Public Consultation: A Framework for NHMRC Assessment and Funding for Clinical trials and Cohort Studies

Submission from Cancer Council Australia and the Clinical Oncology Society of Australia

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Cancer Council Australia represents the national interests of its members, the eight state and territory Cancer Councils. Collectively, after government Cancer Council is the largest funder of cancer research in Australia by a significant margin, investing $65 million in 2016 in direct and partnership grants.

The **Clinical Oncology Society of Australia** (COSA) is the peak national body representing health professionals from all disciplines whose work involves the care of cancer patients.

Contact:

Cancer Council Australia

Paul Grogan (02) 8063 4155; paul.grogan@cancer.org.au
Kate Whittaker (02) 8063 4161; kate.whittaker@cancer.org.au

COSA

Marie Malica (02) 8063 4160; marie.malica@cancer.org.au

Cancer Council is one of the largest non-government funders of cancer research in Australia. In 2017, research grants through Cancer Councils totalled almost $60 million. Cancer Councils directly funded just under $41 million, with a further $19 million contributed by our research funding partners[1].

Questions related to the consultation paper:

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?**

The proposed reforms to the National Health and Medical Research Council Grant Program aim to *"encourage research that is more creative and innovative"*, *"provide opportunities for Australia's best health and medical researchers at all career stages"* and *"minimise the burden on researchers in preparing and reviewing grant applications, allowing them to spend more time on research"*[2]. The below comments are based on how the framework supports the achievement of the aim.

Demonstrating the need for a new study:

An application for funding to the NHMRC must demonstrate the value of the proposed research to advancing the community's understanding of disease and delivery of care, and how it can be utilised to improve health outcomes. Publicly funded research demands a rigorous review of the proposal and consideration of the best use of Australian tax payer funds. Therefore, it is reasonable to require the submission of evidence and justification for the research to ensure the NHMRC is investing in quality projects. Another priority must be the efficient use of resources to contribute to addressing priorities in health.

Proposed clinical trials investigating the effectiveness of an intervention in a single population must provide a comprehensive case as to why it is not feasible to expand the targeted population. The conduct of multiple studies testing similar interventions in single population groups could be an inefficient use of research resources. The proposal to conduct a new prospective study must demonstrate that there is no existing data available to answer the question, and therefore requires the collection of primary data.

The value of research is in the ability to translate the outcomes into practice to effect change. The framework must require investigators to demonstrate how the intended outcomes will impact knowledge, practice or policy. Demonstrating this will also satisfy requirements of engaging 'end users' in the development of the application as it requires consideration of health system, decision makers and utilisation by an individual.

Impact of the requirement to present or conduct a systematic review:

Proposed research must be scientifically valid and the need to undertake a study justified, however, if a systematic review using the PRISMA model must be undertaken this will require additional time and resources. Systematic reviews may be used as a starting point for developing clinical practice guidelines, however, *"as with all research, value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systemic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews."*[3]

The development of a protocol to conduct a systematic review is recommended in PRISMA-P guidelines and it is acknowledged that this must be funded, *"without review protocols, how can we be assured that decisions made during the research process aren't arbitrary, or that the decision to include/exclude studies/data in a review aren't made in light of knowledge about individual study findings?"*[4] and Point 27 of the PRISMA checklist notes the requirement to *"describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review*[5]*."*

Currently, NHMRC grant applications require submission of the scientific premise forming the basis of the proposed research, a rigorous trial design, rationale, objectives, outcomes, patient eligibility criteria, justification for proposed interventions, sample size, analysis plan and proven capacity to undertake the new study. Undertaking and submitting a systematic review using the PRISMA model may not be feasible for an investigator led study and this requirement may delay, or lead to decisions to forgo applications for NHMRC funding.

For academic, investigator led cancer related trials, Cancer Collaborative Trials Group Scientific Advisory Committees review and endorse new study concepts for development. A number of

Scientific Advisory Committees meetings may be held to discuss a new trial concept, provide feedback to investigators and review updates until the committee is able to endorse a concept for trial development. Scientific Advisory Committees members include experienced clinical investigators from multidisciplinary backgrounds who are well placed to assess whether the right questions are being asked, review existing evidence and determine whether a new study is justified. An alternative to conducting a systematic review using PRISMA may be to request detail about the process of Cancer Collaborative Trials Group Scientific Advisory Committee assessment of a new research proposal in an NHMRC grant application.

In the case of global clinical trials for which NHMRC funding is sought to undertake the study in Australia, endorsement of international scientific councils/protocol review committees, or approval from international regulatory bodies could be accepted as justification that an appropriate and relevant review of the study has been undertaken. This documentation could be discussed with the NHMRC prior to applying, to seek recognition of this review as a supporting document.

The findings from a systematic review must be overlayed with health professional consensus to demonstrate that, in addition to conducting the systematic review appropriately, the outcomes are feasible in policy and practice in the Australian context to the benefit of the population.

End users:
There are a variety of stakeholders who may be affected by the outcomes of research, including the individual, healthcare professional and various decision makers. Many Cancer Collaborative Trials Groups support Consumer Advisory Panels comprised of trained consumer advocates who contribute to clinical trial development as members of a Scientific Advisory Committee. Consumers, as recipients of the outcomes from research, are involved in each step of the design and development of new study proposals and this should be documented in funding applications.

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?**

Appropriate study design:
A rigorous study design aids the production of quality research outcomes. A checklist or guidance may be suitable to ensure key elements of the study design have been considered however, investigators must use appropriate methodologies to address each element of the study design.

The SPIRIT Statement is intended to *"facilitate the drafting of protocols and improve their completeness"*[6]. If the NHMRC Framework for Assessment requires all aspects of the SPIRIT Statement to be addressed, the study protocol must be fully developed prior to the submission of an application for grant funding. This requires a significant investment in time, and given a NHMRC application success rate of 15.2% in 2016[7], a significant amount of high quality research goes unfunded.

Many medical research institutes in Australia do not have time and resources available to fully complete a study protocol before funding to conduct the study has been confirmed. While the scientific justification, trial design, intervention, feasibility assessment, statistical plan, milestones, letters of intent from pharmaceutical partners, site expression of interest and a recruitment plan will have been documented, other trial logistics may not be fully outlined. For many research institutes,

the outcome of a funding application determines when resources can be allocated to complete the study protocol.

It should not be necessary for funding applications to address every item in the SPIRIT Checklist which requires the provision of protocol page references. Some items, for example, plans for the collection of trial data, transfer of data, references to where data collection forms can be found, validity of data collection instruments, a model patient informed consent document, composition of a data safety and monitoring committee, and a publication plan will be reviewed by an ethics committee. Therefore, it seems an unnecessary burden for investigators to use unfunded resources to satisfy all elements on the SPIRIT checklist for the Grant Review Panel, when this will be considered by an accredited ethics committee.

If all components of the SPIRIT Statement must be addressed in a grant application this could limit the potential for innovative investigator led studies to be submitted for funding, including those from research institutes with proven track records in conducting successful, high quality clinical trials which improved outcomes for patients.

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?**

Clear milestones are important to ensure the timely completion of a clinical trial or cohort study. Reporting against agreed milestones provides an opportunity to review ongoing investment and should be a requirement for the continuation of support. The NHMRC proposal to allow the Chief Investigator of a funded study to submit an explanation and request to extend or revise agreed milestones is reasonable. The number of times such submissions could be made during the course of the study could be limited to discourage unnecessary extensions to the duration of clinical trials.

Data collection and dissemination:

We support the NHMRC Policy on Dissemination of Research Findings and the requirement of obtaining funding support for the Chief Investigator to ensure all conditions of open access are achieved[8]. Study outcomes must be disseminated broadly to allow access to this information by other researchers and the wider community to maximise benefits from publically funded research.

Recently, 17 international major research funding bodies released a joint statement supporting the World Health Organisation's (WHO) public statement on the public disclosure of results from clinical trials[9]. They demonstrated support for new standards that will require all clinical trials they fund or support to be registered and the results disclosed publicly. It states that *"researchers have a duty to make publicly available the results of their research….Negative and inconclusive as well as positive results must be published or otherwise made publicly available.*[10111213]"

Similarly to principles within the WHO statement, the NHMRC Policy on Dissemination of Research Findings require that any publication arising from NHMRC supported research to be made available in an open access format within a 12 month period from the date of publication. Prospective registration and timely public disclosure of results from all clinical trials is of critical scientific and ethical importance. The timely disclosure of research results reduces waste in research, increases value and efficiency in use of funds and reduces reporting bias, which should

lead to better decision making in health.

4. Do you have other comments about the framework?

Australian investigators must satisfy many requirements prior to conducting high quality clinical trials aimed to improve outcomes for cancer patients. We appreciate that the additional requirements relating to completion of the SPIRIT checklist to be submitted with the grant application, and use of PRISMA to conduct a systematic review, support principles of ethical, scientific and quality research conduct. However, the proposed framework increases the burden on researchers in preparing grant applications, may reduce opportunities for researchers and Cancer Collaborative Trials Groups to submit creative and innovative research proposals and is unlikely to allow researchers to spend more time on actual research.

Well-resourced research institutes may be able to comply with the proposed changes, but researchers from smaller units may not. New trial concepts and opportunities for Australian researchers, at all career stages to lead important new studies could be negatively impacted by the additional requirements.

Priority Framework:
Investigator led research is a significant initiative to develop ideas into projects, however there is also an opportunity for the NHMRC to progress cancer control in Australia by directing a greater proportion of the available funding to priority-driven research, addressing identified gaps and reflecting the burden of different cancers.

A national priority driven cancer research assessment framework would improve coordination of investment in cancer research and funding efficiency. This would focus the use of government funding of cancer research prioritised towards high burden cancer and investigation of clinical variation through investment in health services research. The NHMRC has an opportunity to develop funding streams for investments in priority-driven biomedical and health services research, and assess this when the investigators demonstrates research value.

A focus on priority driven cancer research would increase funding towards population, prevention and early detection trials. One-third of cancers are potentially preventable[14], and delay in the detection of many cancer types, particularly with hard to diagnose symptoms, can significantly impact overall survival. An analysis of total research funding during 2006 to 2011 found the majority of funding was directed to research in biology and treatment, and direct funding to research other in areas, including prevention and early detection, was comparatively low[15].

Implementation of the framework:
If the framework is implemented, the NHMRC must ensure adequate resourcing and support is allocated. The achievement of its intended purpose and the experience of stakeholders, both internal resourcing and external applicants for funding, must be evaluated over time. Particularly for longitudinal cohort studies, the length of the study may not fit into a five year funding cycle, therefore consideration for high impact and valuable primary data studies cannot be restricted by the framework.

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