Question 1. The framework requires all applications for funding to support a clinical trial or cohort study to demonstrate that the proposed study is asking the right questions, and to explain why a new study is needed. The argument must be informed by a relevant systematic review (or a comprehensive and systematic search for studies). Do you have any comments on this requirement?

We agree that proposals to support a clinical trial or cohort study should demonstrate that the proposed study is asking the right questions and explain why a new or additional study is needed. However; the proposed framework, whilst suitable for clinical trials, is not suitable for cohort studies. One of the main roles of cohort studies is to identify risk factors for disease or other health-related conditions. As such, unlike clinical trials, cohort studies tend to involve multiple exposures and multiple outcomes. Doing systematic reviews of every possible exposure-outcome relationship would be impossible. For these reasons, the proposed framework stipulating "either i) a systematic review or ii) a comprehensive and systematic search for, and evaluation of, studies that are relevant" (the latter including a fully documented search strategy, a completed PRISMA checklist and a PRISMA flow diagram, and a summary of the findings of the review) is not suitable for cohort study applications. An exception might be an application for a very focussed analysis of existing cohort data; however, that would presumably be reviewed under a standard epidemiology/public health Grant Review Panel (GRP).

Examples of very successful cohort studies include the 45 and Up Study (Australia), the Framingham Study (US), Nurses Health Study (US), and the European Investigation into Cancer and Nutrition (EPIC; Europe). These cohort studies have produced (and continue to produce) hundreds of research outputs that have had important impacts on policy and clinical practice in many different areas of health (see links to websites below for more details). They continue to be relevant after many years through the collection of biological samples, repeated exposure data, data linkage and collection of long-term outcomes. If a research team was to seek funding to establish a new cohort, or to extend or build upon an existing cohort study, it is hard to see how the PRISMA checklist approach would be sufficient or appropriate to represent the range of analyses and sub-studies, and the benefits, that would come from building or extending the cohort study resource.

For cohort study applications, researchers should be asked to address these questions in a more flexible way. For example, one could ask the investigators to summarise other relevant cohort studies and then articulate why the new proposed cohort study is required (including why the existing studies cannot answer the proposed new research questions).

https://www.saxinstitute.org.au/publications/45-and-up-study-research/
http://www.nurseshealthstudy.org/selected-publications
http://epic.iarc.fr/
https://en.wikipedia.org/wiki/Framingham_Heart_Study

Question 2. The framework requires all applications for funding to support a clinical trial or cohort study to demonstrate that the design of the study is appropriate and to adequately address all items in the SPIRIT Statement. Do you have any comments on this requirement?

The SPIRIT Statement is suitable for clinical trials but is much less appropriate for cohort studies. The proposed framework suggests that the SPIRIT Statement could be modified to include assessment of cohort studies, whereby "interventions" is replaced by "exposures". However, this approach undermines the importance of cohort studies, and will not give appropriate emphasis to the evaluation of different aspects of the cohort study protocol that is required for rigorous peer review. The STROBE Statement, designed for observational studies, could perhaps be adapted for use but is related to the reporting of results rather than protocol development.

Question 3. The framework requires all applications for funding to support a clinical trial or cohort study to clearly articulate appropriate milestones. Progress against milestones will be monitored and failure to meet agreed milestones may result in discontinuation of grant funding. Do you have any comments on this requirement?

We agree with progress being assessed against milestones, provided that this is not unduly burdensome for the investigators. The opportunity to revise and negotiate milestones would be crucial to this milestone requirement, to ensure that individual project circumstances are taken into account. Flagging projects at moderate risk may be a good way to provide assistance to the Chief Investigator, through mentoring or providing suggestions by independent experts for amending the study to meet certain milestones.

Question 4. Do you have other comments about the framework?

The Australasian Epidemiological Association is pleased that the NHMRC is reviewing the way that clinical trials and cohort studies are assessed. Epidemiologists and biostatisticians are frequently involved in designing, conducting and analysing data encompassing both of these study designs, and want to ensure that their contributions to policy and practice, international recognition, and research training, are fully recognised and appropriately funded.

However, we have some major concerns about the proposed framework.

Firstly, cohort studies do not seem to have been given equal weight in designing the new framework, as the text and proposed new requirements are dominated towards clinical trials. The framework is mainly considering cohort studies as a tool for evaluating interventions, but there is no recognition of one of the main roles of cohort studies, which is to identify risk factors for health conditions. Cohort studies can also provide much-needed data about adoption of new treatments and interventions, including assessment of barriers.

We are also concerned about imbalanced assessment criteria and an imbalance of expertise on the new GRP. In particular, the expertise and focus of cohort studies and clinical trials is very different. Moreover, the process for managing conflicts will likely mean that those with the expertise required to assess cohort studies will be out of the room when these applications are being assessed by the panel. For these reasons we highly recommend separate panels for cohort studies and clinical trials.

The proposed framework states that “if feasible, a biostatistician or trial methodologist will review all applications for a clinical trial or cohort study.” We consider it essential for an epidemiologist to be an Assessor of all cohort study applications, and would be essential expertise on the GRP.

Finally, although the Working Group Terms of Reference included “data sharing”, “funding of extension (follow-up) studies”, and “improved assessment procedures”, these did not seem to be addressed in the framework document. Funding of extension (follow-up) studies are particularly important for measuring long-term outcomes from clinical trials and cohort studies (including capturing important health outcomes such as death and chronic diseases). Funding extension (follow-up) studies may not score high for innovation or novelty, but represent a relatively small cost compared to the initial study outlays and can be highly significant by reaping substantial benefits to patients, the community and the health service.

The AEA would be happy to be consulted on any revisions to the framework.