliminary data.
- Additional preliminary data is needed to support the feasibility of many of the experiments being proposed.
  - Insufficient detail on the preliminary work is given to establish the validity of the findings.
  - Lack of negative controls in the preliminary data undermines the evidence.
- The proposal is overly exploratory, without a clear hypothesis.

**Aims/Methodology**

- **The advantages/disadvantages of the model chosen versus other potential approaches were not stated.**
- The reasoning for why the models were selected is unclear.
- The proposed models to be employed have not been widely studied or standardized.
- The aims are interconnected to the point where if one fails, the others cannot be successfully carried out.
- The proposal depends on the completion of an initial, time-consuming process and any delay in this may jeopardize the project.
- The suggested approaches are collectively too speculative and optimistic. The process is likely to prove more challenging than described.
- The method proposed is highly novel, but the case is not made as to why it will be superior to existing methods/approaches.
- Rationale for some of the proposed experiments are not clear.
- **The number of experiments included in the proposal was extremely high and it’s unclear that the project can be completed in the time period proposed.** There are too many experiments included in each aim so that the feasibility of the applicant to execute it was not credible. A more focused approach is recommended.
- The proposal lacks focus as it tries to cover too many areas of research, from basic to clinical aspects.
- The cohort being studied needs to be described in greater detail. Unclear whether results from this cohort will be usefully generalizable.
- The use of a single centre (for a clinical trial) may limit the generalizability. Plans for follow-up studies in other centres would strengthen the proposal.
- The length of the study period (for a longitudinal study) means that significant changes in patient treatment may occur over time which are not accounted for.
- Insufficient detail was given to determine if loss-to-followup estimates were accurate.
- Formal measures need to be provided for the study outcomes.
- Screening approach is overly broad.
- Lack of information on strategies to ensure methodological rigour.
- **More extensive follow-up is needed to determine the durability of the intervention proposed.**
- It is unclear whether the qualitative data being gathered will actually complement the quantitative data as it seems to relate to a different set of phenomena
- It is unclear whether other variables that could be controlled for have been taken into consideration
- For indigenous research, it is not enough to reference indigenous knowledge/Two-Eyed Seeing, there must be some detail provided as to how this will be incorporated into the Aims/Methods. OCAP principles must not just be referenced but detailed and supported with a concrete plan.
- **Need to be clear how long-term follow-up and study compliance will be addressed.**
- The volume of data to be produced and analyzed seems unfeasible and unmanageable. A more specific focus would strengthen the proposal.
- Age of animals to be used should be noted and justified.
- Lack of clarity on the numbers of animals per experiment
- The animal model being used may not actually mimic the disease condition being studied
- Sample sizes and their justifications were not clearly outlined.
- **Unclear if statistical power and analyses were appropriate/power calculations seemed insufficient/inaccurate**
- More detail was needed as to how various datasets would be harmonized.
- Unclear how the data analysis will be adjusted for confounders.
- Methods for dealing with incomplete data were not discussed in detail.
- There is very little indication of how the results of experiments will be interpreted.
- The timelines for the Aims seemed overly long with unclear justification.
- Sex and gender:
  - Although the applicant states gender will be analysed, they are actually looking at sex and the question of gender roles should be examined more specifically in this context
  - Insufficient information provided on the sex breakdown of individuals to be studied.
  - **No information provided on how sex/gender differences will be analyzed.**
  - Sex and gender analyses are conflated or not clearly distinguished from one another.
  - Role of gender is dismissed when there is a clear possibility to analyze.

**Expertise and Resources**

- **The fact that the animal model on which the project depends has not yet been generated makes the feasibility questionable.**
- No letter of collaboration was attached for one critical expert which makes the level of support unclear.
- All collaborations with partner organizations/participating hospitals should be secured before submitting the proposal.
- Unclear whether the analysis technology proposed will adequately illuminate the phenomenon being examined.
- **There is no preliminary data using the technology/model proposed for this project which makes it unclear whether the project will produce useable data.**
- It is not clear if the applicant has any previous experience using the technology proposed.
- The applicant is a new investigator starting in a new position and the resources that will be available including personnel and access to infrastructure seem unclear at this stage. Some preliminary work should be done in the new lab to demonstrate feasibility before a full application.

**Budget**

- There are mathematical errors – the totals provided do not match the explanations as written.
- The time estimates provided for staff do not match the descriptions of the work to be done.
- **The budget for staff and trainees is excessive - there is insufficient work for the number of trainees listed relative to the size of the project.**
- **A clear breakdown of animal costs should be provided to rationalize the high cost of the study.**
- Budget is much higher than other grants being submitted to the same panel without a clear justification for the greater costs

**Grantsmanship**
- Introductory statements are needed to make the proposal accessible to the reader.
- Description of the research is dense and challenging to follow.
- A schematic of the plan of research would assist the reader.
- The proposal is difficult to follow as it leans too heavily on acronyms and jargon.
- The background information was overly dense such that one would have to read the referenced papers to follow it.
- It is not obvious that the specific aims being outlined will actually address the knowledge gap identified in the rationale/literature review. The connection should be clearly drawn.
- Preliminary data that is not relevant to the proposed project should be excluded.
- Aims should be distinct from one another rather than variations on the same thing. Consider merging aims that are conceptually similar.
- Statements for expected outcomes of the aims were too broad and general. The description of expected outcomes should not just restate the aim, but indicate what will be learned and propose alternatives if the results are not as expected.
- The links between the hypothesis, aims, and methods need to be clearly laid out in the text. There needs to be a clear connection between each hypothesis and the method, measures and analysis approach linked to it, rather than providing a long list of methods to be used over the whole project.
- Proposal read more as a program of research than a project with a defined hypothesis and endpoint.
- The order and timing of the analyses proposed needs to be laid out clearly.
- A proposed timeline for the work should be included.
- Pitfalls and mitigation strategies are not appropriately noted.
- Discussion of challenges and mitigation strategies did not reflect the complexity and magnitude of the proposed work.
- In the response to reviews, the applicant has not responded to all the points raised by previous reviewers.
- Complete reviews from previous reviewers were not included in the response.
- Response to reviews evades the questions raised by reviewers rather than answering them directly.
- Figures and tables:
  - Too much supplementary data in the appendices – anything critical should be in the main application.
  - Figures were insufficiently detailed to demonstrate the findings of the preliminary data, which undermines the rationale of the project.
  - Figures were not well described and difficult to understand for a non-expert
  - Images/figures too small/blurry and difficult to read.
  - Data given in figures did not appear to support the content of the proposal.
  - Figures were not inset in the area of the text where they were cited which affected readability.
  - Key data that are referred to were missing from the proposal (i.e., in figures) which rendered the preliminary data unconvincing.
  - The data provided in the figures did not match what was outlined in the text (e.g., sample sizes).
  - It was sometimes unclear which figures reflected existing preliminary data and which did not.

Knowledge Translation and Impact

- The significance of the stated aims should be explained more clearly as there was a concern that the work is incremental in nature. The proposal would be improved by better expressing the novelty and importance of the proposed studies and their outcomes.
- How the proposed work relates to the larger question being asked and how the results could impact treatment need to be clearly demonstrated.
- Community involvement seems like an add-on, community members should be integrated from the start to advise on study objectives and design.
- It was unclear how culturally-specific knowledge systems and approaches would be integrated in the KT phase. KT plans are too academic-focused for a community-based project.
- New insights this project will provide are unclear, as the interventions appear to have been previously tested in patients without effect.
The intervention appears to have been previously tested successfully; grant would have more impact with a stronger commercialization/knowledge translation approach rather than repeating the same intervention.

Only local dissemination/knowledge translation strategies were discussed, when national-level would be appropriate.

The public-facing KT activities proposed seem too ambitious/exceed the scope of the proposed work.

For a basic science proposal, future directions based on the results of the project should be described.

Anticipated contributions such as publications and conference presentations should be described.

The number of publications that are expected relative to the volume of work to be done seemed low considering the importance of publishing for the students involved.