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Association of Australian
Medical Research Institutes

SUBMISSION

A FRAMEWORK FOR NHMRC ASSESSMENT AND FUNDING OF CLINICAL TRIALS AND COHORT STUDIES

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ABOUT AAMRI

The Association of Australian Medical Research Institutes (AAMRI) is the peak body representing medical research institutes (MRIs) across Australia. Our 47 member institutes are leaders in health and medical research, working on an extensive range of human health issues, from preventative health and chronic disease, to mental health, Indigenous health and improved health services. Collectively AAMRI's members employ over 15,000 staff and students and have an annual turnover of more than $1.3 billion. MRIs are engaged in clinical trials at all stages of the research, and in 2015 were involved in over 1,220 clinical trials.

1 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 question, 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).

1.1 Recommendations

The recommendations within the strong rationale section are reasonable. The following comments are offered to help further develop the framework.

1.2 Asking the right question

AAMRI supports the need for the proposed study to demonstrate it is asking the right question through systematic reviews and consultation with end users. The framework states there are three areas to consider in this regard: relevance and importance of the question, quality of studies in the systematic review, and points of differentiation between the proposed study and those in the systematic review.

1.2.1 Differentiation between studies, population specific studies and repeating trials

Differentiation between the proposed study and those found in the systematic review is particularly important when considering the need for further studies, and care must be taken to avoid excluding funding for projects where trials have been undertaken previously.

There are many interventions or exposures that are not population-specific, and there might be cases where there are numerous international examples of where studies have been undertaken, but their findings might not necessarily apply in the Australian context. For example, studies examining health service usage, screening activities, or Vitamin D / sunlight exposure might have different relevance in the Australian context. There can also be problems in extrapolating the results of clinical trials undertaken in a resource rich setting into an Aboriginal setting where the burden of disease may be high, and where the intervention may not work for reasons.

In these cases, applicants should be able to demonstrate their awareness of the international literature, and show the importance of the Australian context for undertaking the study.

1.2.2 Minimal clinical outcome

There has been significant work in some fields to define minimum clinical outcomes. Where these outcomes have been defined these should be used to help justify a proposed study. Where they are not used, a justification should be given as to why not.

1.3 Systematic reviews

1.3.1 Current and up to date review

AAMRI supports the requirement for a systematic review (or a comprehensive systematic search) to form part of a funding application. The framework should make it clear that the systematic review should be current and up to date. It should not be acceptable for an application to rely on a review that is out of date, and to use it to justify the need for a clinical trial. Applications should only be funded if they have reviewed recent developments in the field.

1.3.2 Difference between a systematic review and a comprehensive and systematic search for, and evaluation of, studies that are relevant to the proposal

It needs to be made clearer with regards to the differences between the two different systematic review/search options, and when each can be used. The second option of a *systematic search for, and evaluation of, studies that are relevant to the proposal* sounds like the first option, a *systematic review*. The evaluation aspect within the second option does imply this is a type of review making it difficult to differentiate between the two options.

1.3.3 Resource implications

Undertaking a systematic review for some interventions could be a major undertaking, with significant resource implications. While it is important that such a piece of work is undertaken before funds are committed to the study, it is not clear where researchers and research organisations will need to source the funding to undertake this work.

It will be more difficult for smaller research groups or centres under the proposed model as they are less likely to have the capacity to support a more extensive application process, including the need for systematic reviews and searches. Smaller research groups involved in more niche investigations, such as studying rare diseases or minority populations, may not have the resources to develop competitive applications under this model. This could lead to certain rare diseases or minority population studies from missing out on funding and this might not be in the national interest.

1.3.4 Multiple exposure and multiple endpoints

Many observational cohort studies have been established with multiple exposures and multiple endpoints in mind. It is not clear how the framework could require systematic reviews at each of these exposure outcome combinations. This could only work if a cohort study had just one single hypothesis. Ideally, cohort studies should address multiple questions as this is a more efficient way to undertake research. A potential solution for this issue would be to require a systematic review for clinical trials, and to encourage them to be undertaken where relevant for cohort studies.

1.3.5 End user participation

AAMRI supports the need to consult with the end users of research. However, it is important that the framework does not confuse ‘efficacy’ with ‘effectiveness’ when considering end user participation. The consultation document implies that studies of ‘effectiveness’ are superior to studies of ‘efficacy’. A study with ‘end users’ in mind is very important in many cases, but there are instances where it might not always be the best in terms of evidence for effect. Therefore, it is important not to impose criteria that are too narrow here and some flexibility in terms of assessment is needed.

1.3.6 Identifying ongoing studies

AAMRI supports the minimum requirements to search relevant databases for ongoing or unpublished studies.

1.4 The assessment process

The above points with regards to the need for the Australian context of a proposed study should also be considered within the assessment process, along with the appropriateness of end user engagement within the design of some studies.

2 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.

2.1 Recommendations

AAMRI agrees with the high-level recommendations in terms of showing the design of the proposed research is appropriate, but suggests that the framework addresses the importance of researchers putting forward realistic recruitment targets and research budgets.

2.2 SPIRIT

AAMRI agrees with the need to address all items in the SPIRIT Statement for clinical trials, but does not agree in terms of cohort studies. Instead, it would be more appropriate for proposed cohort studies to address the STROBE Statement for cohort studies.

2.3 The assessment process

2.3.1 Track records

Drawing on the category descriptors from the SPIRIT Statement to score applications is reasonable for clinical trials, but the above comment on the STROBE Statement should be considered before extending this to cohort studies. In addition to these category descriptors the track records of the infrastructure in which the studies are being proposed should also form part of the assessment. This is a notable absence and should be included.

2.3.2 Rewarding realistic proposals

The competitive nature of research funding is putting pressure on researchers to put forward applications that are sometimes unrealistic in terms of their budget or timelines. The pressure to put forward a high-quality application can leave researchers putting forward an implausible recruitment timeline that cannot be met, but nevertheless they can feel compelled to do so because of the review process. This does not serve the research project well, and is unfair on those applicants that put forward realistic timelines.

A similar issue emerges with regards to setting budgets. For large multi-centre outcome trials that require a large budget, researchers frequently feel as though they cannot submit large funding requests as they would be unlikely to be funded by the NHMRC. This can result in funding shortcuts being taken that lead to an increased risk to the project, leading to delays in recruitment and other aspects of the project.

In both cases the assessment process should be rewarding proposals that are realistic in terms of their timeframe and budget.

3 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?

3.1 Recommendations

The requirement to meet appropriate milestones for clinical trials and cohort studies is a reasonable expectation. Flexibility is important and every study will need to develop milestones appropriate to the design of the study.

3.1.1 Recruitment

AAMRI is in favour of the proposal set out earlier in the document for all clinical trials and cohort studies to have a target sample size. There have been past studies that have taken too long or have failed to meet their recruitment targets. Ensuring there is some sort of obligations for investigators to state feasible targets within their application, and to have a plan to reach those targets is a reasonable expectation. However, there might be cases where recruitment targets have not been met but an interim analysis has shown the effect size to be greater than expected, and in such cases, it would be sensible to continue the trial or study.

Guidance is required on how meeting recruitment targets will be collected and monitored, and the efforts made to reduce any administrative and resource implications this causes. The suggested use in the framework of a centralised system such as RGMS would assist in this regard.

3.1.2 Ethics and governance approval

Within the document (but not within the recommendations) an aspirational target of 60 days is established as the time it should take for ethics and governance approvals to be obtained. Within the recommendations it is stated that ethics approval should be received within 12 months of the first payment.

The ethics and governance approval outcomes are critical milestones within any project. For the most part achieving ethics approval within the aspirational target of 60 days should be possible, but it will be more problematic to achieve governance approval in this timeframe. There are a range of issues that can lead to governance approval delays, and frequently these delays are outside the hands of researchers. Multisite and multicentre studies are particularly problematic because MTAs, IP issues, multisite staff appoints and other sorts of agreements must be signed with the sponsoring institutions. Once these agreements get released to other parties then the investigator can lose control of the process, and much time is taken up with legal discussions between the different parties. The timelines then become contingent on parties that have little or no stake in the importance of the timeline of the trial.

Notwithstanding these issues AAMRI does support having an aspirational target and hopes that this can be used to help bring the overall approval timeframe down.

3.2 Milestone monitoring

3.2.1 Removal and pausing of funding

Care needs to be taken when assessing milestones, particularly in relation to ongoing funding decisions. Funding for projects should not be withdrawn lightly, and researchers given the opportunity to demonstrate how they have tried to meet milestones, and be allowed to change the design of the study to respond to changing circumstances that are often outside their area of control. AAMRI is in favour of the proposed approach to negotiate revised milestones where appropriate, and to give researchers additional time to meet revised milestones. Leeway should be extended to researchers where it can be clearly demonstrated that delays that have occurred are clearly outside of their control. For example, some institutions are unable to commence recruitment institutional and governance issues are resolved, and this can lead to further delays.

In addition to renegotiated milestones, and modifying trials, consideration should also be given to pausing funding rather than discontinuing funding altogether if there is a realistic chance of the trial getting back on track and providing useful scientific outcomes. The use of interim analysis can be useful in this regard. For example, if an interim analysis has been undertaken and shows that despite recruitment being lower than expectations there are good levels of effect, then there should be an opportunity to continue and address recruitment issues.

3.3 End of grant

3.3.1 Publishing results

AAMRI agrees that there is an obligation to ensure that the results of all publicly funded clinical trials are published. There are lessons that can be learnt from other research systems to help encourage the publication of results. For example, in the US sponsors are obliged to publish their results through vehicles such clinicaltrials.gov. There are now rules from the Food and Drug Administration (FDA) that state that if they do not enter information about their trial by the time the first patient is enrolled then they cannot use that information or that data as part of their submission to regulators at a later date. It might be possible to learn from such rulings and see if they can apply to particular clinical trials.

3.3.2 Communicating results with trial participants

Where possible there should be efforts undertaken to communicate the results of clinical trials with participants.

4 Question 4

Do you have other comments about the framework?

4.1 Ongoing funding for existing cohort studies

There are many existing cohort studies and trials that have proven outputs. This includes QSKIN, MCCS, D-Health, OPAL and 45 & UP. The framework does not discuss how best to assess and fund these existing studies. These trials have previously been funded through NHMRC Project grant rounds, and funding for these studies is a legacy issue that needs to be addressed. Such studies show increased value when they are followed up with renewed waves of data collection over many decades. The framework should address how funding support for long-term cohort studies could be best handled in the future.

4.2 Decision tree and definitions

The definition provided for cohort studies within the decision chart (Figure 1 and 2) is problematic and will cause a lot of confusion. It is important this is made clearer so that researchers know whether the guidelines apply to their research proposal. The following specific comments are made to assist in redesigning Figure 1 and 2.

4.2.1 Figure 1

Figure 1 implies that clinical registries and uncontrolled trials involve prospective assignment to interventions or exposures. All treatment involves assignment and what is at issue is whether the investigator controls the assignment. Therefore, Box 3.1 in Figure 1 should ask if the investigator controls assignment to interventions (or exposures). In registries and uncontrolled trials, the investigator does not control assignment. Registries and uncontrolled trials share more in common with cohort studies than with clinical trials.

It also is unclear from Figure 1 whether clinical registries and uncontrolled clinical trials are covered by the recommendations within this document. The text of the document implies that they are not covered, but Figure 1 implies that they are covered.

4.2.2 Figure 2

Further clarification is sought with regards two Figure 2. That two of the question boxes ask the same question is confusing. The concepts discussed within the questions overlap, causing potential confusion, and will make it difficult to use the decision chart in practice. There will be cases where some studies could answer both yes and no to any of the seven questions. It would assist if a series of worked examples could be provided for researchers and panels.

There appears to be a mistake in the first question of the last box in Figure 2 which asks, “Is the main purpose of the study: To evaluate clinical efficacy of interventions where proof-of-concept in humans has already been achieved?”. A positive answer to this question would surely indicate that it was not a mechanistic study, but the decision chart implies otherwise.

4.3 Distinguishing between clinical trials and mechanistic studies

It is unclear what the document is trying to achieve by distinguishing between clinical trials and mechanistic studies. The document appears to be implying that mechanistic studies would not be eligible for funding under this framework, but there are many clinical trials and cohort studies that have a mechanistic component to them, adding value to the whole research exercise. Clinical trials that have a mechanistic study component to them should not be jeopardised in terms of their eligibility for funding. It would help if the underlying policy intent behind this distinction could be made clear.

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