Evaluation of the Medical Research Future Fund Clinical Trials Activity: A report on the review or the Medical Research Future Fund's (MRFF) Clinical Trials Activity Initiative

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EVALUATION OF THE MEDICAL RESEARCH FUTURE FUND (MRFF) CLINICAL TRIALS ACTIVITY FINAL REPORT

Prepared for the Department of Health and Aged Care

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EXECUTIVE SUMMARY

Background

The Medical Research Future Fund (MRFF) is a research fund set up by the Australian Government in 2015 to support health and medical research in Australia. The Clinical Trials Activity (CTA) Initiative was established in 2016. Early funding priorities included rare cancers, rare diseases and unmet need, childhood brain cancer, reproductive cancers, and neurological disorders.

The Department of Health and Aged Care (the department) contracted the Institute for Evidence-Based Healthcare (IEBH), at Bond University, to conduct an evaluation of MRFF's CTA Initiative, to assess its progress in achieving the objectives set out in the MRFF 10-year Investment Plan in accordance with the MRFF Monitoring, evaluation and learning strategy, 2020-21 to 2023-24, and to guide future investments in clinical trials activity through the MRFF.

The intention of the evaluation of the MRFF Clinical Trials Activity Initiative was to:

- consider all existing investments on clinical trials made through the MRFF (e.g., progress made through MRFF funded projects)
- consider approaches and the current landscape for clinical trials internationally and nationally in Australia
- suggest opportunities for improving funding and granting arrangements for clinical trials through the initiative and the MRFF more broadly.

Methods

To collect data for the evaluation, we used three complementary methods.

1. Desktop Review Data Set

A desktop review compared MRFF-funded trials with trials funded by comparable funders, including: the National Health and Medical Research Council (NHMRC) in Australia and their subset of trials in the Clinical Trials and Cohort Studies Scheme (CTCS), the National Institute for Health and Care Research (NIHR) in the United Kingdom, Canadian Institute of Health Research (CIHR) in Canada, and the National Institutes of Health (NIH) in the United States. The data was derived from items in the clinical trial registries including the Australian New Zealand Clinical Trials Registry (ANZCTR) and the NIH's National Library of Medicine.

2. Survey Data Set

For each MRFF and NHMRC CTCS-funded grant, we sought two responses – one from the Chief Investigator A (CI-A) and one from an Early to Mid-Career Researcher (EMCR). The survey was open for completion between 4 October and 24 November 2022.

3 Stakeholder Consultation Data Set

To supplement the findings of the Desktop Review (Project 1) and the Survey (Project 2), we conducted interviews with key stakeholders to better understand the key factors contributing to success of funded trials – including recruitment, follow up, and publication. The interviews included comments on data from the Desktop Review (Project 1) and Survey (Project 2), as well as questions about the MRFF Clinical Trial Activity Initiative, and barriers, facilitators, research ethics and governance, and trial funder interactions.

Findings

Characteristics of MRFF-funded clinical trials vs other funders

The registry data analysis (Desktop Review) found that the MRFF-funded trials were broadly similar to trials funded by NHMRC, NHMRC CTCS, NIH and CIHR, and there were a few areas where MRFF-funded trials appeared better on average.

The study design and quality of the MRFF funded trials was broadly equal to or better than most other funders' trials. For example, 16% of MRFF-funded trials are in the "over 1000 participants" category, which is larger than for the other funders, including the NHMRC (full set), CIHR, and NIH (the 16% is smaller than the NHMRC CTCS's 40%, but due to a very small size of the CTCS sample set (n=14), it is difficult to draw meaningful comparisons).

The mix of study designs were comparable across funders. However, there was a notable lack of factorial trials – a very efficient design – across all funders including MRFF. Rates of use of randomised versus non-randomised trial designs, and the percentage of trials that were blinded, were also generally similar for all funders, aside from NHMRC-funded CTCS studies which generally had a higher percentage of randomised trials and blinded trials than other funders.

By far, the most common design was a parallel group trial, but with a modest number of cluster, adaptive, platform, crossover, and factorial studies. Given the recent acceptance by the clinical trials community of adaptive and platform trials – which improve trial efficiency and the speed of addressing new clinical questions – the number being funded is encouraging. In contrast, the small number of factorial designs may require some explicit intervention on the part of MRFF.

The design issues were commented on by some stakeholders, in particular the need for methodological expertise on the Grant Assessment Committees. A related concern was the small number of trials using a "Standardised Outcome Set", i.e. a set of clinically-relevant measures that have been identified by experts by consensus for common reporting in the field/disease area, which is considered best practice, and consideration might be given to encouraging this in the advice to applicants.

The Open Science processes elements available were protocol access and whether individual patient data would be available. Protocol availability was very low for trials of all of the 5 funders examined, but strikingly better for MRFF studies with 22% of protocols being available.

Impact towards MRFF Objectives and Measures of Success

Increased focus of research on areas of unmet need

The range of clinical conditions, interventions and purposes addressed by the research questions of the MRFF-funded trials were, on average, similar to non-MRFF-funded trials. The conditions studied were broad and similar, with the most notable exception being the number of cancer trials particularly of rarer cancers, which was more common for MRFF-funded trials – however, this difference aligns with the priorities and calls of MRFF based on unmet needs. Data on features of the populations studied are limited, but we note that the minimum age, and gender mixes were similar. The categories of interventions studied in MRFF trials were also broadly similar to international funders, although with a higher proportion studying drug treatments, but also with a higher proportion studying prevention.

Several stakeholders interviewed noted as a positive that MRFF guidelines and process encouraged researchers to make sure that they include diverse communities and consumers as part of the trials or studies. Notably, over 20% of trials included a consumer or patient as a chief investigator. However, some stakeholders also noted that the MRFF priority setting was unclear to them, and that the timeframes from call to submission were usually insufficient to allow extensive consumer input on questions and design. Priority setting processes typically take 12-18 months of background work before the final workshop with consumers, clinicians, researchers and funders.

More Australians access clinical trials

Most stakeholders welcomed the MRFF trials initiatives as a clear positive for clinical trials in Australia. Several stakeholders suggested MRFF helped to meet a gap in funding for needed trials, a gap also suggested by Australia's ranking in the middle for numbers of trials per head of population. While the MRFF initiatives have substantially increased the number and range of clinical trials, there have been some barriers to conduct, in particular the site governance or study site approvals, which occurred in over 50% of trials. As is true of most trials, site recruitment and individual patient recruitment were identified as the most common problems for barriers to successful completion for most trials.

Research community has greater capacity/capability to undertake translational research

Positive sentiment was expressed for the early career support provided (via non-trials streams) by the MRFF, as these help to support the capacity for trials more broadly. Stakeholders expressed support for it continuing, though lamented the current low success rates. As might be expected the majority of MRFF funded trials were led by academics, clinicians, with fewer led by consumers, policymakers, or non-government organisations. A critical issue is the need to support clinician-researchers who have the skills to understand the important clinical questions and an understanding of trial design. However, stakeholders suggested the degree of involvement of professional organisations, non-government organisations, industry, and consumers is encouraging, as reflected in the survey finding that NGOs, policy makers, and consumers were among the chief investigators in 10-24% of trials. This involvement is likely to improve translation of findings into practice.

Approximately a quarter of trials included some international patients. While the MRFF initiatives were welcomed and improved support generally, some future opportunities were also identified. In particular, continuity of support for streams of research work has not eased, and continuity to build critical mass of researchers or research groups, working on particular areas. Having consistency of the programs from year to year would be valuable to help with planning of much needed longer-term programs of work.

New health technologies and interventions are embedded in health practice

Clinical trials usually require 1-2 years of start-up and recruitment time, often 2-4 years of follow up, and approximately a year for final analysis, write up and publication. These timelines mean that few MRFF trials have yet completed, with only 10% reported completion of data and only 7 of all MRFF trials published so far, and hence assessing their dissemination and impact is currently limited. This will clearly be a key issue to plan for longer-term follow up to monitor trial completion, publication, and uptake of results.

This consequence of the long timelines of clinical trials also applies to several other measures of success, such as (i) Health professionals adopt best practices faster, and (ii) Increased commercialisation of health research outcomes.

The community engages with and adopts new technologies and treatments

The consumer involvement in grant guidelines, grant assessment, and panel composition has mostly been welcomed by interviewed stakeholders. Some felt there is an opportunity to go further and include community members as full panel members on Grant Assessment Committees. There were also several stakeholder comments about the need for adequate time for researchers to undertake effective consumer and community involvement.

Limitations

The limitations of this evaluation should be mentioned. Most crucially, the incomplete data for many of the items, such as protocol and data availability, which were not mandatory and left unspecified by many researchers in clinical registry records may lead to underestimates of availability. Second, many trials have been disrupted by the pandemic which has created difficulties with site and patient recruitment, as well as diverting the attention of clinicians. Third, few trials have been completed, and hence assessing their dissemination and impact is currently limited.

Conclusion

The MRFF has clearly led to a welcome increase in funding for clinical trials in Australia, and has resulted in trials of comparable size and design quality to that of other funders internationally across the range of metrics. This has been important to the support and development of clinical trials activity in Australia and should continue. Because of the timeframes to complete the trials, as well as the impact of the pandemic, few trials have yet been reported and been translated into practice. This will need to be monitored in the years to come.

Meanwhile there are a number of potential areas for further enhancing the return on investment that the current program offers. Some of these opportunities include:

1. Improved guidance to trial applicants and panels on quality and design options that would be welcomed, such as factorial design trials, and considering inclusion of a special call, or consideration in the assessment criteria, or both.
2. Support for the use of standardised outcomes sets in the guidance, with specific reference to the website of COMET (the database of Core Outcome Measures in Effectiveness Trials).
3. For some topic areas, a specific priority setting process to examine which are the most important unanswered clinical questions within a topic (using a methodology such as The James Lind Alliance) might be considered. For example, such a priority setting process could be held within the topic area of some of the larger clinical trials networks already receiving funding from MRFF.
4. In order to improve long-term monitoring, we would suggest that funding is not triggered until the funded study provides its trial registration number to MRFF, with an agreement to provide the complete protocol (confidentially, if necessary), before commencement of the trial. These would improve the transparency of trials and open science process generally, as well as allow MRFF to more efficiently monitor trials' progress.

The methods tested in this evaluation could be used in the future, to guide minimal data collection from grantees, to allow regular performance oversight and risk management for feedback to MRFF.

These opportunities for MRFF funding for clinical trials may be supported by ongoing clinical trials reform in Australia, which is currently a national priority. Multiple national policy initiatives are currently being undertaken to enhance the clinical trials and health and medical research operating environment, e.g. the National Clinical Trials Governance Framework, and the National One Stop Shop and National Clinical Trials Front Door, with the longstanding goal of making it easier for patients, researchers and sponsors to participate in and conduct trials and research.

BACKGROUND AND PURPOSE OF THE EVALUATION

The Medical Research Future Fund (MRFF) is a research fund set up by the Australian Government in 2015 to support health and medical research in Australia.(1) Under the MRFF's 2nd 10-year Investment Plan, the Australian Government has committed to funding 21 initiatives to support lifesaving research, job creation, and growing Australia's reputation as a world leader in medical research. The Clinical Trials Activity (CTA) Initiative was established in 2016. Early funding priorities included rare cancers, rare diseases and unmet need, childhood brain cancer, reproductive cancers, and neurological disorders.(1) Between 2017 and 2021 (inclusive), 167 trials were funded with the number of funded trials increasing each year (Figure 1).

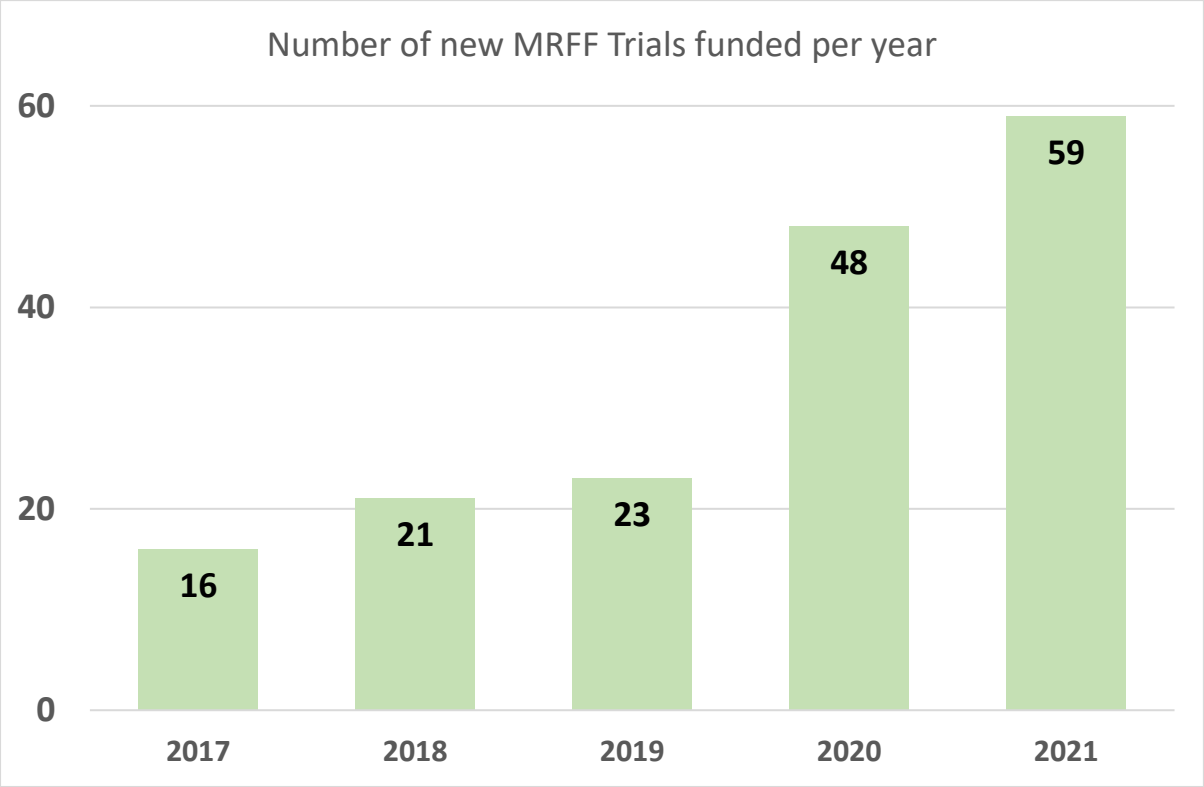

Figure 1 Number of new MRFF trials funded per year (2017-2021 inclusive)

The Department of Health and Aged Care (the department) contracted the Institute for Evidence-Based Healthcare (IEBH), Bond University, to undertake an evaluation of the MRFF CTA Initiative, as well as clinical trials and cohort studies funded through the National Health and Medical Research Council (NHMRC)'s Clinical Trials and Cohort Studies (CTCS) funding stream.

This evaluation consisted of three projects:

Project 1: A Desktop Review of funded trials, consisting of:

- Part A: A Review of MRFF-funded trials

- Part B: A Comparison of MRFF-funded trials with trials funded by comparable funders, including: the National Health and Medical Research Council (NHMRC) in Australia, the National Institute for Health and Care Research (NIHR) in the United Kingdom, the Canadian Institutes of Health Research (CIHR) in Canada, and the National Institutes of Health (NIH) in the United States (U.S. National Library of Medicine)

Project 2: A survey of the MRFF grant recipients and the NHMRC CTCS funding stream grant recipients

Project 3: A comprehensive consultation with key domestic and international stakeholders.

The MRFF Monitoring, Evaluation and Learning Strategy 2020-21 to 2023-24 (Evaluation Strategy) sets out the principles and approach for monitoring and evaluating the MRFF and allows the department to assess impact and outcomes to ascertain whether the MRFF is achieving its intended objectives.(1) The aim of this evaluation was therefore to assess the progress of the MRFF's Clinical Trials Activity's progress in line with the Australian Government's 10-year MRFF Investment Plan (and the Evaluation Strategy), and to guide future investments in clinical trials activity through the MRFF.

The intention of the evaluation of the MRFF Clinical Trials Activity was to:

- consider all existing investments on clinical trials made through the MRFF (e.g., progress made through MRFF-funded projects)
- consider approaches and the current landscape for clinical trials internationally and nationally in Australia
    - For example, situate the analysis of the clinical trial approaches and research areas funded by the MRFF within the overall landscape of clinical trial activity nationally and internationally.
- suggest opportunities for improving funding and granting arrangements for clinical trials through the initiative and the MRFF more broadly.
    - This may include, for example, identifying evidence-based strategies that could improve the efficiency and effectiveness of clinical trial investments or opportunities to enhance the involvement of patients in clinical trial design and implementation.

METHODS AND SCOPE

Three projects comprised the evaluation of the MRFF Clinical Trials Activity and NHMRC's Clinical Trials and Cohort Studies – as follows:

1. Desktop Review Project
2. Survey
3. Stakeholder Consultation

Their methods, scope, and the resulting type and volume of data from each project, is described in more detail below.

Desktop Review Methods and Data Set (Project 1)

Project 1: A desktop review consisted of two parts, part A and part B:

- Part A: A Review of MRFF-funded trials

- Part B: A Comparison of MRFF-funded trials with trials funded by comparable funders, including: the National Health and Medical Research Council (NHMRC) in Australia, the National Institute for Health and Care Research (NIHR) in the United Kingdom, the Canadian Institutes of Health Research (CIHR) in Canada, and the National Institutes of Health (NIH) in the United States.

The data for this project was derived from trial registry information from the following registries, all of which registered at least one MRFF-funded clinical trial:

- Australian New Zealand Clinical Trials Registry (ANZCTR)
- National Institutes of Health's National Library of Medicine (ClinicalTrials.gov)
- European Union Drug Regulating Authorities Clinical Trials Database (EudraCT)
- International Standard Randomised Controlled Trial Number (ISRCTN)

The list of MRFF-funded trials was obtained from the department, and their clinical trial registry information was obtained from the above registries.

The list of trials for each of the comparator funders (NHMRC, NIHR, CIHR, NIH) were obtained as follows:

- NHMRC set of trials was obtained from ANZCTR, for all trials indicating NHMRC as a funder or one of the funders
- NHMRC Clinical Trials Cohort Studies (CTCS) set of studies was obtained from the department, and their data extracted from ANZCTR, or clinicaltrials.gov, or both
- NIH set of trials comprised trials registered in clinicaltrials.gov, identified as interventional studies, and registered subsequently to the analysis by Califf et al (2012)(2), covering the period from 27 September 2010 to 27 April 2022
- CIHR set of trials were those registered in clinicaltrials.gov, identified as intervention studies (Table 1)**.**

Table 1 List of trial data sets and their provenance for each funder

Provenance of the analysed data set for each funder
Data set of the MRFF-funded trials consisted of: • 130 trials with an ANZCTR registration number • 45 trials with a ClinicalTrials.gov (NCT) • 3 trials with a ISRCTN or EudraCT registry number
Data set of the NHMRC-funded trials consisted of: • 2077 trials from the ANZCTR registry
Data set of the NHMRC CTCS-funded trials consisted of: • 24 trials from the ANZCTR registry • 11 trials from the ClinicalTrials.gov registry
Data set of the NIH-funded trials consisted of: • 14,095 trials from the ClinicalTrials.gov registry
Dataset of the CIHR-funded trials consisted of: • 985 trials from the ClinicalTrials.gov registry

Survey Methods and Data Set (Project 2)

For each MRFF and NHMRC CTCS-funded grant, we sought two responses – one from the Chief Investigator A (CI-A) or another Chief Investigator responding on their behalf; and one from an Early to Mid-Career Researcher (EMCR) on that grant (construed as a member of the team who completed their PhD or equivalent within the last 2 to 10 years). It should therefore be noted that the same grant may be represented more than once in the responses provided to the survey. Names of Chief Investigators (CI) were provided by the department, and names of EMCRs were provided by the CI for each grant via email contact.

Potential participants first received an informational email from the department's Health and Medical Research Office (HMRO) or the NHMRC, informing them that the survey was being conducted. Subsequent to this, IEBH staff sent a direct email disseminating survey link (4 October 2022) and two reminder emails (20 October and 9 November 2022). The survey was open for completion from 4 October to 24 November 2022. Of the 359 individuals who received the MRFF survey, 212 provided a complete response (59%). Of the 153 individuals who received the NHMRC survey, 73 provided a complete response (48%) (Table 2).

Table 2 Survey responses

At survey close date (24 November 2022)	MRFF survey (N=359 sent out)	NHMRC CTCS survey (N=153 sent out)
No response	121	70
Accessed*	238	83
Accessed and partially completed	26 (14 accessed with no data, 5 accessed with demographic data, 7 accessed with partial data from Q5).	10 (0 accessed with no data, 6 accessed with demographic data, 4 accessed with partial data from Q5).
Completed	212 (59%)	73 (48%)

*accessed category includes those respondents who: completed the survey, and those respondents who accessed and partially completed the survey

For the MRFF respondents, the greatest proportion of respondents were CI-As (61%), female (54%), whose median time working in research was 13 years. For the NHMRC respondents, the greatest proportion of respondents were, similarly, CI-As (64%), female (58%), although their median time working in research was somewhat shorter, at 10 years (Figure 2). The most frequent response to the question about the highest level of qualification was PhD for both the MRFF respondents (83%) and the NHMRC respondents (94%).

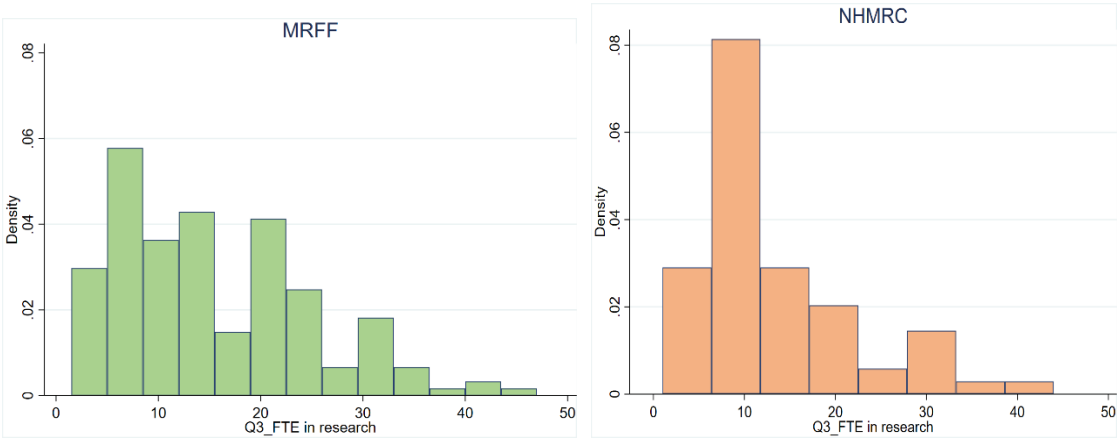

Figure 2 Years worked in research, researchers with (a) MRFF grant; (b) NHMRC grant

Stakeholder Consultation Methods and Data Set (Project 3)

The aim of the Stakeholder Consultation was to supplement the findings of the Desktop Review (Project 1) and the Survey (Project 2) to better understand the key factors contributing to success (including recruitment, follow up, and publication) of funded trials. The consultation focused on barriers, facilitators, research ethics and governance, and trial funder interactions.

The stakeholders were the (broadly construed) members of the research community at the individual and institutional level. The list of interviewees was jointly agreed by the department and IEBH. Each stakeholder was initially approached via an email from the department's Health and Medical Research Office (HMRO), which provided information about the project. If no response was received, up to 2 email reminders were sent by IEBH staff. If no response or a decline was received, the stakeholder was removed from the potential participant list, and an alternate stakeholder was approached using the same process.

The content of the stakeholder interview document was designed jointly by the IEBH and HMRO, and contained agreed-upon data from the Desktop Review (Project 1) and Survey (Project 2), as well as a list of 22 questions about the MRFF Clinical Trial Activity Initiative, trial design, funding, barriers and facilitators, funder roles, etc.

Fourteen stakeholders were interviewed in total, spanning the following categories: grant applicants (both successful and unsuccessful), funders (domestic and overseas), consumer representatives, representatives from Universities or Research Institutes, representatives from collaborative networks, industry and research sector bodies, and Grant Assessment

Committee (GAC) members. Interpretation of the stakeholders' views needs to take into consideration their relatively small number, and their differences of opinions.

Data Synthesis

Data were intended to complement each other, although there were overlaps in the topics or issues covered by the three projects comprising the evaluation.

Where data from more than one project (Desktop Review and Survey, or Survey and Stakeholder Consultation, for example) addressed the same or cognate topic, the data were grouped and narratively synthesised.

Summarised results are presented in the results section of the present report; detailed results are presented in Appendix 1 to this report (separate document).

RESULTS

The findings from the three projects – Desktop Review, Survey and Stakeholder Consultation – are integrated and reported on within 3 sections, structured as follows:

- **Results Section 1: Study Characteristics** – reports the composition of the study teams, justification for conducting the study, study funding, trial networks, regulations, study design, data, and public availability

- **Results Section 2: Study Impacts** – reports the impacts of the studies, e.g. on healthcare, and in terms of commercialisation

- **Results Section 3: Study Challenges** – reports on the challenges around the conduct of the studies, e.g. in terms of design, recruitment, etc.

The vast majority of trials – as reported by 89% of 210 MRFF survey respondents and 97% of 73 NHMRC survey respondents – have *not* completed data collection for the main outcomes. The interpretation of the survey findings, in particular, needs to take this into account.

RESULTS SECTION 1 – STUDY CHARACTERISTICS

Study teams – Summary of results

Study or trial teams included a broad range of participants, as reported by the survey respondents – this was the case for both the MRFF-funded and NHMRC-funded studies (Table 3).

According to 217 survey respondents, over three-quarters of MRFF-funded trials included locally based academics (97%), clinicians (94%), and patients or consumers or carers (82%).

According to 75 survey respondents, over three-quarters of NHMRC-funded trials included locally based academics (95%), clinicians (91%), patients or consumers or carers (80%), and internationally based academics (76%).

Table 3 Study or trial team composition overall

Study or trial team composition overall	MRFF (n=217)		NHMRC (n=75)	
Other (please specify)	13	6%	6	8%
The public (i.e. no lived experience)	14	6%	4	5%
Aboriginal and/or Torres Strait Islander people or communities	17	8%	6	8%
Policy makers	48	22%	20	27%
Industry	53	24%	8	11%
Non-government organisation	71	33%	13	17%
Professional or Peak Associations/Organisations/Bodies	89	41%	26	35%
Academics (internationally-based)	122	56%	57	76%
Patients/Consumers/Carers	179	82%	60	80%
Clinicians	204	94%	68	91%
Academics (locally-based)	210	97%	71	95%
Unsure	0	0%	3	4%

Survey respondents reported that the trial's Chief or Principal Investigators included, most commonly:

- For MRFF investigators: of the 217 who responded to this question, 98% (213 of 217) identified themselves as locally-based academics; the next biggest proportion identified themselves as clinicians (92% or 199/217). (For this question, the respondents were able to select multiple categories to describe themselves).

- For NHMRC investigators: of the 76 who responded to this question, 97% (74 of 76) identified themselves as locally-based academics; the next biggest proportion, similarly, identified themselves as clinicians (88% or 67/76).

Early to Mid-Career Researchers (EMCRs) were very commonly involved in trials; only 1% of MRFF-funded trials and 4% of NHMRC-funded trials did *not* involve EMCRs in any capacity, according to the survey respondents (Table 4).

Two hundred and sixteen MRFF-funded investigators reported in the survey that EMCRs were most commonly involved in their trials as one of the principal investigators (63%) or one of the associate investigators (55%) (Table 4).

Seventy-six NHMRC-funded investigators similarly reported in their survey responses that EMCRs were most commonly involved in their trials as either one of the principal (78%) or associate (53%) investigators (Table 4).

Table 4 Involvement of early-mid career researchers (EMCRs)

In what capacity does the trial involve Early to Mid-Career Researchers?	MRFF (n=216)		NHMRC (n=76)	
Trial does not involve Early to Mid-Career Researchers	3	1%	3	4%
Other (please specify)	20	9%	6	8%
PhD student	56	26%	21	28%
Professional research person	73	33%	25	33%
Site investigator	90	41%	34	45%
Named on the trial as an Associate Investigator	121	55%	40	53%
Named on the trial as Principal Investigator	138	63%	59	78%

Consumers were engaged in the trials in a broad range of roles.

Most frequently, the 207 MRFF survey respondents identified that they engaged with consumers by gathering and implementing their input on the priorities and design of the study (n=166, 80%), or by forming a consumer advisory group for the project (n=94, 45%)

Most frequently, the 70 NHMRC survey respondents identified that they engaged with consumers by gathering and implementing their input on the priorities and design of the study (n=59, 84%), or by forming a consumer advisory group for the project (n=34, 49%)

1.2. Study justification – Summary of results

Reasons for conducting the trial on the topic selected varied.

For the 208 MRFF investigators who responded to this question in the survey, the 5 most commonly offered reasons, were as follows:

- Clinical need (n=71)
- Gaps in knowledge/evidence base (n=39)
- Extending existing research programme (n=37)
- No treatment / inadequate treatment / poor patient outcomes (n=26)
- Favourable pilot/feasibility study / promising findings in existing research (n=16).

For the 69 NHMRC investigators who responded to this question in the survey, the 5 most common reasons cited included:

- Clinical need (n=30)
- Extending existing research program (n=16)
- No existing trial or need for 'stronger' research design (n=14)
- Unresolved health issue/gaps in knowledge (n=9)
- Other (n=7).

The survey respondents reported that their trials were most commonly justified by referring to review of the literature (Figure 3).

For the 229 MRFF survey respondents, the trial was most commonly justified by a literature review of diagnostic or treatment options (n=138, 65%), followed by a systematic review, meta-analysis or both (n=104, 49%).

For the 79 NHMRC survey respondents, the trial was, similarly, most commonly justified by a literature review of diagnostic or treatment options (n=45, 63%), but almost as commonly by a systematic review, meta-analysis or both (n=44, 61%).

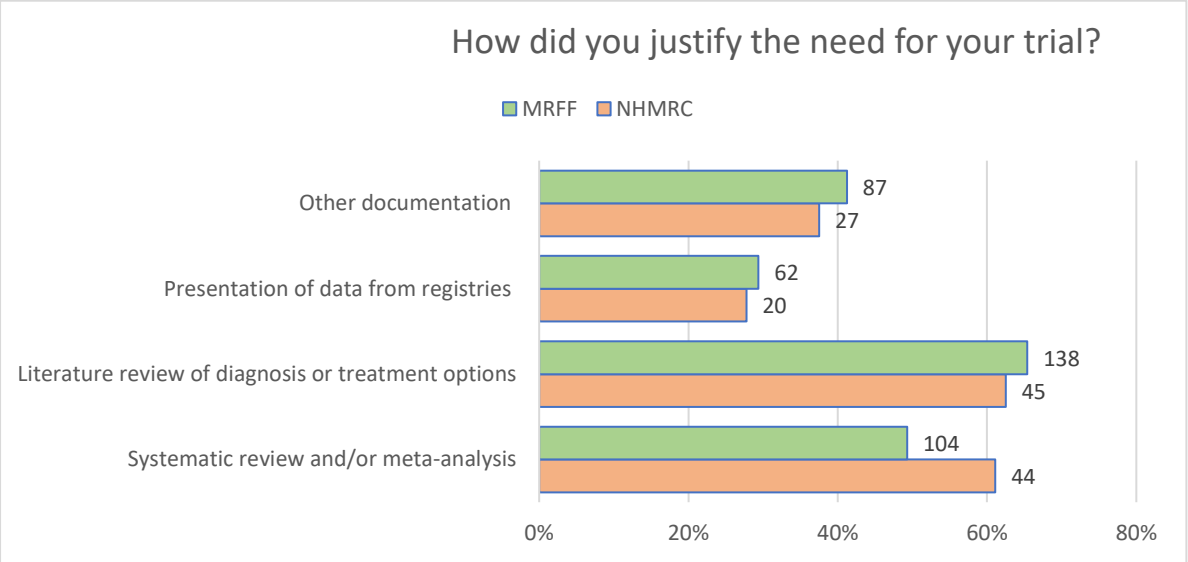

Figure 3 How was the need for the trial justified?

1.3. Study funding – Summary of results

Original funder (MRFF/NHMRC)

Participants in the Stakeholder Consultation commented on their experiences with the MRFF's CTA Initiative as a whole very positively, mentioning its important role in clinical trials, regularity of similar calls, good organisation of the Grant Assessment Committees – with suggestions about enhancement by making consumers full members of the panel, inclusion of health economics expertise, and provision of feedback – and complementary comparisons to NHMRC.

Stakeholders praised MRFF's CTA in particular, as an additional – perhaps even a dominant – source of funding and support for conducting trials in Australia, and filling in a gap in the rarer disease areas which may not be fundable through other avenues. Suggestions were made to allow for adequate time for community involvement, e.g., by looking to UK's processes, considering funding for unmet needs in public health, and funding of core infrastructure for networks. Suggestions to allow spending of MRFF funding overseas were made but may not be feasible due to legislative constraints.

Timing and content of calls for applications has been improved, according to the stakeholders, as timelines for calls are published, although some concerns were raised about the short time-frames and narrowness of the calls, and unclarity about whether some calls are intended to be a one-off call or regularly repeated. Nevertheless, the increased consistency is evident year-to-year and was praised, as was the increased funding for early career researchers.

Co-funding

Survey respondents reported low co-funding of their trials by another body (agency, charity or sponsor). Twenty-five per cent of MRFF respondents and 13% of NHMRC respondents reported co-funding for their trials (Figure 4).

For MRFF respondents to the survey, co-funding was most often received from domestic sources (48%) rather than international sources (31%); for the NHMRC respondents, equal percentage of respondents identified domestic (40%) and international (40%) sources, although the numbers are very small (Figure 4).

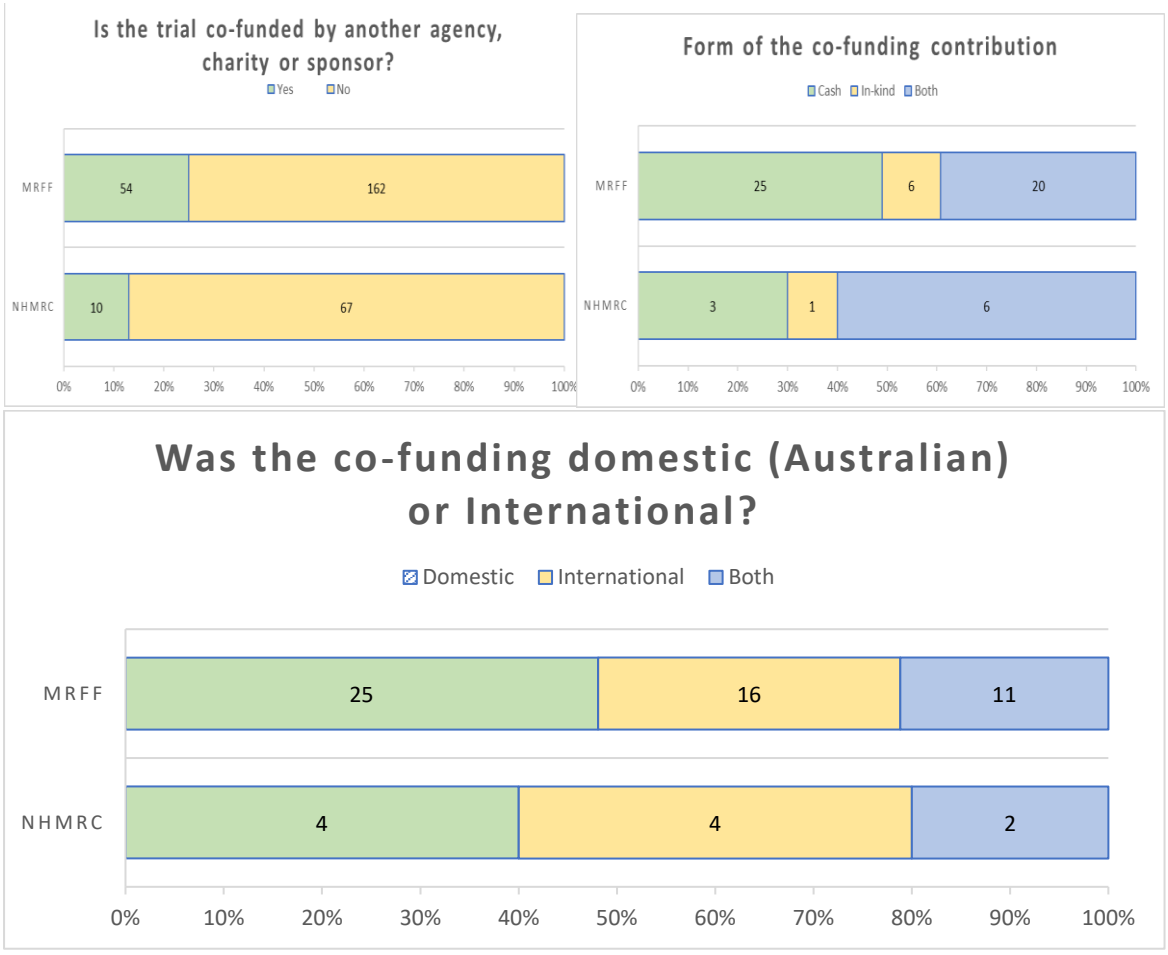

Figure 4 Trial co-funding

Stakeholders observed during the Stakeholder Consultation that the existence of co-funding for both the MRFF-trials and NHMRC-trials is good. Some stakeholders were surprised by its level, having expected it to be lower; others were puzzled by the discrepancy in co-funding between these two granting bodies. Some noted that applications with co-funding in place may be more likely to be successful, and that the existence of co-funding may be necessity-driven as some funders decrease the budget sought in the grant application.

Stakeholders were generally most familiar with co-funding opportunities from philanthropic funders, as well as large pharmaceutical foundations, the UK's Wellcome Trust and New Zealand's Health Research Council (each n=2).

This was echoed by the survey respondents, who most commonly reported receiving co-funding from New Zealand's Health Research Council (HRC), as well as Baxter Healthcare and Industry, or overseas funders such as CIHR and NIHR.

Where a trial had co-funding from another body, most commonly, this took the form of cash contributions for the MRFF respondents to the survey (49%), and *both* cash and in-kind contributions for the NHMRC respondents (60%) (Figure 4). The co-funding was most commonly used to cover costs of treatment and overheads or salary gaps for both the MRFF respondents and the NHMRC respondents.

Funding in practice

Asked about challenges faced in implementing their trials specifically due to budgeting issues, 61% of MRFF survey respondents reported no challenges on account of the budget; however, among NHMRC respondents, equal proportions stated this *was* a challenge (36%) and that it *was not* a challenge (36%).

The most commonly raised concerns were that the budget failed to cover study costs (MRFF survey respondents), and cuts by the granting body to the proposed budget (NHMRC survey respondents).

Funding innovations

Stakeholder Consultation participants suggested innovations in terms of funding arrangements, most commonly referring to an implementation of an expression of interest phase – such as that adopted by New Zealand's HRC or NSW Health – or a dual consideration arrangement, wherein the same application is considered by more than one body (e.g., NHMRC and Cancer Australia arrangement). Gated funding option (milestone-driven) was also cited as a possibility.

1.4. Trial networks – Summary of results

The proportion of trials that were and were not part of a trials network (e.g. Australian Clinical Trials Alliance or other) was similar for the two funders.

For the MRFF-funded trials, 43% were part of a network (whilst 57% were not); for the NHMRC-funded trials, 40% were part of a network (whilst 60% were not).

Table 5 Trials and collaborative networks

Is your trial part of a pre-existing clinical trials collaborative network?	MRFF (n=114)		NHMRC (n=72)	
Yes	90	43%	29	40%
No	120	57%	43	60%
Total	**114**	**100%**	**72**	**100%**

For MRFF respondents (n=89) to the survey who indicated that their trial was part of a network, the most commonly identified network was the Australasian Kidney Trials Network, as identified by 8 respondents.

For NHMRC survey respondents (n=29), the most commonly identified network was the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group (n=4).

For MRFF survey respondents who stated their trial was not a part of a network and who provided a clarification, the most commonly stated clarification was that it was "not applicable" (n=38), or that no relevant network exists (n=29).

Among those NHMRC investigators who stated in the survey that their trial was not part of a network, and provided a clarification, the most commonly stated clarification was that their study was "not a trial" (n=9), or that "no network exists" (n=7).

During the Stakeholder Consultation, the stakeholders presented with these data commented that trial networks tend to be disease-specific – i.e. there may not be a relevant network for certain types of areas or interventions (e.g. behavioural, public health, primary care), and that some types of trials (e.g. industry-funded) may be perceived as not welcomed in public networks. They offered comments supportive of participating in the networks, as network-affiliation may be reassuring to grant reviewers, more collaborative, of higher methodological quality, or more likely to be bigger or practice-changing. However, it was also noted that there are issues around network funding and sustainability – absent those factors, the networks may fail to flourish.

1.5. Regulations – Summary of results

A Data and Safety Monitoring Committee was in place for their study for approximately three-quarters of survey respondents: this was the case for 155 of 210 MRFF respondents (74%) and 52 of 71 NHMRC respondents (73%) (Figure 5).

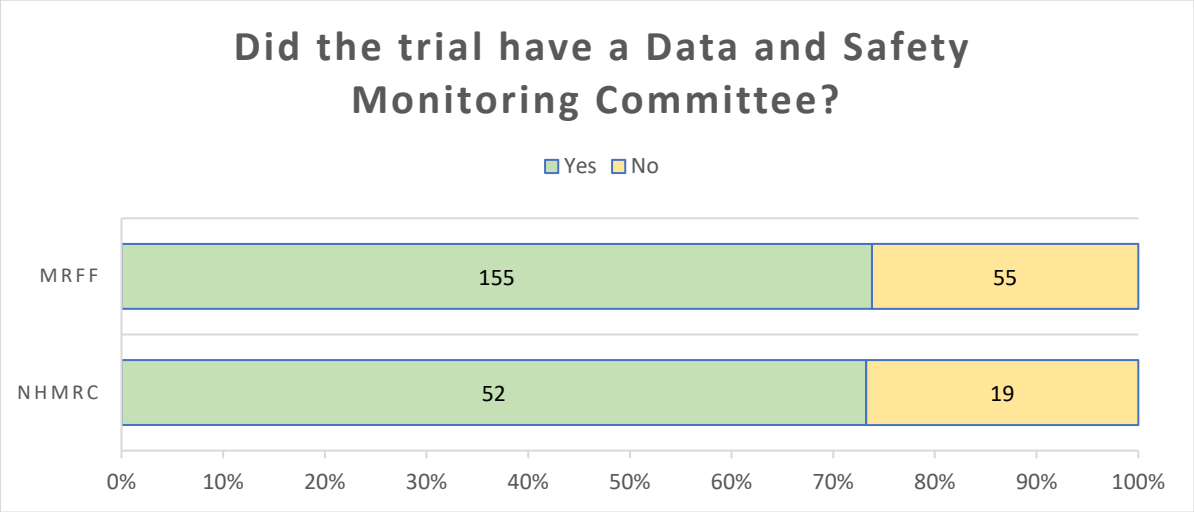

Figure 5 Presence of Data and Safety Monitoring Committee

Most commonly, trials were conducted under the Therapeutic Goods Administration (TGA) rules – 39% of 214 MRFF respondents to the survey (n=83) and 27% of 74 NHMRC respondents stated that was the case for their trial.

The survey showed that the trials commonly had the following rules in place for their trial: an early stopping rule (43% of 193 MRFF and 46% of 69 NHMRC respondents), or a futility rule (20% of MRFF respondents, 25% of NHMRC respondents). Most commonly, respondents indicated that they had an "other" rule in place – 45% of MRFF respondents and 46% of NHMRC respondents – most commonly, free-text responses mentioned adverse events or harms, or Data and Safety Monitoring Committee advice (Table 6).

Table 6 Rules in place for the trial

Were any of the following rules in place for the trial?	MRFF (n=193)		NHMRC (n=69)	
Other	74	45%	24	43%
Benefit rule	17	10%	5	9%
Futility rule	32	20%	14	25%
Early stopping rule	70	43%	26	46%

1.6. Study design – Summary of results

Randomisation

Analysis of trial registry data is challenging, as a large number of trials were categorised as "not applicable" in terms of the trial phase. Among those trials that do report phase, Phase 2 was most common for MRFF-funded trials (37%), and Phase 4 for NHMRC CTCS-funded trials (33%, although the numbers are very small), according to the findings from the Desktop Review (Table 7).

Table 7 Trial phase

Phase	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Phase 0	2	1%	5	0%			428	3%	5	1%
Phase 1	7	4%	55	3%	1	3%	1947	14%	22	2%
Phase 1 / Phase 2	4	2%	10	0%	1	3%	776	6%	19	2%
Phase 2	38	21%	111	5%	2	6%	2851	20%	86	9%
Phase 2 / Phase 3	6	3%	34	2%	3	9%	182	1%	25	3%
Phase 3	34	19%	194	9%	6	17%	622	4%	131	13%
Phase 3 / Phase 4	2	1%	34	2%	1	3%				
Phase 4	10	6%	115	6%	7	20%	470	3%	80	8%
Not Applicable	75	42%	1519	73%	14	40%	6805	48%	617	63%
Total	**178**		**2077**		**35**		**14081**		**985**	

Outcome assessors (47%) and data analysts (42%) were the most commonly blinded (masked) categories among MRFF trials, as well as NHMRC CTCS trials (54% and 37% respectively, according to the Desktop Review findings).

Of MRFF-funded trials, 86% were randomised controlled trials; for NHMRC CTCS this was 89%.

"Parallel arm" was the most commonly used type of randomised design, represented by 71% of MRFF-funded and 77% of NHMRC CTCS-funded trials in the clinical trial registries, analysed as part of the Desktop Review. Slightly lower percentages were provided by the survey respondents: 59% of MRFF respondents and 65% of NHMRC respondents identified parallel arm as the design used in their trial.

Stakeholders commented during the Stakeholder Consultation that very few progressive trial designs were evident – e.g. adaptive trials, cluster, etc. – and remarked on the decrease in factorial trials. They were not surprised by the dominance of parallel arm trials as that design was considered to be the most traditional and easiest way of conducting trials.

Innovative trial designs identified by stakeholders most commonly, included adaptive design, platform, and cluster.

Stakeholders also suggested that MRFF could better support innovative trial designs by explicitly requesting those types of designs (e.g. via dedicated rounds), by scoring them differently, by increasing the duration of the funding cycle to match the trial needs, and by establishing smaller pots of planning money for those types of trials (in the $100-200k range). NIHR was identified as a potential exemplar to consider.

Population

Most commonly, MRFF-funded trials involved between 100-299 and between 300-999 participants (32% and 33% of trials, respectively), based on the analysis of the clinical trial registry data conducted in the Desktop Review.

Of all the funders considered, the NHMRC CTCS-funded trials have the largest proportion of trials in the "over 1000 participants" category, at 40%, however, their number is small (n=14); MRFF's proportion of trials in this category is 16% (corresponding to a larger number of trials – 28) (Figure 6).

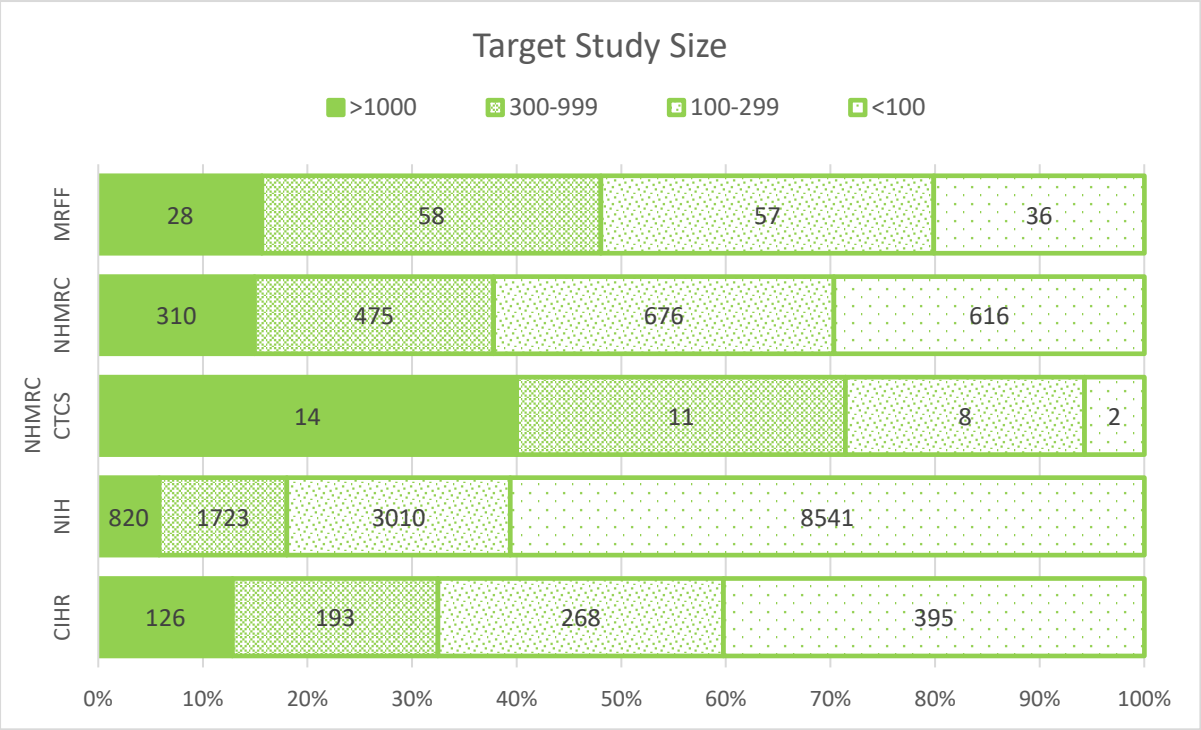

Figure 6 Target study size

Stakeholders commented during the Stakeholder Consultation, that there is a fair amount of consistency between funders in trial sizes, noting that the results for NHMRC CTCS may be skewed by inclusion of cohort studies in the data set, and that the overall trend over time has been towards decreasing study sizes of earlier stage trials (Phase 1 or 2). They also emphasised that sample size is dependent on the study hypothesis, and larger sizes may not be appropriate.

The analysis of the clinical registry data as part of the Desktop Review identified similar patterns for MRFF and NHMRC CTCS-funded studies, in terms of minimum age for trial participants. Majority of trials stipulated the minimum age of between 18-64 years old (72% for MRFF, 69% for NHMRC CTCS). Few trials in general specified maximum age – maximum age was not specified for 67% of MRFF trials and 54% of NHMRC CTCS trials in the clinical registry data.

The Desktop Review also showed that the gender of study participants was predominantly mixed (84% in MRFF studies and 91% in NHMRC CTCS studies).

In terms of conditions studied, the Desktop Review of the MRFF-funded trials and the trials funded by comparable funders, were broadly similar. However, considerably more MRFF-funded (22%) and NHMRC CTCS-funded (20%) trials focused on cancer, than for other funders – i.e., NHMRC (8%); NIH (2%), and CIHR (2%) (Table 8).

Table 8 Conditions studied

Condition	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Cancer	65	22%	301	8%	15	20%	526	2%	6	2%
Reproductive & birth	29	10%	208	6%	8	11%	632	3%	8	3%
Respiratory	*29*	10%	227	6%	4	5%	1372	6%	22	8%
Musculoskeletal & neurological	28	9%	446	12%	6	8%	2710	12%	31	12%
Mental Health	27	9%	541	15%	5	7%	1056	5%	9	3%
Diet, nutrition, lifestyle & public health	23	8%	599	16%	5	7%	61	0%	2	1%
Infection, inflammatory & immune	22	7%	181	5%	13	17%	1755	8%	18	7%
Cardiovascular, stroke & vascular	21	7%	366	10%	6	8%	2095	9%	36	14%
Hepatobiliary, oral, renal, gastrointestinal & urogenital	15	5%	154	4%	2	3%	3116	14%	41	16%
Human Genetics	9	3%	30	1%	1	1%	62	0%	1	
Blood	8	3%	16		2	3%	1087	5%	17	6%
Anaesthesiology& surgery	6	2%	59	2%	3	4%	313	1%	4	2%
Emergency medicine, injuries & accidents	6	2%	117	3%	1	1%	836	4%	9	3%
Endocrine & metabolic			191	5%	3	4%	1495	7%	10	4%
General disorders							1652	7%	17	6%
Ear, eye & skin	1		65	2%			2424	11%	27	10%
Other	12	4%	207	6%	1	1%	1072	5%	4	2%
Total	**301**		**3708**		**75**		**22264**		**262**	

The survey found that Australia-only trials dominated; for 74% of MRFF respondents and 54% of NHMRC respondents, their trial involved only Australian research sites (i.e. was 100% Australia-based) (Figure 7).

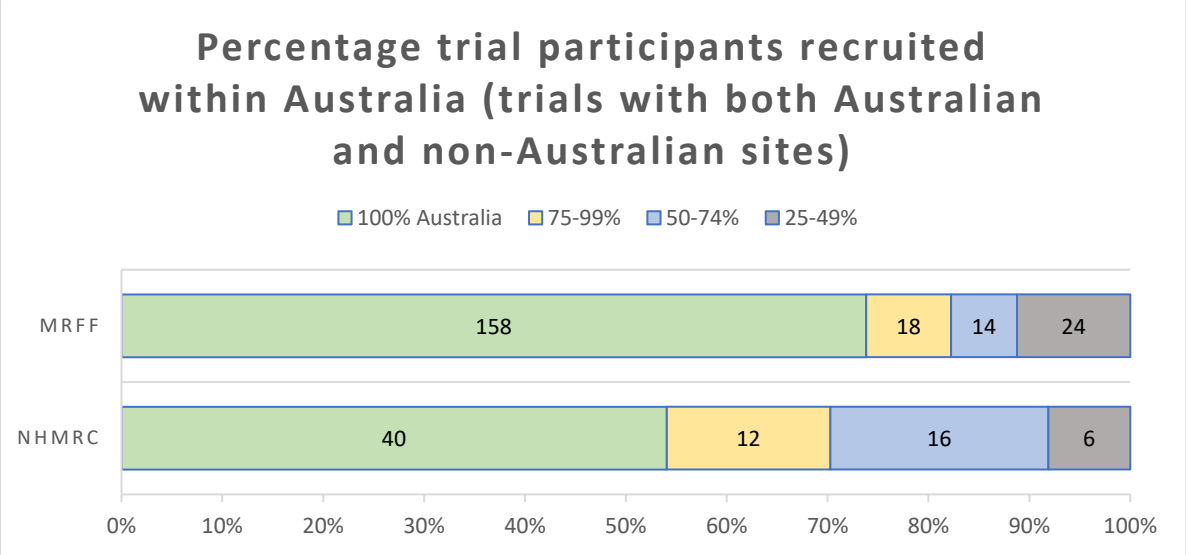

Figure 7 Percentage of trial participants recruited within Australia

Stakeholder Consultation participants suggested that collaborative arrangements with overseas funders may help to increase involvement of overseas sites and participants. This may include adopting a co-funding model like the NIHR's with NHMRC, or a specific funding stream. It was noted that changes in this space may require a change to the 10% rule, which will depend on Government legislation and policy. (The "10% rule" generally limits the expenditure on eligible overseas activities to 10% of the total eligible project expenditure(3)).

According to the survey, the most commonly involved vulnerable populations among the MRFF-funded trials included: Australians from regional, rural and remote areas (59%), and culturally and linguistically diverse populations (53%). NHMRC investigators reported involving, most commonly, Australians from regional, rural, and remote areas (42%), and children and young people (38%).

Intervention

In terms of the trial purpose, the Desktop Review found that the MRFF-funded trials had a higher number of treatment-focused research (67%) compared to the trials funded by the NHMRC CTCS (64%). MRFF-funded research was slightly less prevention-focused (20%) than trials funded by NHMRC CTCS (30%) (Figure 8).

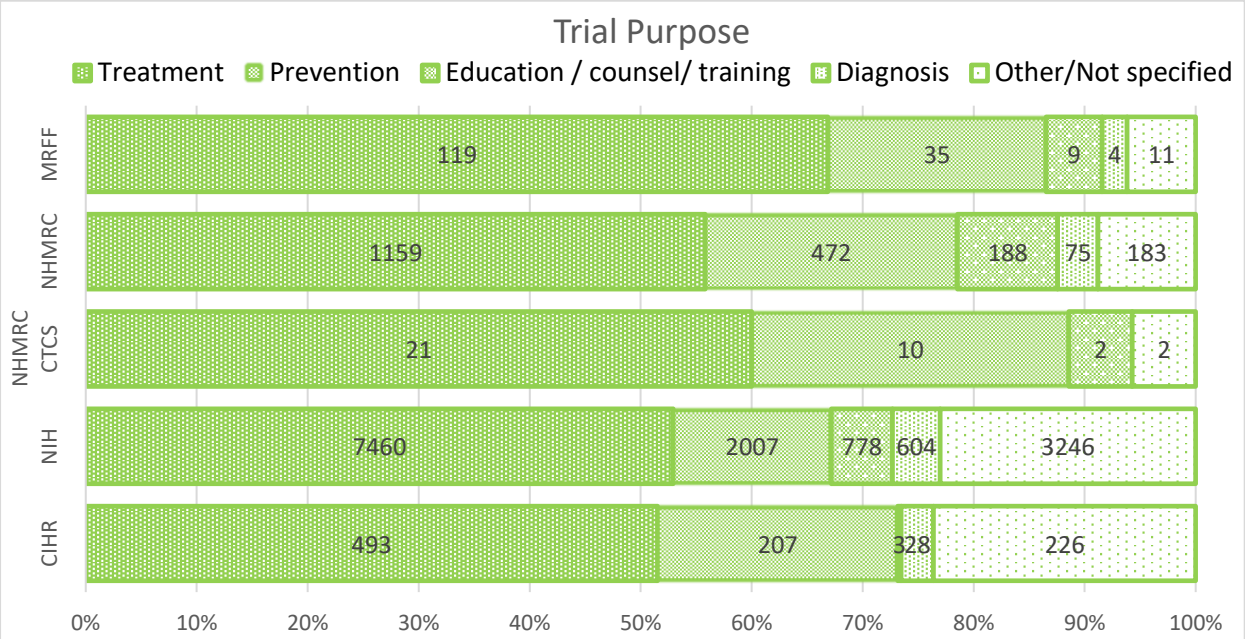

Figure 8 Trial purpose

The proportions of trials in preventative medicine found by the Desktop Review (29% MRFF, 22% NHMRC CTCS), and in treatment areas (61% vs 70%) were generally comparable.

Stakeholders commented during the Stakeholder Consultation, that Australian funders tend to fund more in the public health funding area, and in the pharmaceutical area, than overseas funders. On the other hand, it was also noted that because of the focus on potential commercialisation, there is a potential for neglecting behavioural and lifestyle intervention trials (which could be considered to be public health trials) – the paucity of surgical trials and prevention trials was also noted.

Most commonly, MRFF survey respondents stated that their trial addresses an area of unmet need for which there has been little progress in the development of tools or therapies (54%), or for which there are no satisfactory options for treatment (52%). For the respondents to the NHMRC survey, the trial addresses an area of unmet need for which there has been little progress in the development of tools or therapies (42%), or for which there are no satisfactory options for treatment (37%) (Table 9).

Table 9 How does the trial respond to an area of unmet need

Does your trial respond to an area of unmet need by addressing the following?	MRFF (229 respondents)		NHMRC (79 respondents)	
Health condition for which there are no satisfactory options for prevention	67	32%	21	29%
Health condition for which there are no satisfactory options for early diagnosis or detection	34	16%	13	18%
Health condition for which there are no satisfactory options for treatment	110	52%	27	37%
A condition for which there has been little or no progress in the development of tools or therapies	113	54%	31	42%
Other	27	13%	12	16%
Trial does not address above situations	14	7%	17	23%

Outcomes

For most trials, the survey respondents reported that outcomes in their trial did *not* come from a standardised outcome set such as COMET (the database of Core Outcome Measures in Effectiveness Trials) or OMERACT (Outcomes Measures in Rheumatology). Approximately 60% of respondents (61% of MRFF and 66% of NHMRC) stated their trial's primary outcome did not come from a standardised outcome set (Table 10).

Table 10 Did the trial's' outcome come from a standardised outcome set?

Standardised outcome set	MRFF (n=213)		NHMRC (n=74)	
Yes	42	19.91%	6	8.11%
No	129	61.14%	49	66.22%
Not yet applicable	40	18.96%	19	25.68%
Total	**213**	**100%**	**74**	**100%**

Flaws in design

For the majority of both MRFF-funded trials (78%) and NHMRC-funded trials (89%), difficulties pertaining to flaws identified in the trial design at the post-data collection stage were not yet applicable. Twenty-one per cent of MRFF survey respondents and 11% of NHMRC survey respondents said that they did not identify flaws in the trial design at the post-data collection stage.

1.7. Data – Summary of results

Data linkage

Nearly the same proportion of survey respondents – 74% for MRFF and 71% for NHMRC – reported that they *did not* consider using routinely collected data (e.g. from the PBS, MBS, death registries, etc.) during the planning of their trials (Figure 9).

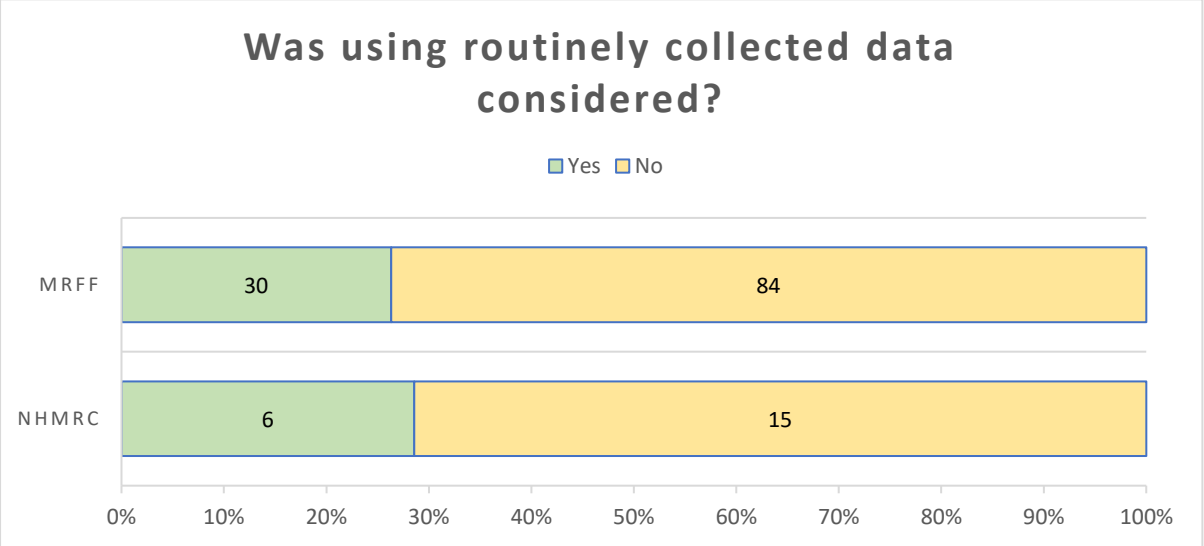

Figure 9 Was the use of routinely collected data considered during trial planning?

When asked whether their trial utilised routinely collected data, more commonly, the MRFF survey respondents reported *not* using routinely collected data (54%, n=114). For the NHMRC respondents, it was more common to *use* routinely collected data (71%, n=52 reported using it) (Figure 10).

For MRFF survey respondents (n=27) who clarified why they did not utilise routinely collected data even though it was considered during the planning of the trial, responses most commonly cited time and cost constraints. NHMRC respondents (n=6) most commonly cited the absence of routinely collected data that was fit for purpose.

For those survey respondents who did use or access this type of routinely collected data, approximately one-half (47%) of 213 MRFF respondents did not experience challenges on account of accessing routinely collected data, although for 43% this was not yet applicable. For the 74 NHMRC respondents, most commonly, this issue was not yet applicable (58%), although a notable proportion (30%) stated this was not a challenge for them. Free-text responses indicated, most commonly, challenges due to delays around approvals or consent issues.

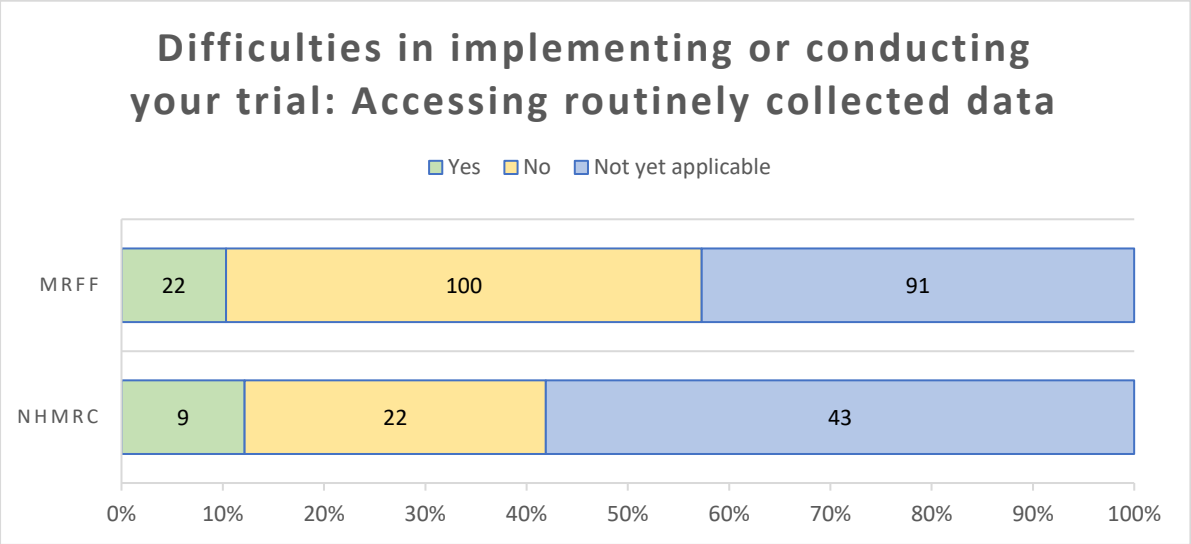

Figure 10 Difficulties in accessing routinely collected data

Individual patient data (IPD)

The majority of MRFF-funded trials (65%, 135 survey respondents) and NHMRC-funded trials (72%, 50 survey respondents) stated that they have made available – or intend to make available – individual participant data to other researchers (Figure 11).

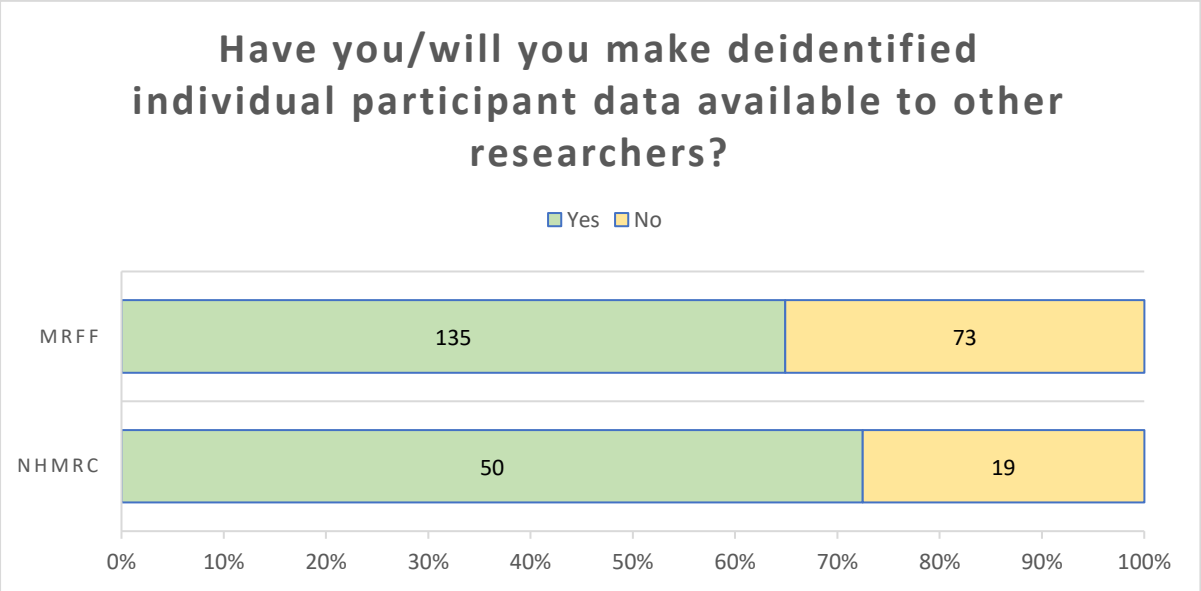

Figure 11 Availability of individual patient data

In comparison, an analysis of the clinical registry data for these funders conducted as part of the Desktop Review, showed that 33% of MRFF-funded clinical trials, 11% of NHMRC (as a whole) and 31% of NHMRC CTCS stream-funded trials, have an individual patient data availability statement.

Most commonly, MRFF (n=237) and NHMRC (n=82) survey respondents reported that they intend to make data available on request (69 for MRFF, 21 for NHMRC) or by depositing the data in a repository or database or platform (21 for MRFF, 12 for NHMRC).

The most common reasons for *not* making individual participant data available to other researchers cited by MRFF respondents to the survey, were that the ethics approval or consent form does not cover or allow this (n=17), and that this may be considered but only under specific circumstances (n=14).

Very few responses were provided by the NHMRC survey respondents. However, most commonly, lack of permission to release (n=3), inappropriateness at this stage or incompleteness of the study (n=3) or other reasons (n=3) were cited.

Stakeholders presented with the above data during the Stakeholder Consultation, mentioned that consent forms need to be standardised to allow sharing, and the perception that sharing data represents a possible violation of ethics rules requires addressing, as ethical considerations ought not to present a barrier to this. They also mentioned that perhaps researchers who do not share the data may simply not know how to do so, and that shareability may also depend on the type of data collected and its purpose.

1.8. Public availability

Summary of results

Protocol availability

Examination of the clinical trial registry data needs to be undertaken with caution, as few studies reported that they made the protocol available. However, the Desktop Review analysis showed that protocols are available for 22% of MRFF studies on clinical trial registries, and 23% of NHMRC CTCS-funded studies (Table 11).

Table 11 Protocol availability

Protocol availability	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Yes	39	22%	302	15%	8	23%	2196	16%	16	2%
No	93	53%	578	28%	16	46%	1339	9%	36	4%
Not specified	46	26%	1197	58%	11	31%	10560	75%	933	95%
Total	**178**		**2077**		**35**		**14095**		**985**	

Stakeholders presented with this data during the consultation supported making protocols available as this enhances trust, and suggested that funders could enforce it by requiring trial registration prior to release of funding. Some were surprised, as there was an expectation that everyone publishes protocols, as there are journals that welcome them. However, others cautioned that this may be an issue of timing (recently funded trials would not have been able to publish a protocol yet), and that there are other means of making protocols publicly available (e.g., via a website devoted to the trial).

Study results availability

The vast majority of trials – 89% of 210 MRFF survey respondents and 97% of 73 NHMRC survey respondents – have *not* completed data collection for the main outcomes (Figure 12). The findings need to be interpreted in light of this.

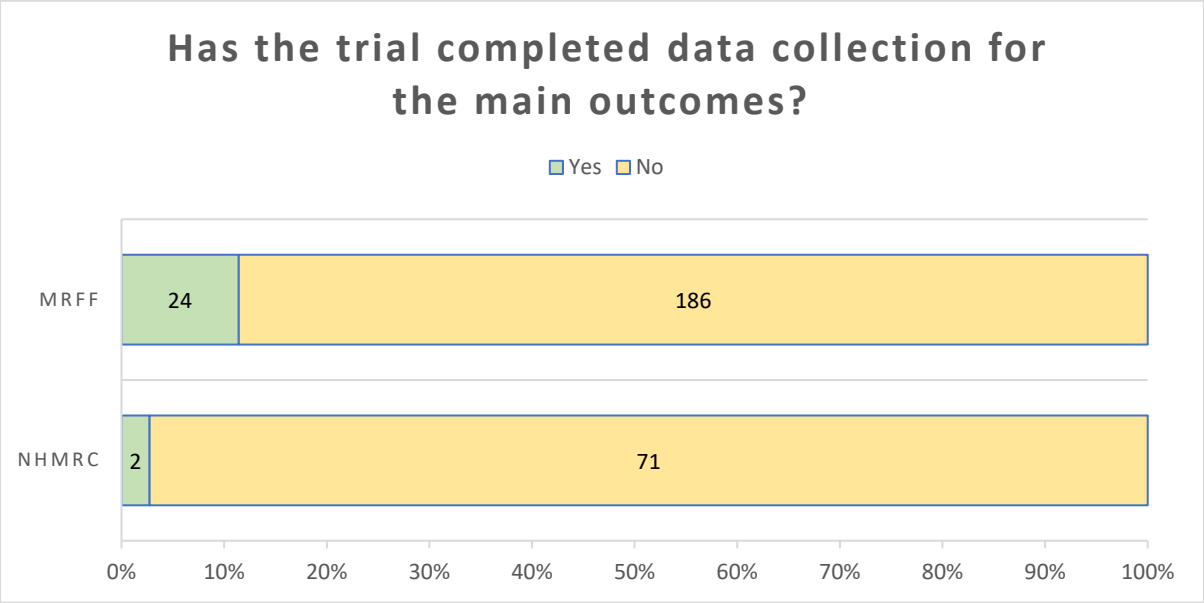

Figure 12 Has the trial completed data collection for main outcomes?

Unsurprisingly, therefore, when asked whether they have encountered challenges around dissemination of trial results, the majority of survey respondents – 84% for MRFF-funded trials and 93% for NHMRC-funded trials – reported that encountering difficulties pertaining to the dissemination of results are not yet applicable to them.

The mean time the survey respondents anticipated it will take to make the results available for others to view after they finish data collection with an MRFF grant was 9.1 months (SD 6.8 months, n=183), and for the NHMRC grant was 9.6 months (SD=6.7 months, n=66) (Figure 13).

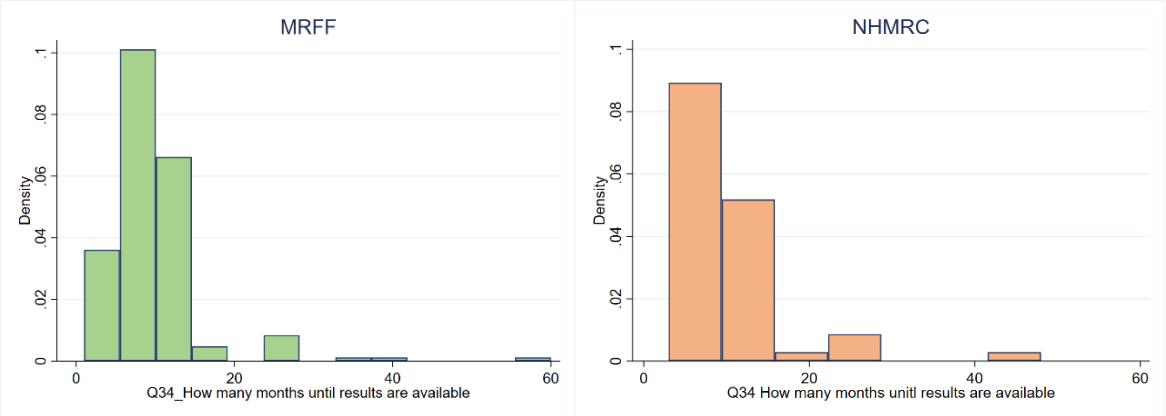

Figure 13 Estimated time (in months) to available results after finish of data collection, researchers with (a) MRFF grant (b) NHMRC grant

Most commonly, survey respondents intended to make their trial results available via academic journals (87% of MRFF respondents, 98% of NHMRC respondents) and at conferences or professional meetings (82% of MRFF respondents, 91% of NHMRC respondents).

Respondents to the survey reported that the trial results are currently available through: an academic journal (29% of MRFF respondents, 0% of NHMRC respondents), preprint server (0% MRFF, 0% NHMRC), conference presentation or abstract (67% MRFF, 0% NHMRC), or trial registry (33% MRFF, 0% NHMRC).

RESULTS SECTION 2 – STUDY IMPACTS

2.1. Impacts – Summary of results

Healthcare impacts

Survey respondents were asked about the anticipated or actual impacts of their trial.

Among the 237 MRFF respondents who provided a response, the most common impact is believed to be a new treatment or intervention (63 responses), or a change or improvement in practice (37 responses). The 82 NHMRC respondents, similarly, most commonly indicated a new treatment or intervention (20 responses), or a change or improvement in practice (19 responses).

The majority of survey respondents (72% of 196 MRFF respondents, 74% of 62 NHMRC respondents), indicated "not applicable" to the question of how the trial findings have been used to change healthcare. For those to whom the question applied, the top answers were: results were presented to clinical or health groups (9% of MRFF respondents), or that they were cited in clinical guidelines (10% of NHMRC respondents).

For 10% of 210 MRFF survey respondents and 11% of 70 NHMRC survey respondents, their trial identified or validated a new health technology. However, for the greatest proportion of respondents – 51% for MRFF and 52% for NHMRC – this was not yet applicable. Free-text responses most commonly identified a new intervention (both MRFF respondents and NHMRC respondents) and new drug selection process (NHMRC respondents) (Table 12).

Table 12 New health technologies or interventions

Have there been any new health technologies or interventions (e.g. drug, diagnostic, technological or similar development) identified or validated through your trial?	MRFF (n=210)		NHMRC (n=70)	
Yes	22	10%	8	11%
No	82	39%	26	37%
Not yet applicable	106	51%	36	52%
Total	**210**	**100%**	**70**	**100%**

Commercialisation

For relatively few survey respondents – 3% (6 of 208) MRFF respondents and 0% (0 of 71) NHMRC respondents – there *were* commercialisation opportunities arising from the trial. These commercialisation opportunities included: new apps or interventions, licencing a drug, a spin-out company and interest from another funder to pilot an adaptation of the trial (Figure 14).

However, these results need to be interpreted in context of the limited number of completed trials – as noted above (see section 1.8, Study Results Availability), 89% of MRFF respondents and 97% of NHMRC respondents to the survey indicated that their trials *have not yet* completed data collection for the main outcomes.

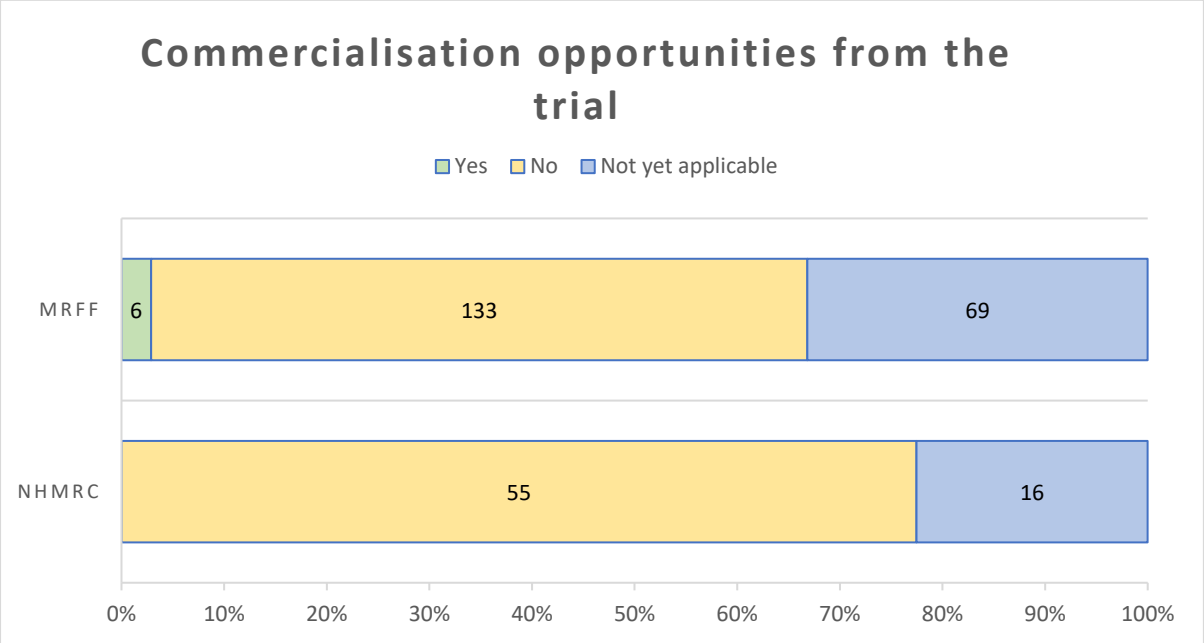

Figure 14 Commercialisation opportunities

Barriers or difficulties around commercialisation reported by the survey respondents focused on the lack of advice (e.g., commercial, legal), coordinating multiple organisations, time, and university-related challenges.

RESULTS SECTION 3 – STUDY CHALLENGES

3.1. Challenges around conducting the studies – Summary of results

Design/setup

Very few respondents – 8% of 213 MRFF survey respondents, and 8% of 74 NHMRC survey respondents – encountered difficulties in coming to an agreement on protocol details for their studies.

Similarly, few survey respondents reported encountering challenges in implementing or conducting their trials due to ethics approvals: 22% of MRFF respondents, and 16% of NHMRC respondents said they encountered these challenges (Figure 15).

Conversely, many respondents to the survey, did report difficulties in implementing or conducting their trials due to issues around governance or study site approvals and contracts: 53% of MRFF respondents and 35% of NHMRC respondents stated that they experienced these challenges. Most commonly, these challenges focused around delays due to the execution of contracts (Figure 15).

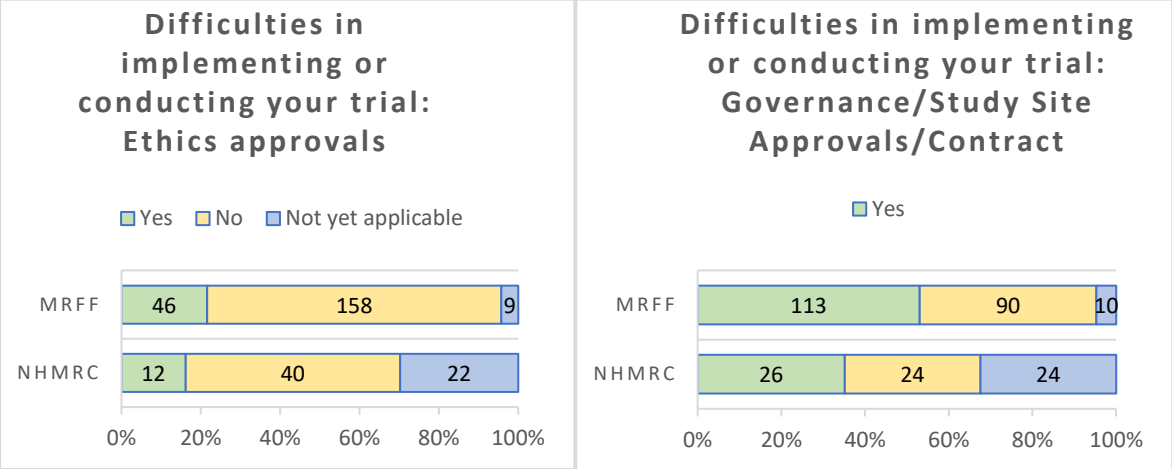

Figure 15 Difficulties in implementing the trial: ethics and governance

The majority of MRFF respondents (67%) and NHMRC respondents (51%) to the survey did not report difficulties in implementing or conducting their trials due to issues around the availability of trial materials such as drugs or data collection instruments.

Recruitment

Difficulties due to site recruitment or setup were not common for MRFF survey respondents – 48% stated they did not encounter these. For the NHMRC respondents, most commonly, the question was not yet applicable (39%), although a sizeable proportion said they did not encounter these difficulties (35%).

For 46% of MRFF survey respondents and 30% of NHMRC, there were challenges around recruitment of trial participants – although it is worth noting that for 51% of NHMRC respondents, this question was not yet applicable (Figure 16).

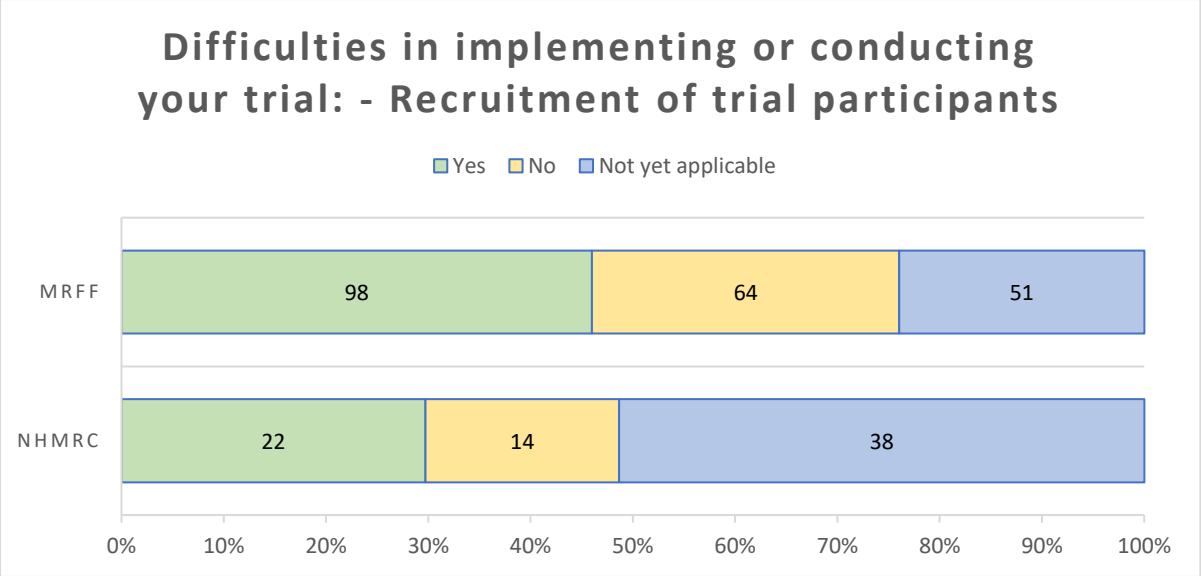

Figure 16 Difficulties in implementing the trial - participant recruitment

The majority of survey respondents (66% of MRFF respondents and 47% of NHMRC respondents) reported no difficulties with recruitment of trained trial or research personnel (although for a sizeable 32% of NHMRC respondents, this issue was "not yet applicable") (Figure 17).

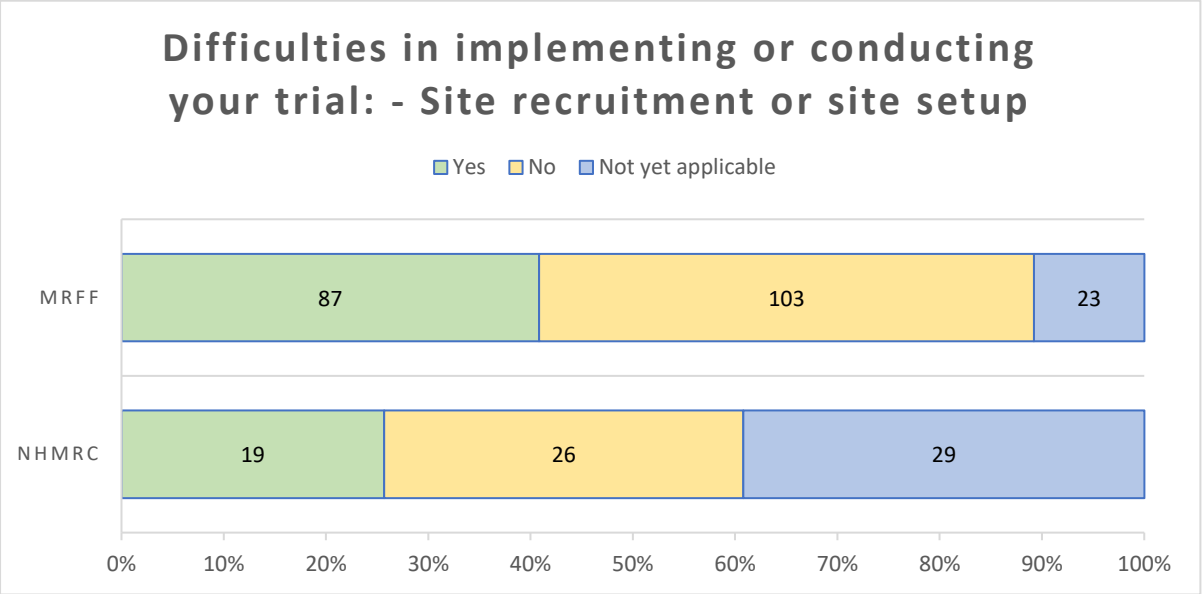

Figure 17 Difficulties in implementing the trial - sites

Few survey respondents – 3% of MRFF respondents and 1% of NHMRC respondents – reported difficulties in accessing biostatistical support.

As few trials have completed data, the majority of survey respondents stated "not yet applicable" to the question about experiencing data analysis issues at post-collection stage (83% of 209 MRFF respondents, 91% of 71 NHMRC respondents).

Presented with these findings during the Stakeholder Consultation, the stakeholders commented that the time to obtain site-specific approvals has decreased, but that it may not be possible to simplify the process. Some suggested, however, that funders may have a role to accelerate its timing, for example, by standardising a contract between institutions, or establishing standard charges for budget items. Patient or participant recruitment issues were suggested to be underestimated, and that a more accurate picture could have been obtained by surveying trial managers rather than investigators. It was also noted that COVID has impacted recruitment and the extensions to funded trials may not have been sufficient, although some of the recruitment issues may be mitigated by pilot-testing of the inclusion criteria. Lack of research and trial personnel was noted, due to issues around pay discrepancy with contract research organisations, duration to recruit these individuals, and lack of targeted training.

Other

Other challenges considered, included the fidelity and uptake of the trialed intervention. This was rarely experienced, with 62% of MRFF respondents to the survey stating that it was not a challenge they experienced in their trial. For the majority of NHMRC respondents (60%), this question was not yet applicable; although a sizeable proportion (35%) reported that this was not the case for their trial (Table 13).

Table 13 Disruptions due to the COVID-19 pandemic

Disruptions due to the pandemic	MRFF (n=213)		NHMRC (n=74)	
Yes	168	79%	34	46%
No	39	18%	15	20%
Not yet applicable	6	3%	25	34%
Total	**213**	**100%**	**74**	**100%**

Conversely, the majority of MRFF respondents (79%) and just under half of the NHMRC respondents (46%) to the survey reported difficulties in implementing or conducting their trials due to COVID-19 related disruptions. Most commonly, those involved patient recruitment, delays to study start or completion, and staff availability for both MRFF and NHMRC respondents.

Barriers and facilitators

During the Stakeholder Consultation, the stakeholders identified recruitment and ethics as some of the main barriers to efficient conduct and successful outcomes for funded trials in Australia.

The stakeholders' suggestions for reducing these included, among others: lack of university-based clinical trial centres with core staff could be assisted by looking to the UK's system of accredited clinical trial units; consideration of National Institute for Health and Care Research's (NIHR) patient and public involvement initiative; endorsement of trials by clinical trial networks as those provide internal peer-review prior to submission to a funding agency; and praise for the MTPConnect programme (which has received MRFF grants).

Stakeholders participating in the consultation identified staffing issues as one of key resource constraints for future research capacity in Australia. These included a lack of health economic and biostatistical expertise, as well as research coordinators and trial staff more generally, and challenges around staff training and salaries. They suggested looking to UK and New Zealand for possible approaches for addressing these issues.

DISCUSSION

This evaluation of MRFF clinical trials was based on three components: a document analysis from the data on clinical trials registry information for each trial (Desktop Review); a Survey of the lead and an Early to Mid-Career Researcher from each trial (Survey), and interviews with a diverse set of stakeholders about the MRFF trials program with presentation of the findings from the registry and survey analysis (Stakeholder Consultation). The methods build on previous evaluations of clinical trials programs(2, 4), with comparable, but more detailed, findings. The most common methods of funder analyses of research impact(5) are document analysis (80%), surveys (40%), and semi-structured interviews (39%), but using all three, as in the present evaluation, is uncommon(6, 7).

Measures of Success

The registry data analysis found that the MRFF-funded trials were broadly similar to trials funded by NHMRC, NHMRC CTCS, NIH and CIHR, and there were a few areas where MRFF-funded trials appeared better on average.

The study design and quality of the MRFF funded trials was broadly equal to or larger than most other funders' trials. For example, 16% of MRFF-funded trials are in the "over 1000 participants" category, which is larger than for the other funders, including the NHMRC (full set), CIHR, and NIH. (The 16% is smaller than the NHMRC CTCS's 40%, but due to a very small size of the CTCS sample set (n=14), it is difficult to draw meaningful comparisons).

The mix of study designs were comparable across funders. However, there was a notable lack of factorial trials – a very efficient design – across all funders including MRFF. Rates of use of randomised vs non-randomised trial designs and the percentage of trials that were blinded, were generally similar for all funders, aside from NHMRC-funded studies which generally had a higher percentage of randomised trials and blinded trials, than other funders.

By far, the most common design was a parallel group trial, but with a modest number of cluster, adaptive, platform, crossover, and factorial studies. Given the recent acceptance by the clinical trials community of adaptive and platform trials – which improve trial efficiency and the speed of addressing new clinical questions – the number being funded is encouraging. In contrast, the small number of factorial designs may require some explicit intervention on behalf of MRFF.

Factorial trials are an efficient design which addresses two or more questions in the same group of patients, but generally requires only the same sample size as that for a single question(8). For example, a "2 x 2" factorial trial randomises patients to treatment A, treatment B, both or neither, but each treatment can be analysed separately as it is balanced for the other treatment. Provided there is no interaction between treatments (or one is ineffective) then factorial trials often represent a "free lunch" of getting two (or more) trials for the cost of a single trial. Despite their efficiency, they have been underused in medical

research(9). Improving reviewer and panel knowledge in these design issues is clearly desirable.

The design issues were commented on by some stakeholders, in particular the need for methodological expertise on the grant review panels: “if you want really good science, you need to have really good methodological oversight of the peer review process.”

Of some concern was the small number of trials using a “Standardised Outcome Set”, and consideration might be given to encouraging this in the advice to applicants. Standardised or core outcomes sets are agreed standardised set of clinical outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of health or health care(6, 7). These outcomes sets can provide more reliable and valid outcome measures for clinical trials, allow more straightforward comparisons across trials, and simplify the process of meta-analysis. For example, COMET(10) is a UK-funded database of such core outcomeshttps://www.comet-initiative.org/ . The justification for their use, and a link, could be provided in guidance to trial applicants.

Increased focus of research on areas of unmet need

The range of clinical conditions, interventions and purposes addressed by the research questions of the trials were, on average, similar to non-MRFF-funded trials. The conditions studied were broad and similar, with the most notable exception being the number of cancer trials, which was more frequent for MRFF-funded trials. However, this difference aligns with the priorities and calls of the MRFF. A recent analysis(11) comparing the disease burden with MRFF-funded trials noted that “the current trend of MRFF distribution suggests targeted, disease-based funding provided through the MRFF tends to go to disease groups with a high death burden and does not target disability burden”.

Data on features of the populations studied were limited, but we note that the minimum age, and gender mixes were similar. The interventions studied in MRFF trials were also similar to international funders, although with a higher proportion studying drug treatments, but also with a higher proportion studying prevention.

The stakeholders interviewed noted that MRFF guidelines and process encouraged researchers to make sure that they include diverse communities as part of the trials or studies. However, they also noted that the priority setting was unclear and that timeframes were usually insufficient to allow extensive consumer input: “Priority setting process takes several months to set up… the calls don't allow that.” For example, some groups have used a modified “James Lind Alliance” priority setting process(12, 13) which typically takes 12 to 18 months of background work before the final workshop with consumers, clinicians, researchers and funders(14).

Some areas are also under-represented, in particular "unmet need in public health, or it [the MRFF calls] hasn't been well aligned necessarily with available clinical trial expertise within those." Stakeholders asked how the priorities fit with the burden of disease, and one mentioned the option of using explicit criteria for unmet need and priority setting such as the 5 proposed by Australia & New Zealand Musculoskeletal Clinical Trials Network (ANZMUSC)(15), which include:

(1) extent of stakeholder consensus,
(2) social burden of health condition,
(3) patient burden of health condition,
(4) anticipated effectiveness of proposed intervention, and
(5) extent to which health equity is addressed by the research.

More Australians access clinical trials

Most stakeholders welcomed the MRFF trials initiatives: which ensured they were "able to get a few things funded that we couldn't have gotten funded in other initiatives," commenting that "MRFF has really allowed a lot more clinical trials to be funded" and that it is "a huge positive." This unmet need for more clinical trials in Australia is reflected in Australia's middle ranking of trials per head of population, with about half that of the top ranked countries(16). A long-term follow-up of increased trial funding by the NIH in the USA found "a dramatic increase in the number of registered clinical trials and clinical trial enrolment associated with CTSA [Clinical and Translational Science Award] grant award"(17). The MRFF has seen the increase in registered trials, but details on patient enrolment will require longer follow up.

While the MRFF initiatives have substantially increased the number and range of clinical trials, there have been barriers to conduct. In addition to the challenges encountered in the pandemic, survey respondents identified a number of difficulties in conducting their trial. The most commonly reported problems were with the site governance or study site approvals, which occurred in over 50% of trials. As is true of most trials, site recruitment and individual patient recruitment were identified as the most common problems for barriers to successful completion for most trials. Similar barriers were identified in a survey of UK trials units, which found that local approval (53%) and recruitment (44%) were the most common problems(18).

Research community has greater capacity and capability to undertake translational research

Stakeholders expressed positive sentiment for the early career support, though lamented the low success rates currently, but certainly supported continuing this initiative. As might be expected, the majority of MRFF funded trials were led by individuals who identify themselves as academics or clinicians, with smaller numbers led by consumers, policymakers, or non-government organisations.

A critical issue is the need to support clinician-researchers who have the skills to understand the important clinical questions and an understanding of trial design. However, the degree of involvement of professional organisations, non-government organisations, industry, and consumers is encouraging. Approximately, a quarter of trials included some recruitment of patients internationally.

While the MRFF initiatives were welcomed and improved support generally, some future opportunities were also identified. In particular, the well-recognised challenge of continuity of support for streams of research work has not eased, and some stakeholders commented on the need for continuity to build critical mass of researchers or research groups, working on particular trials and particular disease areas. Having consistency of the programs from year to year would be valuable to help with planning of much needed longer-term programs of work.

New health technologies and interventions are embedded in health practice

Clinical trials usually require 1 to 2 years of start-up and recruitment time, often 2 to 4 years of follow up, and approximately a year for final analysis, write up and publication. These timelines mean that few MRFF trials have yet completed, and hence assessing their dissemination and impact is currently limited. This will clearly be a key issue to monitor.

This consequence of the long timelines of clinical trials also applies to several other measures of success, such as (i) Health professionals adopt best practices faster, and (ii) Increased commercialisation of health research outcomes.

The community engages with and adopts new technologies and treatments

The consumer involvement in grant guidelines, grant assessment, and panel composition has mostly been welcomed. Some stakeholders felt the need to go further and include community members as full panel members on ground reviews. There were also several stakeholder comments about the need for adequate time for researchers to undertake effective consumer and community involvement.

Another indication of engagement is the co-funding of studies. About a quarter of the trials had some co-funding. This co-funding was provided by a vast range of different organisations – most of whom only co-funded one MRFF trial – which included health services, pharmaceutical and device companies, and other research funders. Co-funding most commonly covered the cost of treatment, which would be appropriate particularly if the co-funder was the supplier of the treatment. The next most common were costs of either: (i) follow up investigations or (ii) sub-studies, which is an appropriate use of co-funding and should be facilitated. Some other reasons for co-funding included salary gaps, infrastructure, and equipment may have been included in the main grant and is worth investigating further.

Open Science

The Open Science processes elements available were protocol access and whether individual patient data would be available. The protocol availability was low for all studies, but strikingly better for MRFF studies with 22% of protocols being available. The low availability of protocols has been noted by others, with the UK's Medical Research Council (MRC) still only achieving a 35% availability(19).

Limitations

The limitations of this analysis should be mentioned. Most crucially, the incomplete data for many of the items, such as protocol and data availability, which were not mandatory in clinical trial registry records, and left unspecified by many researchers.

The survey had several limitations. First, many trials have been disrupted by the pandemic which has created difficulties with site and patient recruitment, as well as diverting the attention of clinicians. Second, few trials have yet completed, hence assessing their dissemination and impact is currently limited. Third, the survey was intended to capture multiple views (senior vs EMCR) per grant, and so interpretation of these results should take into account that a proportion of trials (36% out of 165 unique grants for MRFF; 26% out of 61 unique grants for NHMRC) are represented more than once. Finally, the survey response rate was only 59% for MRFF and 48% for NHMRC, and so may not be fully representative of all recipients of trial funding.

However, some of the issues that may not have been identified due to the survey response rate, may have been identified through the Stakeholder Consultation also conducted as part of the overall evaluation.

CONCLUSION

The MRFF has clearly led to a welcome increase in funding for clinical trials in Australia and has resulted in trials of comparable size and design quality to that of other funders internationally, across the range of metrics. This has been important to the support and development of clinical trials activity in Australia and should continue. Because of the timeframes to complete the trials, as well as the impact of the pandemic, few trials have yet reported and been transferred into practice. This will need to be monitored in the years to come.

Meanwhile there are a number of potential areas for further enhancing the return on investment that the current program offers. Some of these opportunities include:

1. Improved guidance to trial applicants and panels on quality and design options that would be welcomed, such as factorial design trials, and considering inclusion of a special call or consideration in the assessment criteria
2. Support for the use of standardised outcomes sets in the guidance, with specific reference to the website of COMET (the database of Core Outcome Measures in Effectiveness Trials)
3. For some topic areas, a specific priority setting process to examine which are the most important unanswered clinical questions within a topic (using a methodology such as The James Lind Alliance) might be considered. For example, such a priority setting process could be held within the topic area of some of the larger clinical trials networks already receiving funding from MRFF
4. In order to streamline long-term monitoring, we would suggest that funding is not triggered until the funded study provides its trial registration number to MRFF, with an agreement to provide the complete protocol (confidentially, if necessary) before commencement of the trial. These would improve the transparency of trials and open science process generally, as well as allowing the MRFF to monitor trials progress more efficiently*
5. The methods tested in this evaluation could be used in the future, to guide minimal data collection from grantees, to allow regular performance oversight and risk management for feedback to MRFF.

These opportunities for MRFF funding for clinical trials may be supported by ongoing clinical trials reform in Australia, which is currently a national priority. Multiple national policy initiatives are currently being undertaken to enhance the clinical trials and health and medical research operating environment, e.g. the National Clinical Trials Governance Framework, and the National One Stop Shop and National Clinical Trials Front Door, with the longstanding goal of making it easier for patients, researchers and sponsors to participate in and conduct trials and research.

* Automated tracking of trials has become more common(20), and could provide regular “desktop” updates between intermittent surveys and interviews.

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