EVALUATION OF THE MEDICAL RESEARCH FUTURE FUND (MRFF) CLINICAL TRIALS ACTIVITY APPENDIX 1

Prepared for the Department of Health and Aged Care

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Table of contents

List of Tables

List of figures

DETAILED RESULTS SECTION 1 – STUDY CHARACTERISTICS

1.1. Study teams - Detailed results

Study or trial team composition overall:
According to 217 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 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 1 Study team composition

	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 and/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%

As very few "other" responses were provided by the MRFF and NHMRC respondents (19 in aggregate), the responses have been amalgamated to protect responder privacy, and the number of responses within each category was suppressed. Because some respondents identified more than one group, the total did not add up to 19. The responses included:

- Clinical trial managers
- Clinical Trials Group
- Community/patient organisation
- Disease experts
- Health economists
- Health sector representative
- Healthcare providers
- NGO
- Peak organisations
- Policy/decision-makers
- Program manager
- Public
- Research coordinators

- Software developer
- Statistician
- Study not yet started
- Study participants (co-design)
- Unclear answer
- Unsure

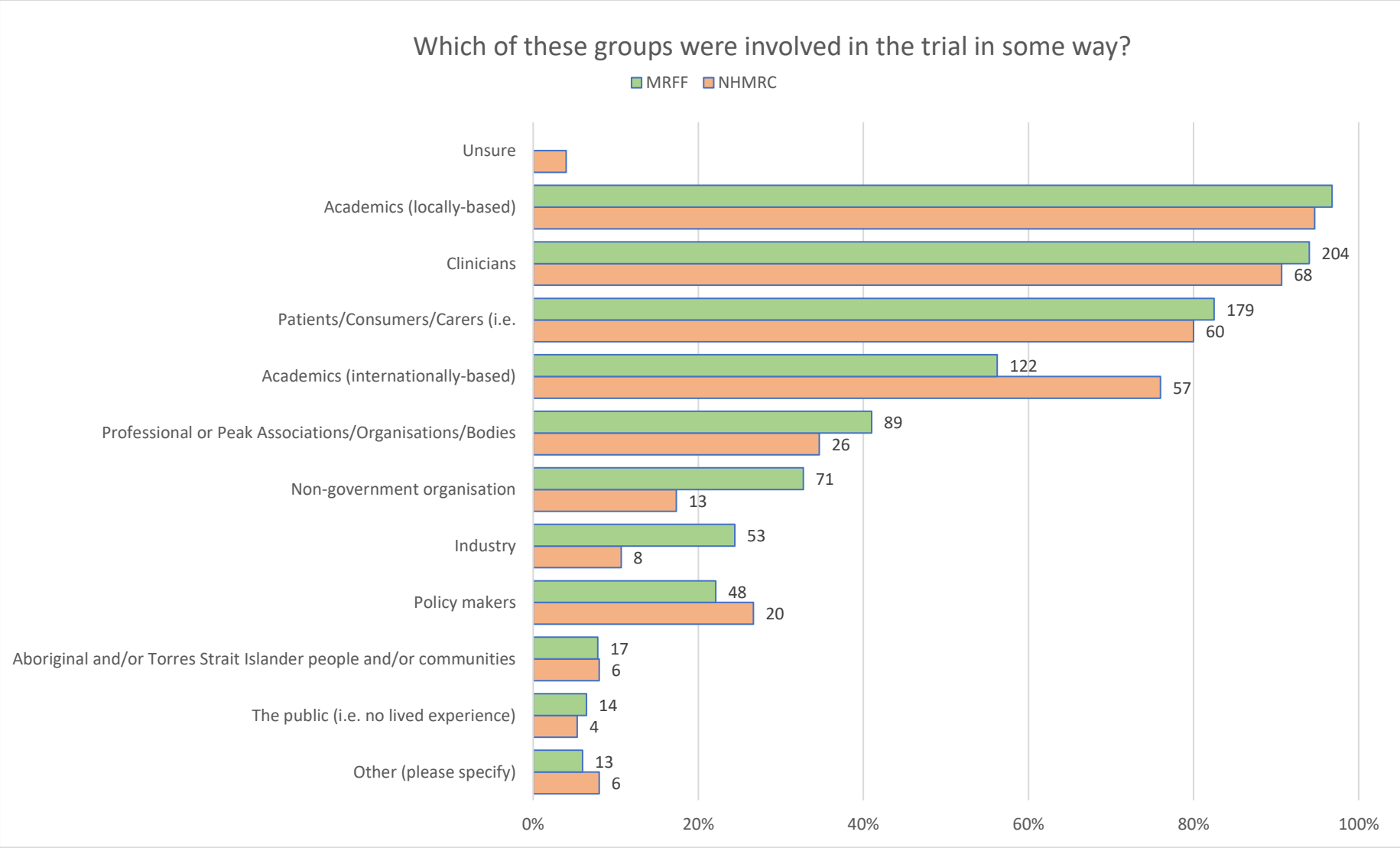


Figure 1 Study team composition

Individuals from which of the following groups were named as Chief or Principal Investigators on the grant application?

Of the 217 MRFF investigators who responded to this question, the greatest proportion, 98% (n=213) identified themselves as academics who are locally based. The next biggest proportion were clinicians (92%).

Of the 76 NHMRC respondents to this question, the greatest proportion, 97%, identified themselves as academics who are locally based, and clinicians (88%).

Table 2 Chief or Principal Investigators

	MRFF (n=217)		NHMRC (n=76)	
Unsure	2	1%	1	1%
Aboriginal and/or Torres Strait Islander people and/or communities	11	5%	7	9%
Other (please specify)	17	8%	3	4%
Non-government organisation	20	9%	4	5%
Policy makers	21	10%	12	16%
Professional or Peak Associations/Organisations/Bodies	29	13%	10	13%
Patients/Consumers/Carers	59	27%	19	25%
Academics (internationally based)	75	35%	46	61%
Clinicians	199	92%	67	88%
Academics (locally based)	213	98%	74	97%

(Note: Respondents were able to select more than one option, thus the total adds up to more than 100%.)

As 20 respondents in aggregate (MRFF and NHMRC) responded “other” and provided additional details, their responses have been amalgamated to preserve anonymity and the numbers of responses within each category suppressed. Because several respondents provided multiple answers, the total did not add up to 20. The responses included:

- Consumers/patients
- Early/mid-career investigator
- Educator
- Field work
- Health Economist
- Industry
- Research coordinator
- Statistician
- Trial design
- Unclear answer

In what capacity does the trial involve early-mid career researchers (EMCRs)?

216 MRFF-funded investigators reported that EMCRs were most commonly involved in their trials as one of the principal investigators (63%) or one of the associate investigators (55%). Only 1% of respondents indicated that their trial did *not* involve EMCRs at all.

76 NHMRC-funded investigators similarly reported that EMCRs were most commonly involved in their trials as either one of the principal (78%) or associate (53%) investigators, although 4% reported no involvement of EMCRs of any kind.

Table 3 Involvement of early-mid career investigators

	MRFF (n=216)		NHMRC (n=76)	
Trial does not involve early-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%

Twenty-six respondents selected “other” as their response (20 from MRFF and 6 from NHMRC) and provided a free-text response. To protect respondent anonymity, responses from the MRFF and NHMRC respondents have been amalgamated, and numbers within each category suppressed. Responses are presented in alphabetical order:

- Chief Investigator
- Data collection
- Intern
- Medical monitor
- Not applicable
- Part of working groups
- Postdocs
- Project Coordinator/Manager
- Site Lead
- Staff / support staff
- Trial Coordinator
- Trial Steering Committee
- Unclear/unknown

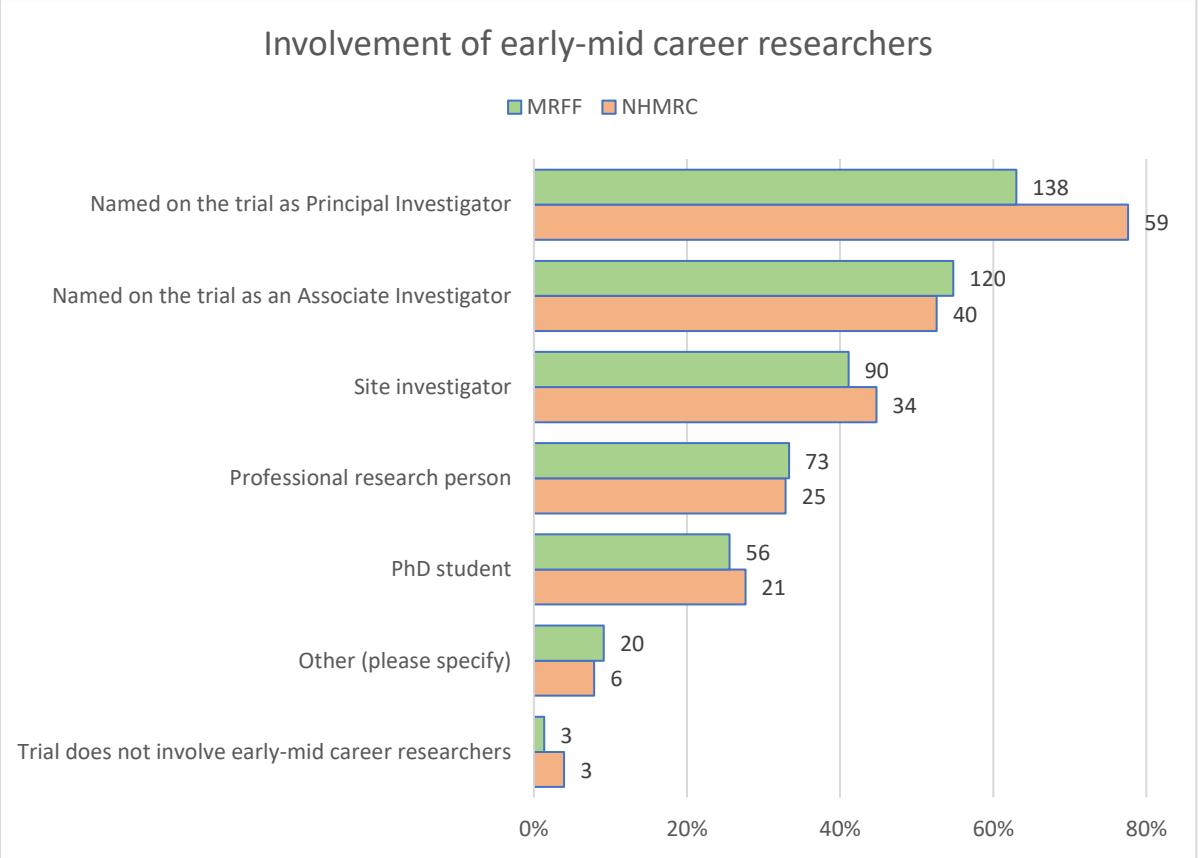


Figure 2 Involvement of early-mid career investigators

In which of the following ways has your trial engaged with consumers?

Most frequently, the 207 MRFF 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 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%)

Table 4 Engagement with consumers - MRFF

MRFF respondents	N (207 respondents)
Gathered and implemented consumer input on the priorities and design of your study	166
Formed a consumer advisory group for your project	94
Met with community representatives about your study	82
Presented your work at consumer forums (e.g. events hosted by patients' groups - science week events)	72
Had consumers actively participate in gathering/analysing the results of your study	40
Made the results of your study freely available and accessible for lay readers	28
Successfully deployed a strategy to ensure groups that are traditionally underrepresented are included in your study	24
Other (please specify) Responses provided: this is still in planning stages; consumer as one of the investigators (CI or AI); consumer as part of the trial management or steering committee; as part of dissemination; will share the results with consumer/community/patient groups	21
None of the above	16
Produced new public health education campaigns	12
Grand Total	**555**

Table 5 Engagement with consumers - NHMRC

NHMRC respondents	N (70 respondents)
Gathered and implemented consumer input on the priorities and design of your study	59
Formed a consumer advisory group for your project	34
Met with community representatives about your study	27
Presented your work at consumer forums (e.g. events hosted by patients' groups- science week events)	18
Other (please specify) Responses provided: co-design (e.g. consent materials, information materials); members on steering committee; formed an advisory group; not yet started but planned; as part of the project team; will disseminate information to consumer/community forums	11
Successfully deployed a strategy to ensure groups that are traditionally underrepresented are included in your study	8
Had consumers actively participate in gathering/analysing the results of your study	7
Made the results of your study freely available and accessible for lay readers	5
Produced new public health education campaigns	3
None of the above	2
Grand Total	**174**

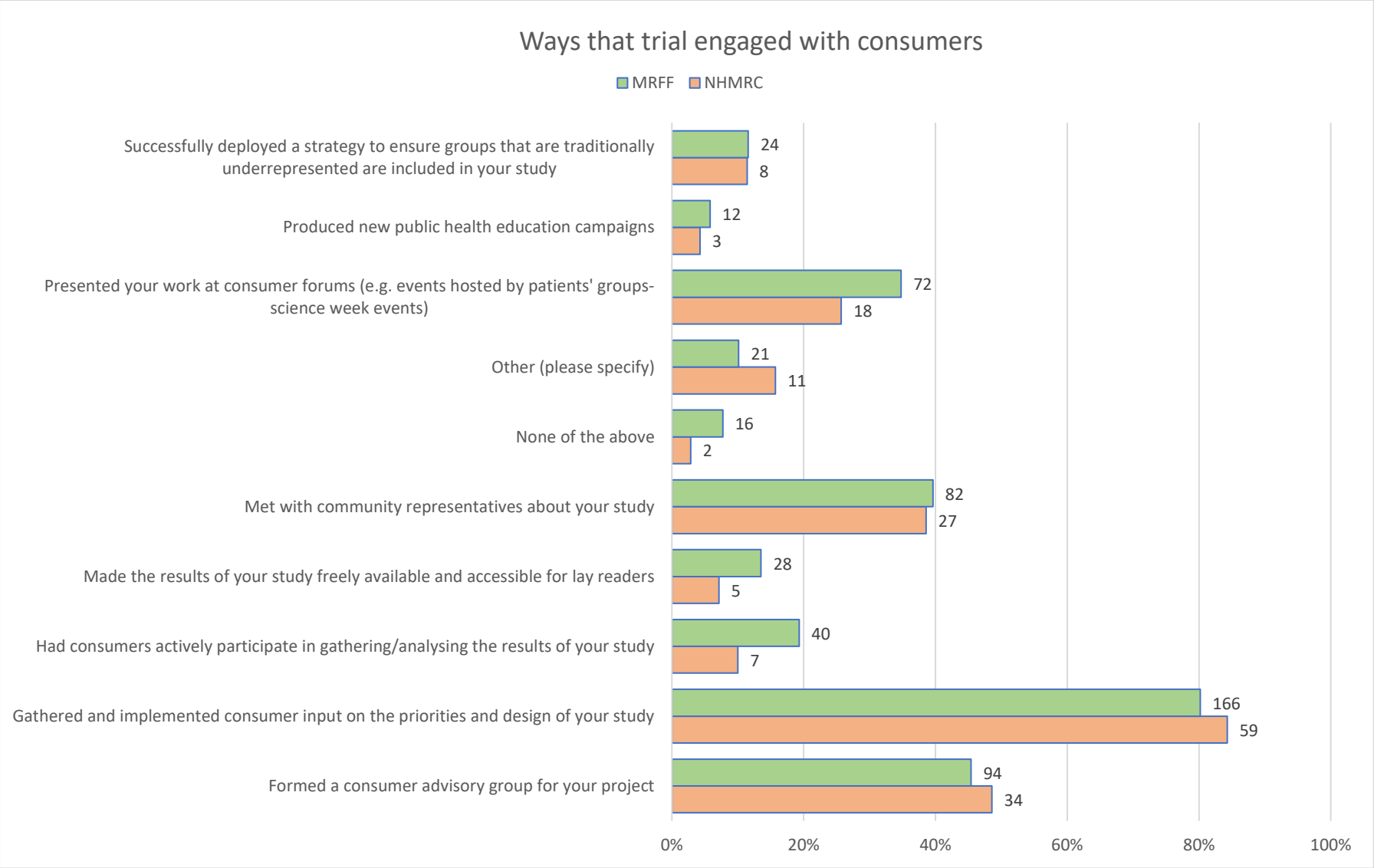


Figure 3 Engagement with consumers - MRFF & NHMRC

1.2. Study justification – Detailed results

What was the reason for conducting the trial on this topic?

208 of 238 MRFF investigators responded to this question. The 15 most common reasons cited, are provided in the Table, below:

Table 6 Reason for conducting the trial - MRFF

MRFF: Reason for conducting the trial (208 respondents)	N	Sample quote/s
Clinical need (general or generic comment)	71	"Saw the issue in clinical practice" "Definitely an issue in clinical practice"
Gaps in knowledge/evidence base	39	"Lack of evidence base" "recognition that treatment has been understudied in this population" "Lack of research in the area"
Extending existing research programme	37	"is an extension of existing research program" "the project builds on the research team's previous projects"
No treatment / inadequate treatment / poor patient outcomes	26	"no efficacious treatments" "To improve outcomes for a rare patient population which has historically had extremely poor outcomes" "Woefully inadequate patient outcomes"
Favourable pilot/feasibility study / promising findings in existing research	16	"Building on successful pilot work" "Promising signals from previous trials"
Unmet need	12	"Address areas of unmet need" "stemmed from our research on unmet needs"
No existing trial / need for 'stronger' research design	11	"no adequately powered RCTs to date" "there were some potential advantages of intervention but not adequate evidence to confirm this; so to conduct an RCT of the intervention"
Existing collaboration or approached by other researchers or industry	11	"collaborator approach" "We have good collaboration nationally and internationally, so it made sense to harness the goodwill and enthusiasm"
Burden of disease	11	"Major public health issue facing society" "National priority area" "To test an intervention of the effect of a major health issue"
Lack of data for specific population groups	7	"sub-population that might benefit from the intervention" "needed to be assessed in people with high risk"
Consumer priority	7	"Consumer priority" "Strong interest from families"
To inform policy/guidelines	5	"to inform international and national guidelines, and the policies of national screening committees" "schools of opinion that current guidelines are not supported by high quality evidence"
Practice variation	5	"clinical practice variation" "variations in clinical practice"
Equity	4	"equity of service delivery"

		"Key need to address social inequities in health in this population"
Growing/suggestive body of evidence	4	"growing evidence" "Emerging data"

69 of 83 NHMRC investigators responded to this question. The most common reasons cited (n=13, exhausting all categories), are provided in the Table, below:

Table 7 Reason for conducting the trial - NHMRC

NHMRC Reason for conducting the trial (69 respondents)	N	Sample quote/s
Clinical need	30	"Clear unmet need in clinical practice" "saw the issue in clinical practice"
Extending existing research program	16	"extension of existing research programme" "Extension of existing programme by verifying subgroup findings in previous phase 3 RCT"
No existing trial or need for 'stronger' research design	14	"Pioneering study" "Gap in evidence base for effective interventions"
Unresolved health issue/gaps in knowledge	9	"Ongoing, largely unresolved health issue" "Clinical practice and recent publications questioning our long-standing "current" management"
Other	7	"Comprehensive review of literature" "The cohort study proposal was informed by our team's prior research and close collaboration with policy makers, service providers and community" "We are investigating whether there has been a generational change in rates of [condition] and risk factors for this"
Favourable pilot study	5	"Promising pilot data" "Extension of existing 4-yr programme of pilot work"
Burden of disease	3	"Major [Disease area] priority disease" "[Disease] pose huge burden on the society."
To inform policy	2	"Important policy gap articulated in international guidelines"
Lack of data for specific population groups	2	"clarifying need in a [specific] population" "heterogeneity analysis showing benefit in [age group indicated] patients"
Improve implementation of effective therapy	2	"To extend substantially the use envelope for a highly effective therapy"
Practice variation	2	"Clinical practice is heterogeneous and polarized"
Lack of data for Australian population	1	"Basically, an absence of high-quality prospective data on [disease area], especially pertaining to Australia"
Area of interest	1	"was in my area of interest"

(The answers add up to more than 69 as some respondents mentioned multiple reasons. Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Which of the following did you do to help justify the need for your funded trial?

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

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

Table 8 How the trial was justified - MRFF & NHMRC

	MRFF (229 respondents)		NHMRC (79 respondents)	
Systematic review and/or meta-analysis	104	49%	44	61%
Literature review of diagnosis or treatment options	138	65%	45	63%
Presentation of data from registries	62	29%	20	28%
Other documentation	87	41%	27	38%

(Note: Respondents could select multiple options, hence the total does not add up to 100%).

The responses provided by MRFF respondents who selected 'other' are listed in the table below. As some respondents provided multiple justifications for their trial, the total does not add up to 87.

Table 9 How the trial was justified - MRFF free text responses

MRFF responses	N
Pilot data	33
Previous studies	17
Research experience	13
Qualitative evidence	4
Community engagement / consultation	4
Guideline	4
Preclinical data	4
Review (other type)	3
Lab data	3
Community engagement / consultation	2
Expert opinion	2
Priority setting	2
Survey	2
Animal data	2
Systematic review/s	1
Literature review	1
Unsure	1
Collaborator interest	1
Policy documents	1
Grand Total	**100**

The responses provided by NHMRC respondents who selected 'other' are listed in the table below. As some respondents provided multiple justifications for their trial, the total does not add up to 27.

Table 10 How the trial was justified - NHMRC free text responses

NHMRC responses	N
Pilot data	15
Previous studies	6
Guideline	2
Qualitative evidence	2
Review (other type)	1
Clinical practice	1
Systematic review/s	1
Not a trial	1
Research experience	1
Grand Total	**30**

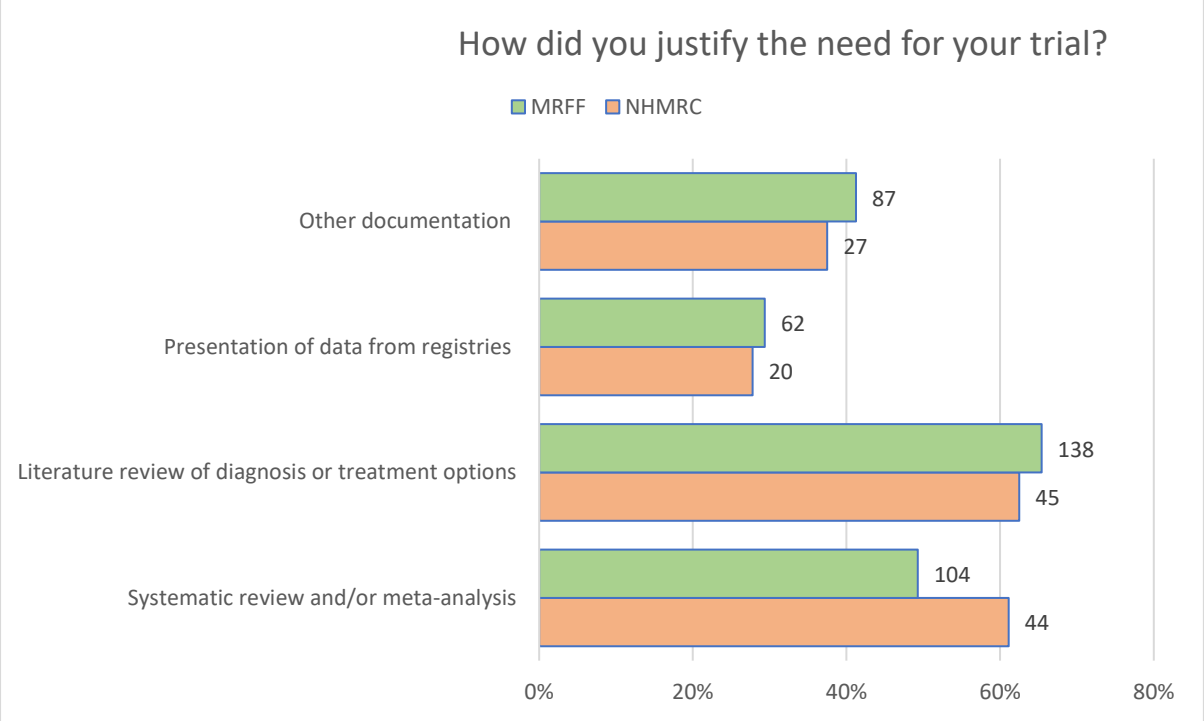


Figure 4 How the trial was justified - MRFF & NHMRC

1.3. Study funding – Detailed results

Original funder (MRFF/NHMRC)

Can you comment on your experience (with MRFF's CTA) so far?
No data was presented as part of this question.

The stakeholders commented on: their experiences with the MRFF's CTA scheme as a whole, on research topics, the review by the Grant Assessment Committee, the post-Grant Assessment feedback, interactions with the MRFF itself, and the relationship of MRFF to other funders. The following issues, comments or questions were identified under each category:

MRFF CTA scheme as a whole
- The scheme has been good (a general observation)
- The scheme is good at bringing larger groups together, e.g. academic researchers and clinicians working in the health system
- It has a really important role in clinical trials

Research Topics
- Similar calls come out annually, allowing applicants to prepare
- Has the community been consulted in regard to priorities for future research, and is diversity considered as part of that?
- There is a lack of focus on the translational component

Review by Grant Assessment Committee
- The panel was well organised
- Consumer members on the panel are currently not full members, unlike in the UK or Canada
- The outcome of the panel review may vary, depending on whether its members are experienced or not
- Value for money consideration suggests that health economics expertise should be required
- The panel members represent a spectrum of skills, experience and expertise – at times, this may have led to sub-optimal peer review

Post-review feedback by Grant Assessment Committee
- There is a lack of feedback to panel members about whether the evaluated project was funded
- Incomplete/missing feedback to researchers means they will miss out on a learning opportunity

Interactions with the MRFF itself

- MRFF interactions have been very helpful/good

MRFF relationship to NHMRC / other funders

- The organisation of the panel was like the NHMRC's – it was well organised
- Application process was like the NHMRC's, and it was a good experience
- MRFF does not clearly differentiate itself from other funders, in particular the NHMRC
- The CTA initiative provides an additional avenue for clinical trials funding [in context of the discussion of the difficulty in obtaining funding from other funders]

Do you have any general thoughts about MRFF's role in the clinical trials landscape in Australia?

No data was presented as part of this question.

The stakeholders shared their thoughts about the MRFF or CTA as a whole, about the role of community involvement, research topics, application processes and outcomes (N.B. this area is outside of the scope of the present evaluation), and MRFF's relationship to NHMRC or other funders. The following issues, comments or questions were raised under each category:

MRFF/CTA as a whole

- They may be the dominant funding mechanism for trials. So, it makes a positive contribution
- It is unclear if we need it, but it is good to have if it matches one's area of research
- It is not clear if it is fair or equitable
- It possibly brings in more money to the sector
- It appears to have a large amount of money and therefore is valuable to clinical trialists
- MRFF has become very important because of the change in NHMRC structure – Ideas Grants are not geared towards funding trials, and some people have Investigator Grants but not many
- It has brought more money into the sector
- It is great having more money in the sector, but it seems to result in a constant grant cycle
- I liked the EMCR concept but heard there was only a 5% success rate so perhaps as the scheme matures, there will be more money. The challenge is in funding the early stages of the career
- It provides another avenue to get grants for trials (beyond NHMRC)
- It is a great positive (general observation)
- MRFF fills in a gap in the rarer areas, and it's important in terms of filling gaps

Community involvement

- Both MRFF and NHMRC ask for community involvement but there is no time to carry it out in a meaningful or effective way. For example, a priority-setting process takes time to set out, and the calls just don't allow for that. E.g. a James Lind Alliance priority setting process takes 3 months to a year.
- We can look to other funders to see what they do, and adapt it. The United Kingdom appears to be good at this.

Research Topics

- There are quite unusual topics coming up. It is good for those topics because they probably cannot get support anywhere else
- Rationale for some of the calls or their origin has been a bit opaque
- The topics have not been well aligned with unmet need in public health, or the available clinical trial expertise available in those areas
- Suggestion for funding of core infrastructure for networks

Application process and outcomes

These comments are reported here for completeness and transparency, although it is noted that MRFF's administrative processes are outside of the scope of the evaluation, as they are being addressed through MRFF's internal review procedures.

- They are more like tenders than traditional grants – the respondent thought this was fine
- There is a little more notice [of upcoming grant opportunities] than previously – it is probably maturing and moving to a 'calendar rhythm' but not quite there yet
- Do we know how much support is directed towards the industry versus others?

MRFF relationship to NHMRC / other funders

- It is not clear how MRFF differs from NHMRC – is it meant to add, complement or replace?
- In [a low incidence clinical area], we need to work internationally. So it is frustrating that all the money must be spent in Australia
- Although we had elite collaborators in [jurisdiction/s], we were not permitted to spend that money in [jurisdiction]

What do you think the MRFF clinical trials initiatives are doing well (and should retain) … and what might it do differently?

No data was presented as part of this question.

The stakeholders offered comments focusing on the MRFF's support for clinical trials, and the timing and content of the calls, other process-related issues, and other relevant comments. The following issues, comments or questions were raised:

Support for clinical trials

- MRFF is doing well in that they are supporting clinical trials
- MRFF has allowed more trials to be funded because prior to MRFF, there was just the NHMRC CTCS scheme, which tends to focus on large trials for common conditions
- Support for trials in unmet need should be encouraged – they are 'unmet' because not much research has been done in that area
- MRFF is doing well putting more money into clinical trials – this should continue
- MRFF has funded some work that could not have been funded through other initiatives

Timing and content of calls

- MRFF has made a great progress by publishing a full list of timelines for the calls throughout the year
- There is a lot of open calls for genomics and genome-wide studies – it seems disproportional, at the cost of other important areas especially post pandemic (e.g. non-communicable disease catchup that will have to happen)
- Many calls are very narrow, and it is challenging to fit the trials that need to be done into the topic
- Short time-frames for the grant mean that a trial essentially has to be ready to match the call/topic
- MRFF has call projections or forewarnings, but these tend to be general (e.g. that the call will open between July and December), with the actual call coming at the end of that period (e.g. December) and with a tight deadline (e.g. February). This timeline in particular covers the summer break, school holidays, etc.
- Consistency in programs year-to-year is valuable because it allows for planning
- The timelines can be very tight for grant submission
- A lot of calls can cover a researcher working on a broad area – but if a researcher works in a more niche area, it can be trickier to find a suitable call from MRFF and an Ideas Grant (NHMRC) or a more broader CTA call (MRFF) may be the solution
- Continuity could be an issue – some calls are a one-off call, so there is not an ongoing support for work in a specific area, which does not allow for critical mass of researchers or research groups to be built
- It is not always clear what kinds of calls will be released – the lead-time can be a challenge

Other process-related issues

- Rules around CIs being on a number of applications per round limits the amount of money being directed to the same group/s (the Stakeholder regarded this as a positive)
- 'Unmet need' could be separated from rare cancers and rare diseases – they should all be their own streams
- Community members should be full panel members – this can be facilitated by providing support and training
- The bar to get MRFF funding is lower
- Quality of peer review is less rigorous at MRFF
- MRFF panels should have methodologists on them to have good quality science
- MRFF favours clinician-researchers which is a good thing
- The application process has many odd risk assessment stuff and other extra documentation which does not seem to add value to design or delivery of proposed research.
- Grant assessment should have criteria for consumer and community involvement
- Schemes should standardise requirements – e.g. 1 page CV vs 2 page CV, top 10 papers vs top 5 papers, etc.
- The differential between the funding portals – business.gov and Sapphire – should be harmonised. All applications should go through Sapphire.
- Diversity on the review panels should be encouraged
- Consumer engagement in studies should be supported right from the start, e.g. from the design stage of the study. This may be achieved via funding guidelines.
- I do not know what the current process is for priorities – who decides, is it fair, equitable, does it involve increased health, etc.

Other relevant comments

- MRFF decisions can be quicker than NHMRC, but that may have been a one-off, due to the election timing and government going into caretaker mode
- It is unclear if MRFF has a set strategy – it seems to be doing a lot of things, but it is not clear how those are linked with priorities, burden of disease, etc. The link could be transparent
- Ensuring the One Stop Shop is implemented would be a great service to clinical trial research in Australia
- Understanding MRFF's support of early commercialisation of medical research, how the funds are being used, would be very helpful – e.g. in terms of dollar value or the number of projects

Are there any other general comments you would like to make about the MRFF CTA?
No data was presented as part of this question.

The stakeholders offered general comments addressing: topics or areas, processes, early career researcher issues, and strategic direction. Issues, comments or questions raised, included:

Topics or areas
- The MRFF has some basic science-oriented topics, but it is very clinically-oriented. This makes it difficult for basic scientists.
- Is there any attention paid to the makeup of study participants (age, gender, ethnicity, etc)

Processes
- MRFF topic guidance can be a bit vague
- Applicants do not receive reviewer comments, so it is unclear whether the application was bad, or good but there were too many other applicants. The comments would be useful.

Early career researchers
- Increased money for early career individuals
- Limit on grants an individual may hold is a good one, as it precludes funnelling of money to several, very senior individuals
- Are there rewards for mentoring more junior staff or involving them as CIs on the grant?

Strategic direction
- Co-funding is an important area to consider
- Conditional funding for implementation should be part of the funding package for trials that are successful.
- There is currently a lack of dialogue between the governments, healthcare system, and the clinical trial ecosystem

Co-funding

Is your trial co-funded by another agency, charity or sponsor?

Most commonly the trial was not co-funded by another body, for either the MRFF grant recipients (75%) or the NHMRC recipients (87%) responding to the survey.

Table 11 Is the trial co-funded

	MRFF (n=216)		NHMRC (n=77)	
	n	%	n	%
Yes	54	25%	10	13%
No	162	75%	67	87%
Total	**216**	**100%**	**77**	**100%**

Co-funding of trials – Stakeholder reactions

The stakeholders were presented two figures and two tables. The two figures displayed the data from the survey of the MRFF and NHMRC investigators, about the number of trials co-funded (from Desktop Review); tables provided data about the source of co-funding and its use (Survey Project). (see below)

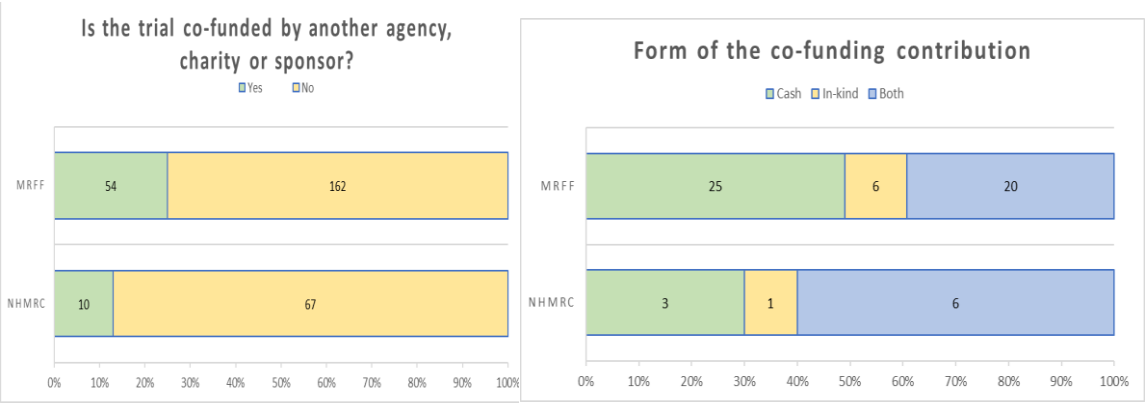


Figure 5 Co-funding details

Table 12 Source of co-funding

Source of funding?	MRFF (n=52)		NHMRC (n=10)	
	n	%	n	%
Domestic	25	48.08	4	40
International	16	30.77	4	40
Both	11	21.15	2	20
Total	**52**	**100**	**10**	**100**

Table 13 What was the co-funding used for - MRFF

MRFF (52 respondents): What was the co-funding used for?	N
Costs of treatment	29
Overheads/salary gaps	23
Costs of follow-up investigations	18
Costs of a sub-study	16
Other (please specify)	14
International expenditure	11
Infrastructure	10
Equipment	7

In response to the data presented, the stakeholders made observations about individual funders or compared them to each other; and suggested various explanations for the data presented. The following issues, comments or questions were raised:

Observations about individual funders/comparisons between funders

- It's very good that 31% of MRFF co-funding comes from international sources
- It seems there is a lot of co-funding money – I am surprised
- MRFF emphasises the importance of having a project partner, whilst NHMRC does not say much about co-funding from partners
- Why is there such a disparity between NHMRC and MRFF?
- Co-funding makes sense given the cost of treatment – e.g. treatment for [disease area] is often funded by the pharmaceutical sponsor, and the application to the NHMRC or MRFF is for the extra costs of the trial (e.g. salaries)
- MRFF does not send money overseas; it is interesting to see international co-contribution here
- I am not surprised – I would think most trials have some kind of contribution from other sources, they are not fully funded by MRFF or NHMRC

Suggested explanations for the observed results

- It seems that if you apply with co-funding, the chances of getting the grant are higher
- Good that co-funding is not just from Australia, but also overseas as well
- Some of the in-kind support may be a bit made up because grants require it
- Do applicants need to have co-funding to increase the chance of receiving the grant?
- Funding bodies e.g. NHMRC often remove some of the budget requested in the grant – and sometimes the study can deal with this, and sometimes not, and co-funding has to be sought elsewhere
- It is good to see a lot of cash co-funding – I thought more of it would be in-kind
- I suspect there is a greater in-kind contribution than recognised, e.g. from universities
- Some trials are funded as a 'grant-in-aid' because the grant is insufficient to cover the full cost of the trial
- Increasingly, trials have an investigator with an investigator grant which meets the shortfall for the trial – e.g. some are conducting pilots with the investigator grant money

Other observations

- Co-funding may involve financial conflicts of interest, which may compromise scientific objectivity and introduce bias
- If IP arises, the grant administering institution holds the IP. But if a grant is publicly funded, shouldn't it be for public good?
- Does this data take into account cases where the trial is run with NHMRC funding, but the person running the trial has fellowship funding e.g. from a health service?
- Placebo funding is difficult to obtain, and few companies in Australia make them. I would like to see the government take this on – we are too small a country for competition to work, and overseas supply chains get interrupted
- Researchers need to include a more diverse population in clinical trials, given the proportion of Australians who are born overseas/have parents born overseas / speak a different language – as well as people from so-called "vulnerable" groups. Funders could start tying additional cash support for studies that involve those groups
- Salaries and university overhead costs are a problem
- There is no short-term, external funding for e.g. staff onboarding. What approaches can be implemented for more sustainable long-term funding to avoid the stop-starts?

Which other trial funders are you familiar with (i.e. have submitted to, reviewed for, been on panels for, etc)?

No data was presented as part of this question.

The stakeholders most commonly mentioned familiarity with philanthropic funders (n=5), as well as large pharmaceutical foundations, the UK Wellcome Trust and New Zealand's Health Research Council (each n=2). (Table below).

Table 14 Known other funders

Other Trial Funders	Number of respondents
Philanthropic funding	5
Large pharmaceutical company foundations	2
UK Wellcome Trust (global charitable foundation)	2
New Zealand Health Research Council (HRC)	2
Companies fund themselves	1
European JPND	1
Funding Million Minds Mental Health Research Mission	1
Non-government Heart Foundation	1
NGO's and research charities	1
Ruth Foundation	1
US FDA	1

Who are the co-funder(s) [for your trial]?

Due to few survey responses to this question from the NHMRC respondents (n=9), data is amalgamated with the MRFF respondents (n=52) to prevent deidentification.

Because respondents typically identified multiple co-funders, the total list will not add up to 61 (i.e., 52+9).

Most commonly identified co-funders included: Health Research Council of New Zealand (n=6), Baxter Healthcare (n=5), and Industry not further specified (n=5).

Table 15 Who are the co-funders for your trial?

Co-funder	N
Health Research Council of New Zealand	6
BAXTER Healthcare	5
Industry (not specified)	5
CIHR	3
NHMRC	3
NIHR	3
Queensland Gov/Queensland Health	3
Anonymous donor	2
Children's Hospital Foundation	2
Cystic Fibrosis Foundation	2
Merck	2
Multiple (not further specified)	2
Prostate Cancer Foundation Australia	2
Tour de Cure	2
University of Queensland	2
ALLG	1
ANZDATA	1
Australian and New Zealand College of Anaesthetists	1
Australian Brain Cancer Mission	1
Belgian equivalent of NHMRC	1
Better Evidence And Translation in Chronic Kidney Disease (BEAT-CKD)	1
BrAshAT	1
Carries Beanies for Brain Cancer and the Mark Hughes Foundation	1
CCTG	1
Cerebral Palsy Alliance	1
Channel 7 Telethon Trust	1
Chinese University of Hong Kong	1
CORR	1
CSL-Seqirus	1
Cure Brain Cancer Foundation	1
Day One Therapeutics	1
Dementia Australia	1
Dementia Centre for Research Collaboration	1
DFAT (COALAR)	1
DGF	1
Emergency Medicine Foundation	1
EORTC	1
Equity Trustee's	1
Factors Group	1
Financial Markets Foundation for Children	1
Foundation of Prader-Willi Research	1
Gates foundation	1

Grant [reference deleted for anonymity]	1
Health services	1
Ian Potter foundation	1
Industry (software)	1
Invent -VTE	1
Jack Ma Foundation	1
La Trobe University	1
Leukemia foundation	1
Lions Clubs	1
Local health districts in NSW and Victoria	1
Maddie Riewoldt's Vision Foundation	1
Medibank	1
Metropolitan Health Research Infrastructure Fund	1
MRFF	1
National Centre Infections in Cancer	1
OCRF	1
Otsuka Australia Pharmaceutical Pty Ltd	1
Peter Mac Callum Cancer Centre	1
PKD foundation Australia	1
Professional organisations	1
St Jude Children's Research Hospital	1
Sylvia & Charles Charitable Foundation	1
Takeda Co. Ltd	1
Telethon Perth Children's Hospital Research Fund	1
THANZ (Thrombosis and Haemostasis Society of Australia and New Zealand)	1
The George Institute for Global Health	1
The Ritchie Centre	1
Thrombio Pty Ltd	1
U.S. Alzheimer's Association	1
UK University of Liverpool	1
Universidad del Desarrollo	1
University of Sydney	1
Unsure	1
Wesley Medical Research	1
Western Australia Child Research Fund	1
Singapore NRMC	1

Was the co-funding [for your trial] domestic (Australian) or International?

For the MRFF respondents to the survey, most commonly, the co-funding was from domestic sources (48%). For the NHMRC respondents, equal percentage of respondents identified domestic (40%) and international (40%) sources, although the numbers are very small.

Table 16 Domestic or overseas co-funding

	MRFF (n=52)		NHMRC (n=10)	
	n	%	n	%
Domestic	25	48.08	4	40
International	16	30.77	4	40
Both	11	21.15	2	20
Total	**52**	**100**	**10**	**100**

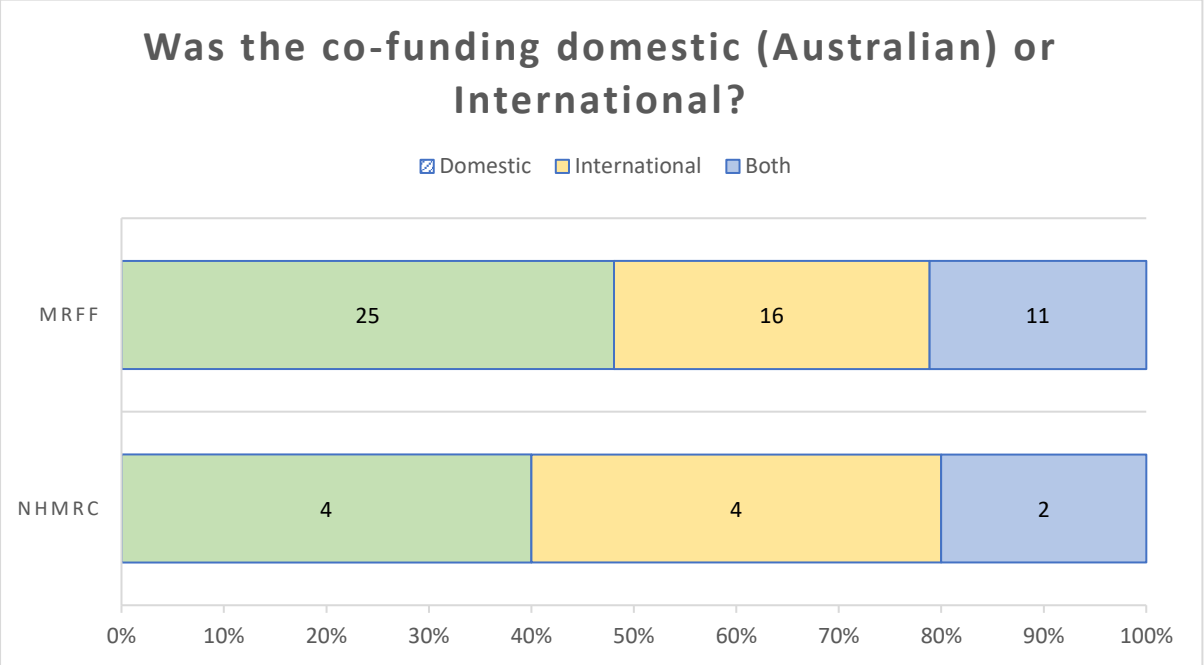


Figure 6 Domestic or overseas co-funding

What form is the co-funding contribution?

Where a trial had co-funding from another body, most commonly, this took the form of cash contributions for the MRFF survey respondents (49%) and *both* cash and in-kind contributions for the NHMRC respondents (60%).

Table 17 Form of co-funding contribution

	MRFF (n=51)		NHMRC (n=10)	
	n	%	n	%
Cash	25	49%	3	30%
In-kind	6	12%	1	10%
Both	20	39%	6	60%
Total	**51**	**100%**	**10**	**100%**

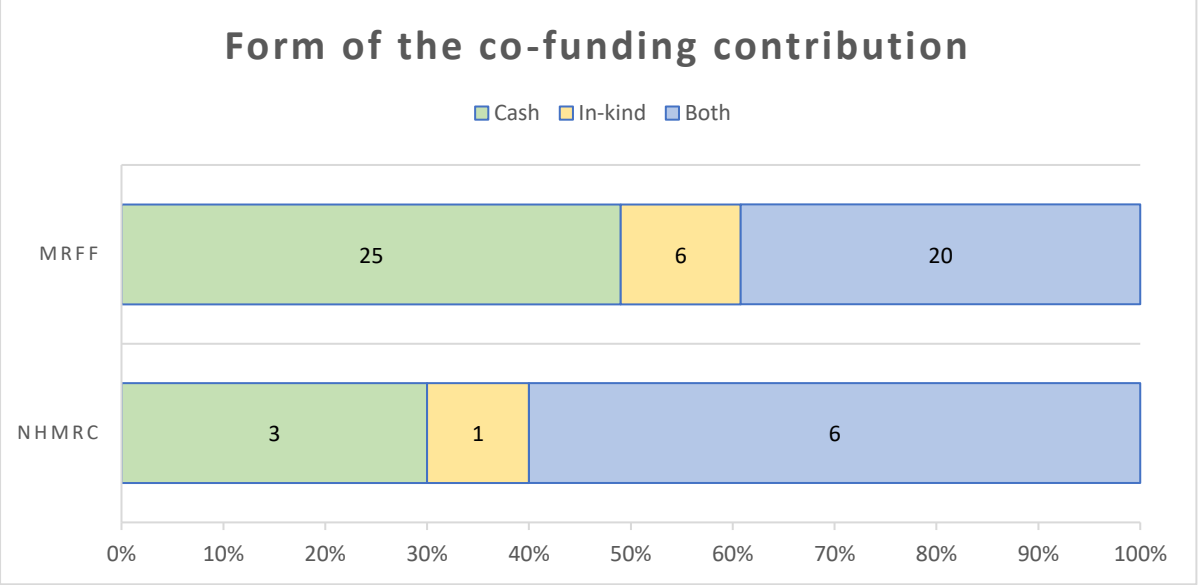


Figure 7 Form of co-funding contribution

What was the additional funding required for?

For the 52 MRFF respondents to the survey, most commonly, the additional funding was to cover the costs of treatment (n=29, 23%) or the overheads/salary gaps (n=23, 18%).

For the 10 NHMRC respondents, most commonly, the additional funding was, similarly, required to cover the costs of treatment (n=5, 20%) or overheads/salary gaps (n=5, 20%).

Table 18 What was the co-funding required for - MRFF

MRFF Responses (52 respondents)	N
Costs of treatment	29
Overheads/salary gaps	23
Costs of follow-up investigations	18
Costs of a sub-study	16
Other (please specify)	14
International expenditure	11
Infrastructure	10
Equipment	7
Grand Total	**128**

*does not add up to 100% because many respondents selected multiple options

Table 19 What was the co-funding required for - NHMRC

NHMRC Responses (10 respondents)	N
Overheads/salary gaps	5
Costs of treatment	5
International expenditure	4
Costs of follow-up investigations	4
Other (please specify)	2
Infrastructure	2
Costs of a sub-study	2
Equipment	1
Grand Total	**25**

*does not add up to 100% because many respondents selected multiple options

As only 16 respondents in aggregate provided additional detail, their responses have been amalgamated to preserve anonymity. Some respondents indicated more than one type of expenditure, hence the total does not add up to 16. The expenditure examples included:

- Additional study sites (n=3)
- Research activities/costs (n=2)
- Start-up costs (n=2)
- Statistical/methodological/or other expertise (n=2)
- Recruitment (n=1)
- Monitoring (n=1)
- Databases (n=1)
- Equipment (n=1)

- Our funding is the 'additional funding" for another study (n=1)
- Advertising (n=1)
- Development (n=1)
- Unclear answer (n=1)
- Inclusion of additional population group (n=1)
- Knowledge translation (n=1)

Funding in practice

Budget

For 61% of the MRFF survey respondents – that is, a majority – there were no challenges in implementing or conducting their trial due to budget issues.

Among the NHMRC respondents, the same proportion stated this was a challenge (36%) and that it was not a challenge (36%).

Table 20 Budget challenges

	MRFF (n=213)		NHMRC (n=74)	
Yes	55	26%	27	36%
No	130	61%	27	36%
Not yet applicable	28	13%	20	27%
Total	**213**	**100%**	**74**	**100%**

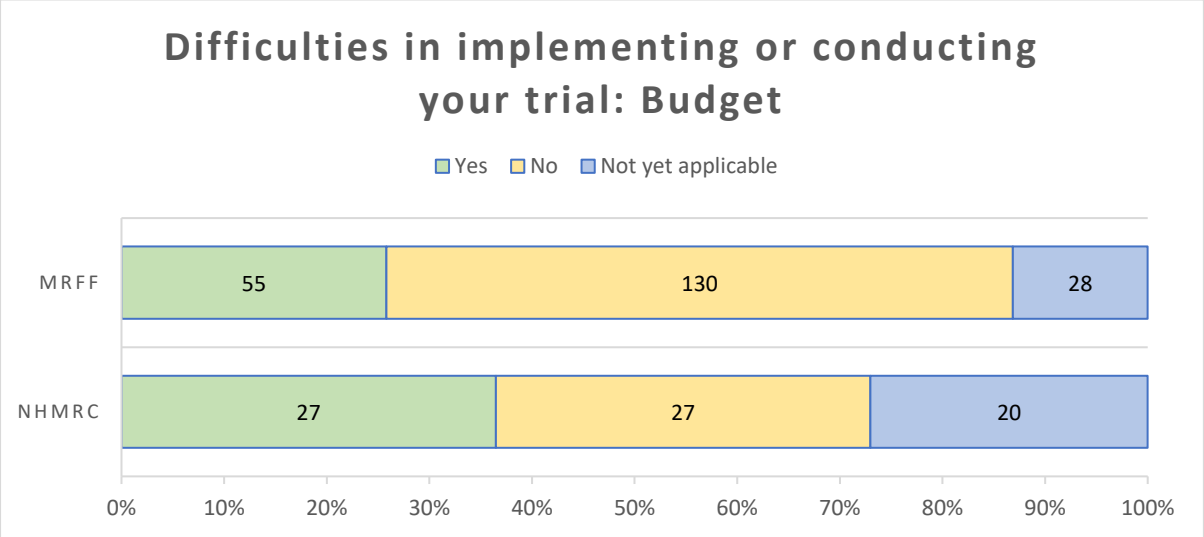


Figure 8 Budget challenges

54 MRFF respondents provided free-text responses which cited, in aggregate, 77 issues. Most commonly, these mentioned budget's failure to cover study costs (n=19) and staff salary shortfalls (n=17).

Table 21 Budget challenges - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 54)	Sample quote(s)
Budget failed to cover study costs	19	"Insufficient budget due to slower than anticipated progress" "budget was totally inadequate and additional costs due to ethics and COVID factors" "budget creep due to long set-up period from contract delays"
Staff salary shortfall	17	"The misalignment between NHMRC PSP levels and University salaries and on costs means we were operating at a 30% deficit before the trial even started." "Funding of positions well below University award rates, combined with EA [enterprise agreement] salary increases, makes it impossible difficult to staff the trial at the requested levels. University support is often not provided for such salary gaps, forcing appointments at reduced fractions." "Had to pull in funds from other sources to pay researcher for the final year."
Impact on recruitment	11	"recruitment needs to be extended" "Slow recruitment has stretched the budget" "Low budget makes uptake of recruitment slower as sites prioritise trials with better payments"
Costs increased	9	"Increased timelines = increased costs" "We are over budget due to the pandemic causing delays in getting started and having to pay more for the procurement of study drug."
Have/had to seek additional funding	8	"We will need to seek additional funding to fully support the trial and substudies" "budget from MRFF was less than requested and insufficient to complete the study. Therefore we had to seek out industry funding as well to make the study viable, which we were able to successfully accomplish"
Granting body decreased proposed budget	4	"Our budget was cut [by ~30-40%] - this drastically affected the money we have been able to offer sites and meant we have been unable to support participant travel and other associated costs. Commercial partners have provided in kind support to aid our trial due to lack of funds"

		"We are underfunded for what we aimed to do and so are struggling to implement all aspects of our plan." "Shoestring budget as total pool was only [N million] so slashed the grant."
Staffing stress	2	"Not able to employ the required staff to execute the study to its full potential. This caused delays in trial start-up, execution and maintenance of the trial. This caused significant stress to the staff working on the trial."
Unclear answer	2	
Change to project scope	2	"Because of the delays/impacts discussed in previous comments, and the very tight timeline, we did not have sufficient resources to complete all phases of the project, hence had to adapt and change the scope."
Site management	1	"Challenges in site and protocol cost management"
Patient reimbursement	1	"reduced per patient payments"
Not applicable	1	
Grand Total	**77**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

27 NHMRC respondents provided free-text responses which cited, in aggregate, 38 issues. Most commonly, these mentioned granting body's decrease to the proposed study budget (n=8), staff salary shortfall (n=7) and increase to costs (n=7).

Table 22 Budget challenges - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 4)	Sample quote(s)
Granting body decreased proposed budget	8	"Budget was cut at point of funding, by around 10%" "Over [$ amount indicated] sliced off what we asked. Costs of research proposed exceeds budget. We are making cuts" "The approved budget is insufficient for the trial designed, but is a very good starting point."
Staff salary shortfall	7	"NHMRC does not adequately fund staff salaries or oncosts." "NHMRC grants never pay the full salaries + on costs for projects, and yet expect all of the work to be done for a fraction of the true cost. It's untenable." "cutting the [research staff position indicated] salary from the budget resulted in significant financial stress and redesign of aspects of the study."
Costs increased	7	"Due to the Pandemic, the cost of important aspects of the trial such as procurement and distribution of study medication, in a [study design described], ballooned significantly. " "Flow on effect of medication difficulties (blow out in budget secondary to initial underquote) affect overall budget and so ability to conduct the trial."
Budget failed to cover study costs	6	"Budget increased with slow HREC and governance, impact of pandemic." "Budget estimations were made to tight with the intention to be more competitive at the selection stage. We therefore need to subsidize the study with other available funds."
Had to seek additional funding	4	"we had our budget cut and are seeking the gap funding from other sources. If we are unsuccessful we will need to work out how to conduct the trial" "We have been successful in building extensively on this [NHMRC-awarded grant budget] budget through international grants and other NHMRC/MRFF grants"
Impact on recruitment	3	"Due to slow recruitment, we need to look at additional sites, which comes with additional costs" "likely need for prolonged recruitment"
Patient reimbursement	2	"Asked for budget doesn't realistically cover the on costs. Per patient payments are at the lower end."
Not applicable	1	
Grand Total	**38**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Funding innovations

Are there useful funding arrangements or innovations within those that MRFF might consider?

No data was presented as part of this question.

The stakeholders made specific suggestions for funding arrangements or innovations that MRFF might consider, or raised other relevant comments. The following issues, comments or questions were mentioned:

Suggestions for funding arrangements or innovations

- An expression of interest phase is useful - New Zealand's HRC does this, it is very brief
- For translational grants, NSW Health have an expression of interest round
- Grant writing takes a long time, and they may or may not be successful – EOI might be helpful
- Sometimes the second round of the EOI-style applications is double the work and the application is still unsuccessful
- Equity, Diversity and Inclusion within trials is an area that has been ignored
- Not a lot of trials have pilot data – so a two-stage funding approach might help with that, and also be a very good test of feasibility
- An arrangement like NHMRC's with Cancer Council, where the same application is considered by both if a box is ticked – would save the applicants time, as it means not having to write two separate applications
- A two-level application process, with an EOI that is half or a quarter-size of a full application, so applicants don't spend a lot of time writing applications that are uncompetitive
- There is a lot of Australian-Canadian research via the NHMRC's scheme – so suggest an approach where an applicant submits for a study to be conducted in both countries, but e.g. the Canadian one reviews, and the Australian commits to funding the Australian side
- It is important for studies to consider people from migrant / multicultural backgrounds – perhaps a monetary incentive to broaden the study's inclusion criteria might help
- Clinical trials are increasingly running based on the same protocol in multiple regions around the world – but if an applicant applies to a funder, often no funder wants to be the first. Inter-funder schemes where each commits some money could help
- Gated funding option, like in the industry – if a project does not meet a milestone, then it does not continue – although this might increase the administrative workload for the MRFF

Other relevant comments

- MRFF funding tends to focus on specific areas (e.g. cancer) – work outside of those areas (e.g. women's health) does not seem like a priority
- Funding one-country arm of a multinational trial is useful – no funder wants to be the first, but once one arm gets the funding, the others do as well
- MRFF calls for funding are very focused, so what happens sometimes, is that a big trial is 'salami-sliced'. Multiple grants are put in for different outcomes, but they are all applications for the same trial, just repackaged – e.g. one for cardiac outcomes, one for cerebrovascular outcomes, etc.

- Use of data beyond the trial's completion should be designed from the outset – innovations in this space would be helpful
- One Stakeholder was aware of a situation where an applicant submitted for one of the MRFF schemes but the application exceeded the allowable co-contribution level and was disqualified – this can be seen as an inappropriate disincentive
- Partnering of MRFF with industry is really important in areas where there is no commercial imperative to develop or test, or in areas where the focus is predominantly "public good"
- It is currently difficult to get parallel funding in Asia – e.g. Singapore, Korea have internal schemes but not external
- There is a big gap between the funding and the university salaries for NHMRC; probably less so for MRFF
- One trial model is having a national centre, which ensures data standards, oversight, etc., and regional hubs using local expertise – this would produce a health equity benefit and include those who are normally excluded from clinical trials
- There is a need for the healthcare system to have a process to feed to the funding agencies the information about clinical problems, unmet clinical or gaps

1.4. Trial networks – Detailed results

Is your trial part of a pre-existing clinical trials collaborative network? (e.g. the Australian Clinical Trials Alliance (ACTA), or a non-ACTA network, or an ad-hoc/informal network)?

For both the MRFF and NHMRC-funded trials, the survey found that the split between trials that are and are not part of a trials network was similar: 43% of MRFF-funded trials were part of a network (57% were not), and 40% of NHMRC-funded trials were part of a network (60% were not).

Table 23 Is the trial part of a collaborative network?

	MRFF (n=114)		NHMRC (n=72)	
Yes	90	43%	29	40%
No	120	57%	43	60%
Total	**114**	**100%**	**72**	**100%**

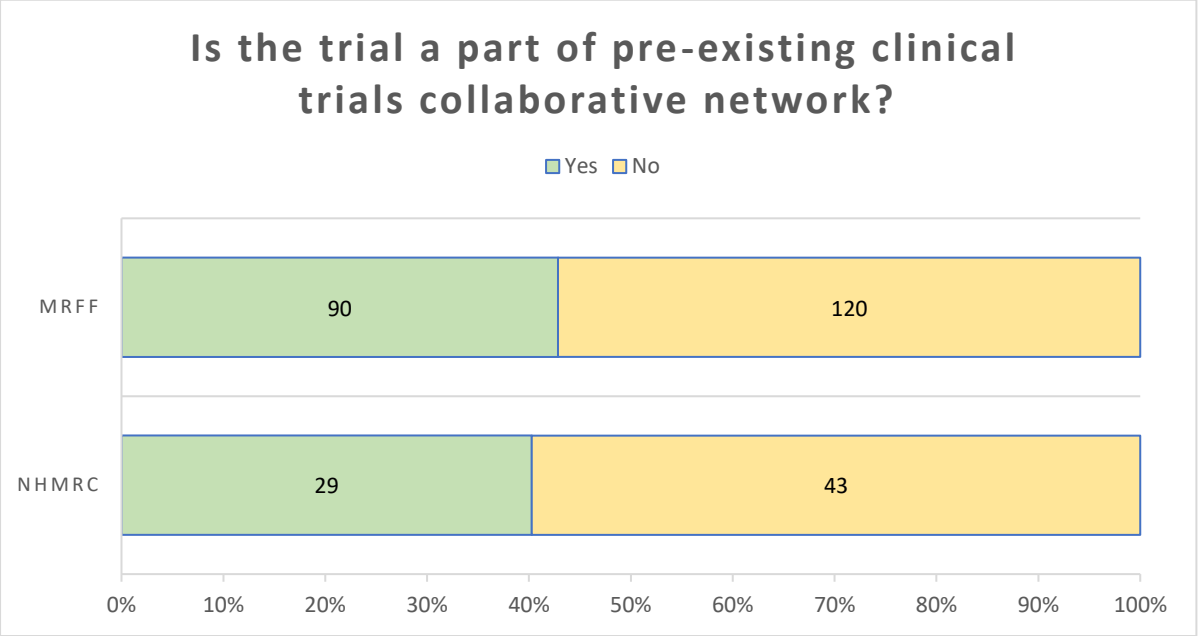


Figure 9 Is the trial part of a collaborative network?

Which network was your trial a part of? [for those stated their trial was part of a network]
88 of 89 MRFF investigators who said their trial was part of a pre-existing clinical trials collaborative network responded to this question (some indicated involvement with more than 1 network). The most commonly identified network was the Australasian Kidney Trials Network, identified by 8 respondents.

Table 24 Which network was your trial a part of - MRFF?

Network location	Name of clinical trial network (number of responses indicating this network)
Australia/NZ	Australasian Clinical Trials Network (1)
	Australasian Kidney Trials Network (8)
	ANZGOG (2)
	ANZCA CTN (2)
	IMPACT (3)
	MASC (3)
	ACTA (1)
	ASID CRN (Australasian Society for Infectious Diseases CRN) (1)
	ANZACT (2)
	THE AUSTRALIAN AND NEW ZEALAND INTENSIVE CARE SOCIETY CLINCIAL TRIALS GROUP (ANZICS CTG) (7)
	THE AUSTRALASIAN COLLEGE FOR EMERGENCY MEDICINE CLINCIAL TRIALS NETWORK (ACEM CTN) (1)
	Australian Cerebral Palsy Clinical Trials Network (AusCP-CTN) (1)
	ANZCHOG Australian and New Zealand Childrens Haematology/Oncology group (4)
	Australian and New Zealand Neonatal Network (ANZNN) (1)
	Primary care collaborative cancer clinical trials group (4)
	Growing Minds Australia (GMACTN) (1)
	ASTN (Australasian stroke trial network) (2)
	ALLG (7)
	COGNO (3)
	VicRen (Uni of Melbourne) (1)
	AGITG (Australasian Gastro-Intestinal cancer trials group) (1)
	DACRIN (drug alcohol clinical research network NSW) (1)
	ARTnet Australasian Radiopharmaceutical Trials Network (2)
	ANZMUSC (2)
	ACEM CTN (1)
	Curtin University Clinical Trials Centre (1)
	Neurodevelopment Australia (1)
	TROG Cancer Research (1)
	THANZ-CTG (Thrombosis and Haemostasis Society of Australia and New Zealand Clinical Trials Group (1)
	Rural Primary Care Trials Network (PARTNER) (1)
	Dementia Research Network for Neuroimaging, Clinical Trials and Implementation (DNET) (1)
	National Centre for Infections in Cancer (network of collaborators) (1)
	CTANZ - Clinical Trials Network Australia and New Zealand - Royal Australasian College of Surgeons (1)

International	Paediatric Research in Emergency Departments International Collaborative (PREDICT) (2)
	ACCT (Alzheimer's Clinical Trials Consortium) (1)
	Interfant (international network) (1)
Ad hoc/ informal	15
Unsure (answer does not make sense)	7

28 of 29 NHMRC investigators who said their trial was part of a pre-existing clinical trials collaborative network responded to this question (some indicated involvement with more than 1 network). The most commonly identified network was ANZICS CTG (n=4).

Table 25 Which network was your trial a part of - NHMRC?

Network location	Name of clinical trial network (number of responses indicating this network)
Australia/NZ	ANZICS CTG (4)
	ACTA (2)
	Interdisciplinary maternal and perinatal Australasian collaborative trial (IMPACT) network (3)
	Australian Epilepsy Clinical Trial Network (2)
	ANZMUSC (1)
	ANZNN (1)
	Australian and New Zealand Intensive Care Society Paediatric Study Group)(ANZICS PSG) (1)
	ANZCA CTN (1)
	ASID Clinical Research Network (2)
	ALLG (1)
	The Australian arm of the trial is being run by AKTN (1)
	DACRIN (2)
	Australasian Malignant Pleural Effusion (AMPLE) network (1)
International	PREDICT (Paediatric Research in Emergency Departments International Collaborative) (1)
	The CAB-V network (1)
Unclear or other	(4)

Why was your trial *not* part of a network? [if trial was not part of a network]

Among those MRFF investigators who responded that their trial was not part of the network, and provided a response to this question, the reason was most commonly: "not applicable" (n=38) or that no relevant network exists (n=29).

Table 26 Why was your trial not part of a network – MRFF

Reason cited (MRFF respondents)	Number of respondents	Example quote/s
No answer provided (blank)	126	
Not applicable	38	"not applicable" "outside of disease area"
No relevant network exists	29	"No applicable network" "No relevant network exists"
Unsure/don't know	16	"I don't know - I could also be wrong as I'm not sure"
Other	8	"Collaboration between research group and [relevant national] organisation already established." "It's a good suggestion" "Trial was established in response to grant opportunity which identified an area of unmet need"
It is part of a network	5	"Part of [name] Network" "[name] network"
Not a trial	5	"not a clinical trial"
Unaware of this option	2	"Did not know about these networks at the time of writing the application"
Lack of benefit	2	"We didn't think it would add value"
Not considered/no reason for not joining a network	2	"Not considered"
Network unsupportive of the trial	1	"The particular network my specialty is affiliated with seemed to want to kill my trial rather than support it"
Not yet/might be in the future	1	"It could be in the future"
Overseas trial	1	"[jurisdiction where the trial is based] trial"
Tried to but did not succeed	1	"We approached the [name] Network for inclusion. They indicated a preparedness to promote the trial if we could secure host sites. However, [they] advised they were oversubscribed with industry funded trials and could not host additional trials."
Grand Total	**237**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Among those NHMRC investigators who responded that their trial was not part of the network, and provided a response to this question, the reason was most commonly: "not a trial" (n=9) or that "no network exists" (n=7).

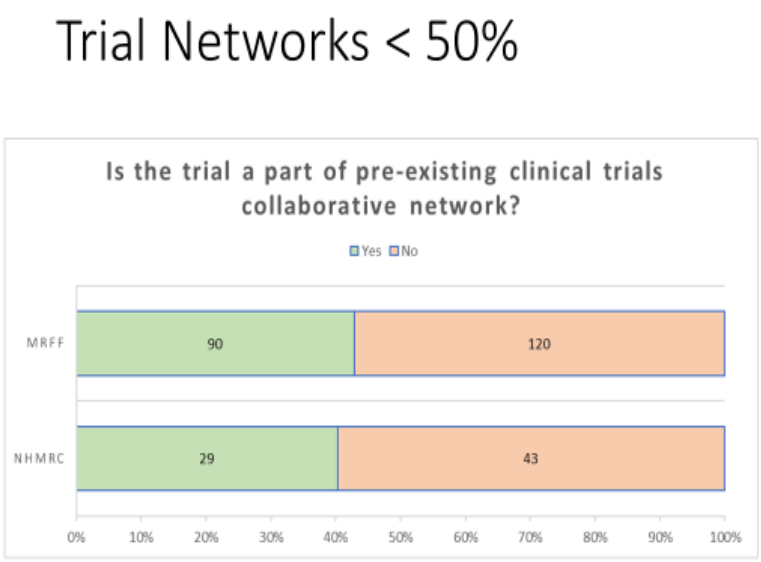
Table 27 Why was your trial not part of a network - NHMRC

Reason cited (NHMRC respondents)	Number of respondents	Example quote/s
No answer provided (blank)	47	
Not a trial	9	"it is not a trial" "cohort study"
No relevant network exists	7	"No appropriate network exists"
Not yet / might be in the future	6	"It could be in the future" "Relevant network [name] currently being established"
Unsure / don't know	6	"Not sure" "my role in the project hasn't extended to some of these high level planning things"
Not applicable	5	"Not relevant" "Not required"
Don't understand this question	1	"I don't even know what you mean by a "network""
Overseas trial	1	"overseas trial"
Grand Total	**82**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Use of trial networks – reactions or comments?

The stakeholders were presented with data on the proportion of trials that were a part of clinical networks, and reasons offered for why a trial was not part of a network (from the survey).



Reason cited (MRFF respondents)	Number (237)
no answer provided (blank)	*126*
Not applicable	**38**
No relevant network exists	**29**
Unsure / don't know	16
Other	8
It is part of a network	5
Not a trial	5
Unaware of this option	2
Lack of benefit	2
Not considered / no reason for not joining a network	2
Network unsupportive of the trial	1
Not yet / might be in the future	1
Overseas trial	1
Tried to but did not succeed	1
Grand Total	**237**

Figure 10 Use of trial networks

In response to being presented with the above data, the stakeholders offered comments about issues pertaining to the networks, mentioned MRFF- or CTA-specific issues, or made other relevant comments. The issues, comments or questions raised, included:

Issues pertaining to networks

- Trial networks tend to be disease-specific – this may not be applicable to areas like behavioural change or public health interventions. Not everything can be networked.
- A lot of investigators who conduct trials, are not just doing trials – they would not necessarily be a part of a network
- It may be more reassuring to a reviewer that there is a collaborative network, as there is more likely to be pilot data
- Industry-led trials use private organisations but there is a perception that they are not welcomed within the public networks
- Networks seem to submit applications for trials that are frequently getting funded – the trials ask better questions, are bigger, collaborate more, the design is better. Trials that are part of the network tend to be better.
- There are issues around sustainability and funding for networks – key people need to drive them, otherwise they do not flourish
- There are areas that do not have a national network – e.g. primary care.
- One of the successes of ACTA has been to facilitate network formation for many areas
- The bigger, practice-changing trials tend to come out of the networks
- A lot of the networks are Australian and New Zealand – which technically makes them international, but the clinical trial ecosystem is one

MRFF/CTA-specific issues

- MRFF has many calls for small, rare diseases – it would make sense for those to recruit outside of Australia, as well.
- MRFF currently does not allow money to be used for overseas recruitment – this is a problem
- I am not sure why MRFF do not currently focus only on trials
- MRFF makes it challenging to spend money overseas – there is a 10% limit.

Other relevant comments

- Some international settings may not have relevance to Australia, because their health systems are quite different
- I support recruiting outside of Australia

1.5. Regulations – Detailed results

Did your trial have a Data and Safety Monitoring Committee?

For approximately three-quarters of respondents to the survey (74% for MRFF respondents and 73% for NHMRC respondents), a Data and Safety Monitoring Committee was in place.

Table 28 Did your trial have a Data and Safety Monitoring Committee?

	MRFF (n=210)		NHMRC (n=71)	
Yes	155	74%	52	73%
No	55	26%	19	27%
Total	**210**	**100%**	**71**	**100%**

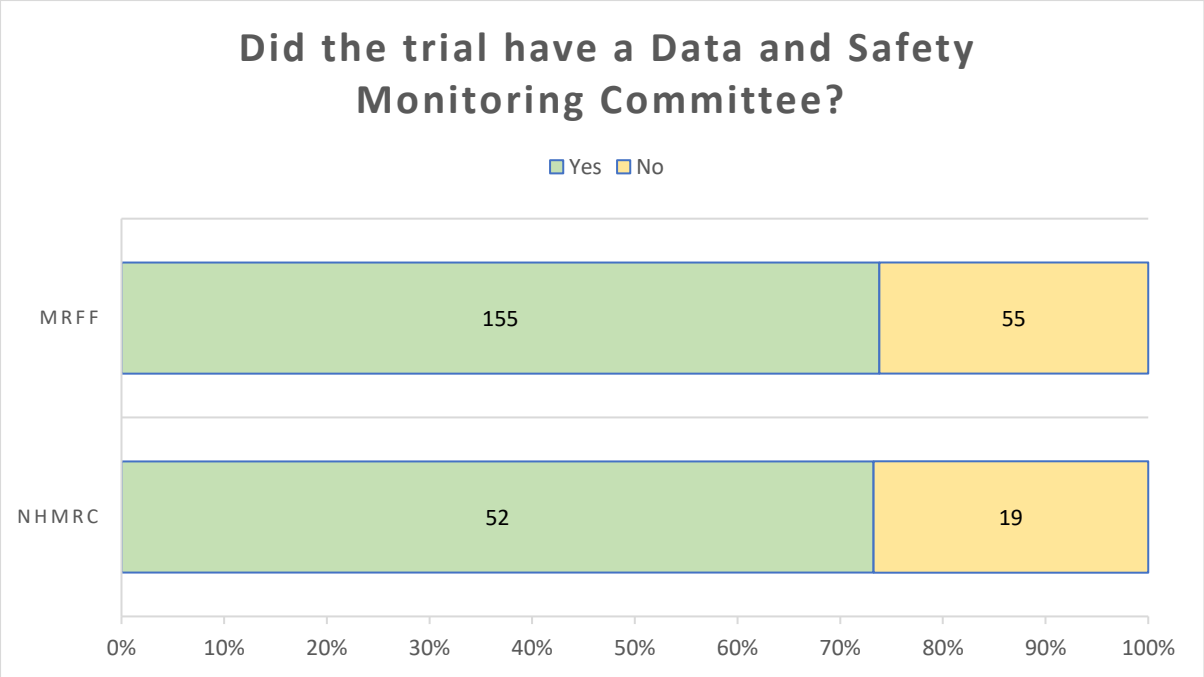


Figure 11 Did your trial have a Data and Safety Monitoring Committee?

What regulations or processes was your trial conducted under?

Most commonly, trials were conducted under TGA rules – 39% of MRFF survey respondents and 27% of NHMRC survey respondents stated that was the case for their trial.

Table 29 What regulations or processes was your trial conducted under?

	MRFF (n=214)		NHMRC (n=74)	
TGA	83	39%	20	27%
FDA	2	1%	3	4%
Other	6	3%	6	8%
N/A	119	56%	45	61%
Missing data	4	2%	0	0%
Total	**214**	**100%**	**74**	**100%**

As only 12 respondents in aggregate (MRFF and NHMRC survey respondents) provided additional detail, their responses have been amalgamated, and intervention- or condition-specific details suppressed to preserve anonymity. The examples provided, include:

- A specified country or countries under whose rules the trial is conducted (n=3)
- A particular organisation under whose rules the trial is conducted (n=1)
- CTN [Clinical Trial Notification] rule (n=2)
- Non-TGA approved intervention or agent (n=2)
- Investigational intervention or agent (n=1)
- Trial investigates drug/s that are within their licenced indication/standard of care (n=2)
- Trial has not yet started but will be conducted per TGA rules in the future (n=1)

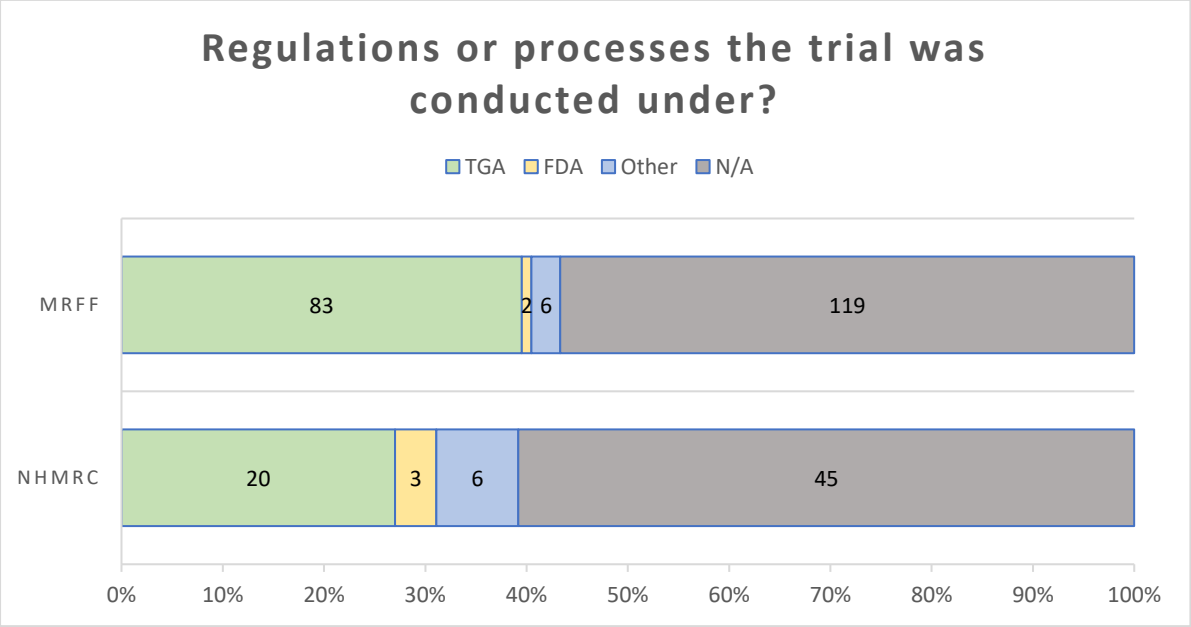


Figure 12 What regulations or processes was your trial conducted under?

Were any of the following rules in place for the trial?

Most commonly, MRFF survey respondents reported that there was an "other" rule in place (45%) or an early stopping rule (43%).

Most commonly, NHMRC respondents reported that there was an early stopping rule (46%) or an "other" rule in place (43%), in their trial.

Table 30 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%

The MRFF respondents who selected the "other" option and provided a text response (n=68), indicated the following rules in place (table, below):

Table 31 "Other" rules in place for the trial - MRFF

Response (MRFF respondents)	N
No	26
N/A	21
Adverse Events/Harms rule	8
Data Safety Monitoring Board advice	4
Trial not yet started/to be determined	3
Unsure	2
No interim analysis planned	2
None of the above	1
Unclear answer	1
Grand Total	**68**

The NHMRC respondents who selected the "other" option and provided a text response (n=21), indicated the following rules in place (table, below):

Table 32 "Other" rules in place for the trial - NHMRC

Response (NHMRC respondents)	N
N/A	9
No	4
Trial not yet started/to be determined	2
Statistical plan/thresholds	2
Safety	1
Adverse Events/Harms rule	1
Data Safety Monitoring Board advice	1
None of the above	1
Grand Total	**21**

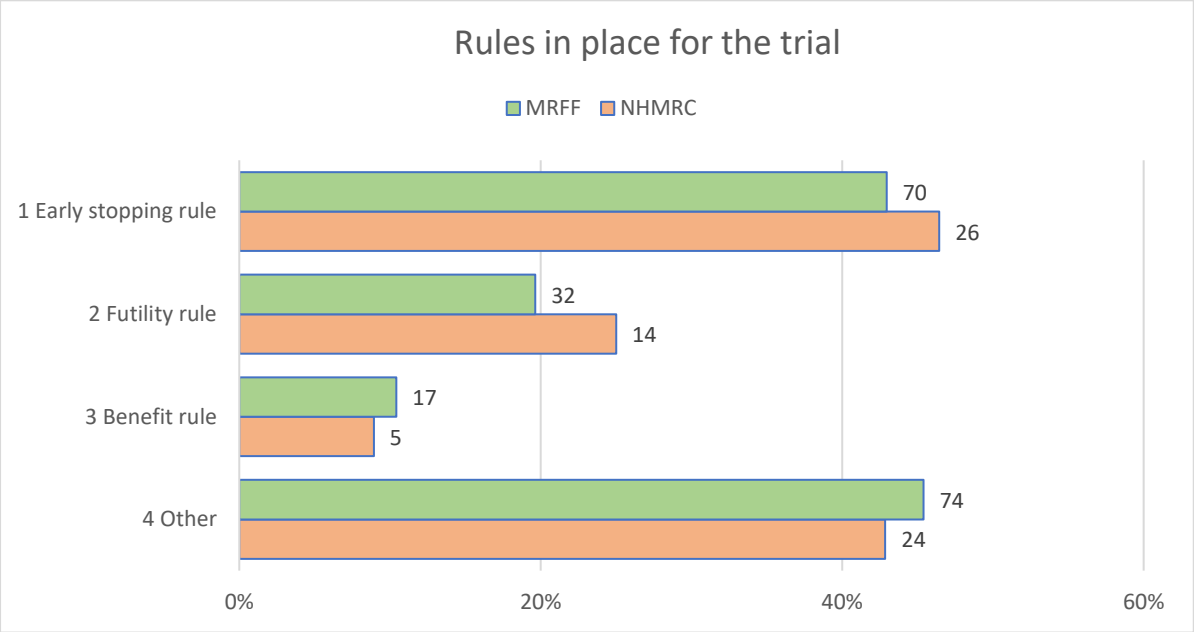


Figure 13 "Other" rules in place for the trial - MRFF & NHMRC

1.6. Study design – Detailed results

Randomisation

Study phase: Trial phase (0 to 4)

Desktop Review showed a large number of "not applicable" categorisations of phase for assessed trials, which made it difficult to compare the trial phases. This may be due to the number of drug research funded trials, which comprise, respectively: MRFF (41%), NHMRC (13%), NHMRC CTCS (39%), NIH (29%), and CIHR (24%). The phase-concept is not usually utilised in non-drug clinical trials.

Table 33 Trial 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**	

In the table below, the selection "not applicable" was omitted. The early research phases are 0, 1, and 2, whereas the later phases are 3 and 4. The NIH had the lowest proportion of late phase trials (18%), whereas the NHMRC CTCS had the highest proportion (81%). The MRFF (50%), CIHR (65%), and NHMRC (68%) fall somewhere in the middle.

Table 34 Trial phase - excluding "not applicable"

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Phase 0	2	2%	5	1%			428	6%	5	1%
Phase 1	7	7%	55	10%	1	5%	1947	27%	22	6%
Phase 1/Phase 2	4	4%	10	2%	1	5%	776	11%	19	5%
Phase 2	38	37%	111	20%	2	10%	2851	39%	86	23%
Phase 2/Phase 3	6	6%	34	6%	3	14%	182	3%	25	7%
Phase 3	34	33%	194	35%	6	29%	622	9%	131	36%
Phase 3/Phase 4	2	2%	34	6%	1	5%				0%
Phase 4	10	10%	115	21%	7	33%	470	6%	80	22%
Total	**103**		**558**		**21**		**7276**		**368**	

Blinding (masking)

Different groups could be blinded in trials, including participant, clinician/therapist, outcome assessors, data analysts and investigators. Blinding of all involved in a trial is preferred, but not always possible. The Desktop Review showed that the blinding of research participants was comparable between MRFF-funded and non-MRFF-funded trials, excluding NHMRC-funded trials. The NHMRC-funded trials had a larger percentage of blinding across all categories, particularly the outcomes assessor (88%) and data analyst (73%). The proportion blinded will vary by type of study, for example, drug trials are generally more readily placebo controlled and hence more readily blinded.

Table 35 Blinding (masking) of the trial participants and investigators

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	n/N	%	n/N	%	n/N	%	n/N	%	n/N	%
Clinician/Therapist	48/175	27%	285/713	40%	10/35	29%	1623/14095	12%	152/985	15%
Data Analyst	55/130	42%	517/713	73%	13/35	37%				
Investigator	14/45	31%					2967/14095	21%	260/985	26%
Outcomes Assessor	82/175	47%	624/713	88%	19/35	54%	3199/14095	23%	393/985	40%
Participant	58/175	33%	398/713	56%	13/35	37%	3470/14095	25%	287/985	29%

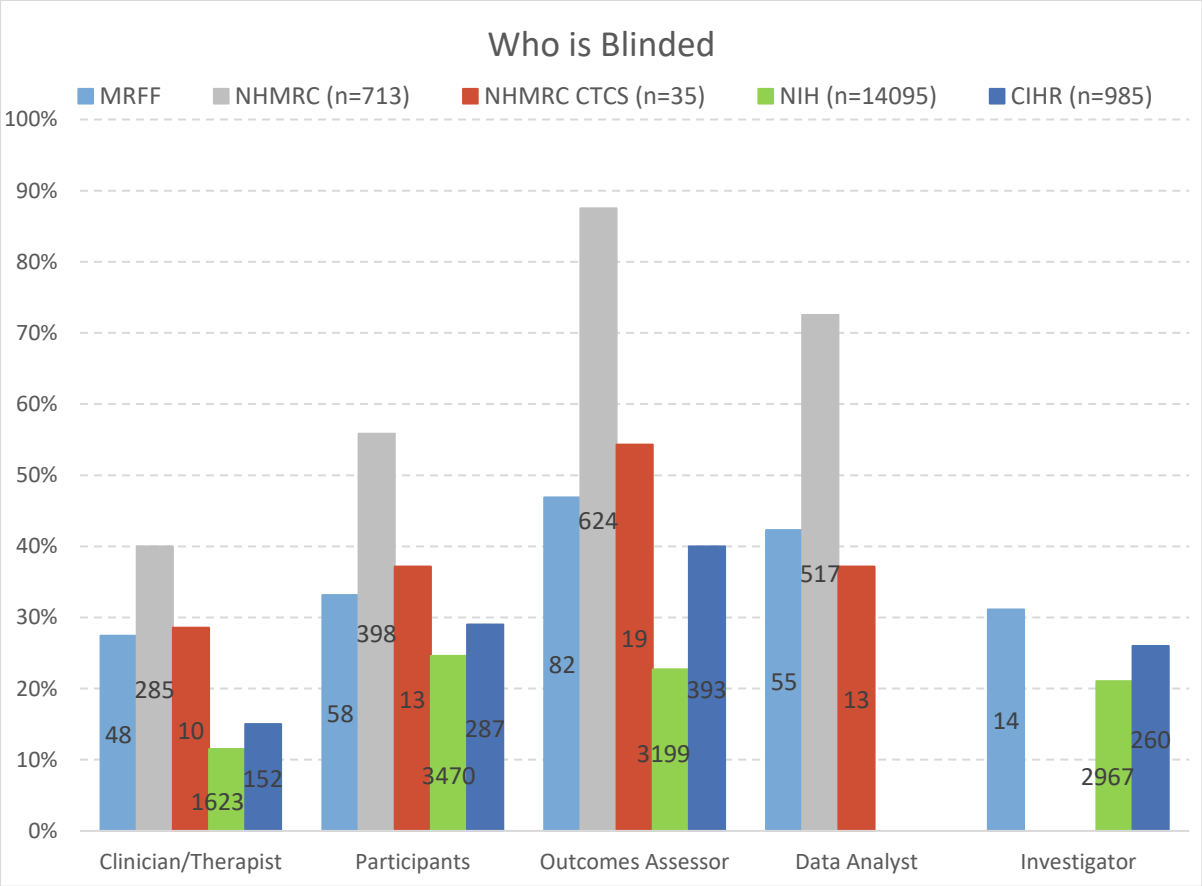


Figure 14 Blinding (masking) of the trial clinicians, participants, outcome assessors, analyst, and investigators

Allocation: randomised vs non-randomised

The Desktop Review showed that MRFF, NHMRC, and CIHR had comparable proportions of randomised and non-randomised trials (79% or higher). The proportions of NIH studies differed from other funders; only 62% of NIH studies were randomised trials, while 28% were not coded. Due to the limited number of studies available, comparisons with NHMRC CTCS trials were difficult to evaluate.

MRFF, CIHR, NIH, NHMRC and NHMRC CTCS had no record of adaptive trials, and only provided the following categories: 'Randomised', 'Non-Randomised' or 'Not Applicable'/'Null'.

Table 36 Method of allocation (randomised or not) of trial participants to the intervention

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Randomised controlled trial	141	86%	1650	79%	31	89%	8685	62%	828	84%
Non-randomised trial	23	14%	244	12%	1	3%	1437	10%	57	6%
Not Applicable	14	10%	183	9%	3	9%	3973	28%	100	10%
Total	**178**		**2077**		**35**		**14095**		**985**	

Type of randomized design

The Desktop Review showed that, for all funders, parallel group controlled trials were the most prevalent type of study design. MRFF-funded trials (71%) were comparable to the NHMRC CTCS (77%) and CIHR (72%). Notable was the smaller number of factorial designed trials (1%) in the MRFF, and it may be possible to increase this research type (other studies have 3-4% factorial-designed trials). As above, none of the trials records indicated that innovative trial designs – for example, adaptive or platform trials – were conducted. It is possible that trialists conducting adaptive or other innovative trial designs indicated this by selecting 'Other' or 'Not Specified' categories.

Table 37 Type of randomised design used by the trials

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Parallel	127	71%	1304	63%	27	77%	8010	57%	714	72%
Single Group	15	8%	127	6%	1	3%	4355	31%	135	14%
Crossover	5	3%	179	9%	2	6%	877	6%	84	9%
Factorial	2	1%	62	3%	1	3%	374	3%	38	4%
Sequential Assignment	3	2%					475	3%	12	1%
Other	6	3%	111	5%	2	6%				
Not specified	20	11%	294	14%	2	6%	4	0%	2	0%
Total	**178**		**2077**		**35**		**14095**		**985**	

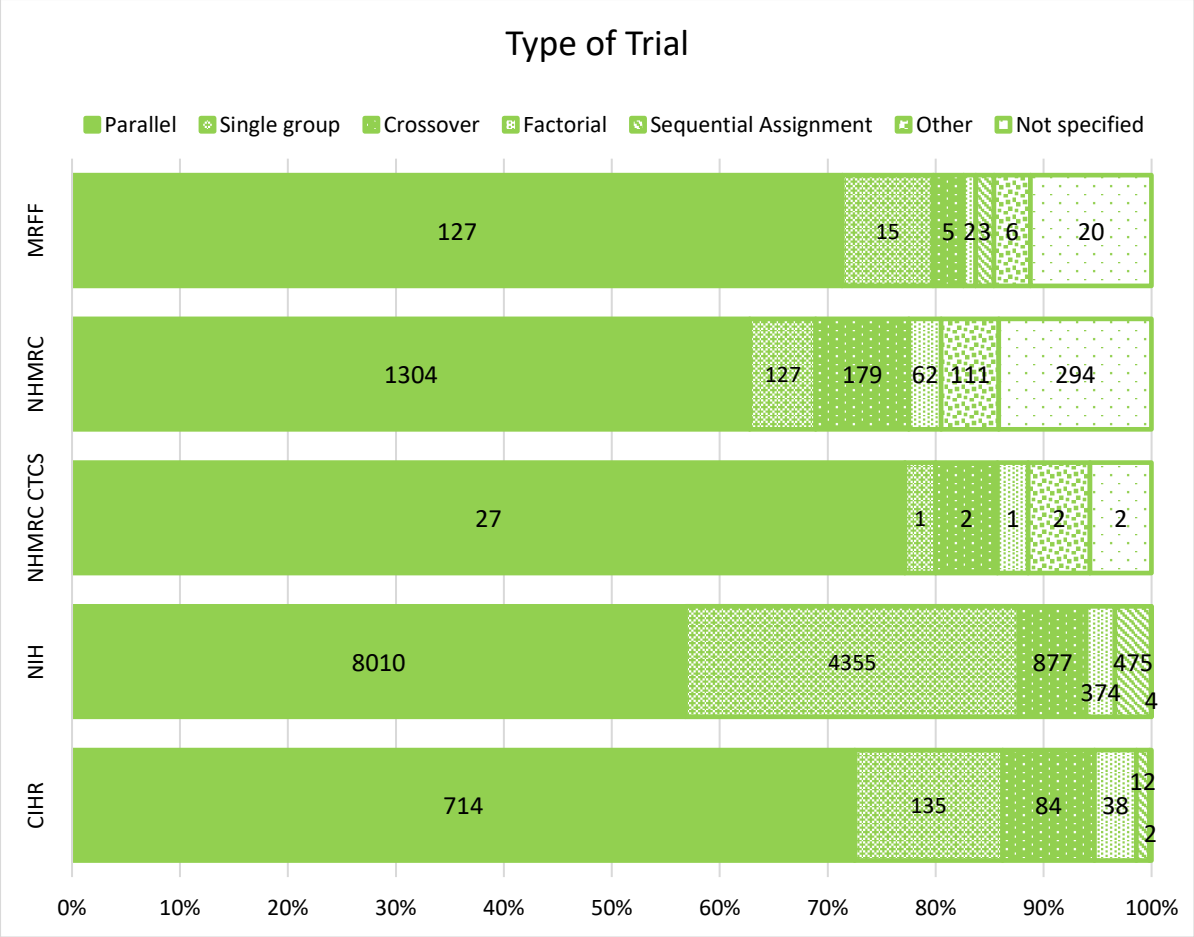


Figure 15 Type of randomised design used by the trials

What study design(s) does your trial use?

The survey respondents indicated that the most commonly used study design, for both MRFF-funded trials (59%) and NHMRC-funded trials (65%), was parallel. Factorial and crossover designs were used very infrequently (3% or less for both funders).

Table 38 What study design(s) does your trial use?

	MRFF (n=211)		NHMRC (n=74)	
Parallel	125	59%	48	65%
Cluster	19	9%	9	12%
Adaptive	14	7%	6	8%
Platform	11	5%	4	5%
Factorial	6	3%	1	1%
Crossover	7	3%	1	1%
Other (please specify which design)	53	25%	17	23%

To protect respondent anonymity, the responses provided under "other," by the MRFF and NHMRC respondents have been amalgamated. As some categories were identified by very few respondents giving rise to the possibility of reidentification, the numbers for each type of design are intentionally suppressed. The types of study designs reported, included (in alphabetical order):

- Before and after study
- Cohort study
- Cross sectional study
- Extension study
- Feasibility study
- Implementation study
- Multiple designs
- Non-controlled study
- Not a trial
- Observational (no further detail) study
- Phase 1 study
- Pilot study
- Pragmatic study
- RCT
- RCT nested within a study
- Registry study
- Single arm study
- Stepped wedge study
- Waitlist study

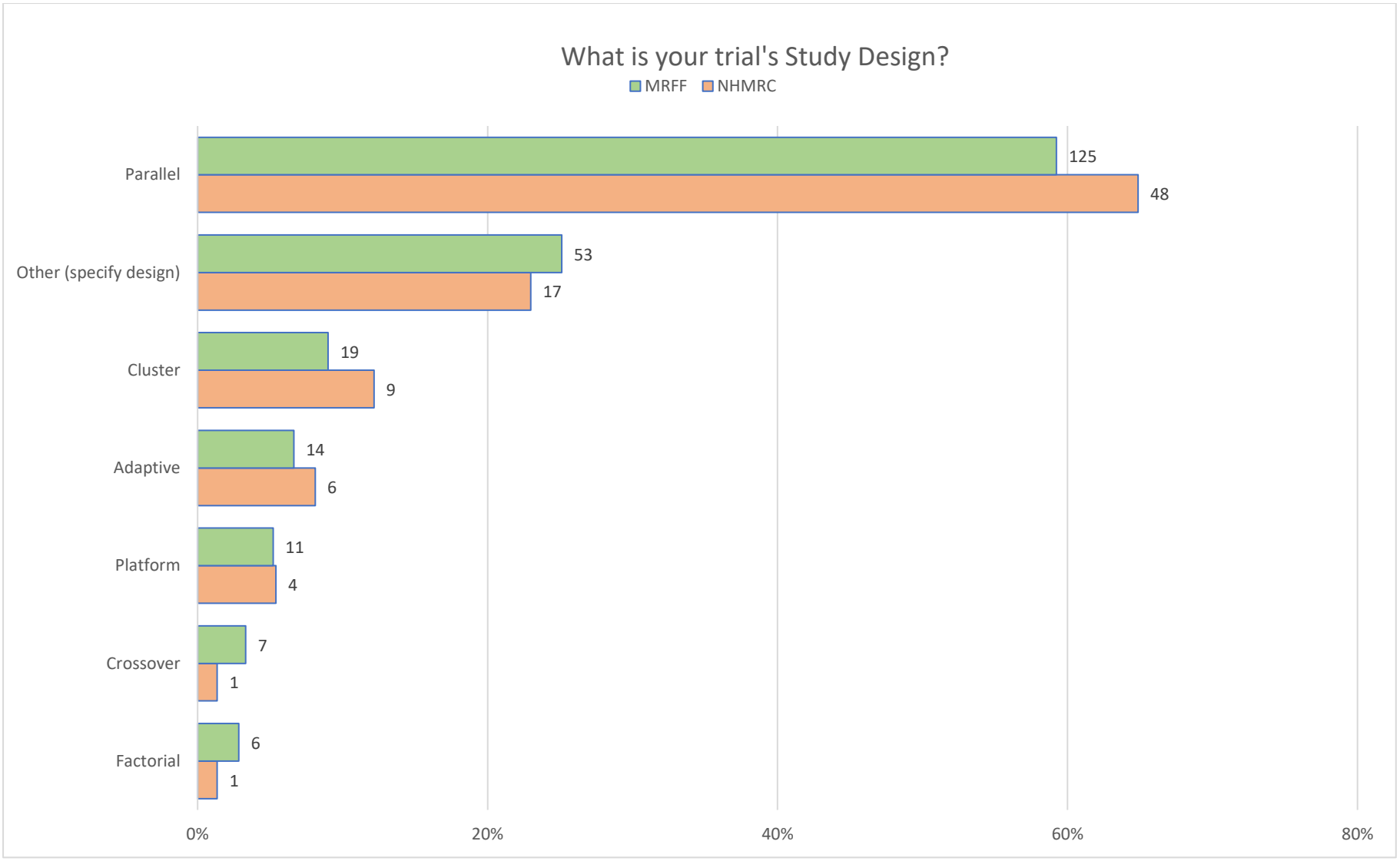


Figure 16 What study design(s) does your trial use?

Stakeholder comments on types of trial designs

The stakeholders were presented with two figures – one from the Desktop Review, showing the types of trial designs funded by the key funders, and one from the Survey Project, with the respondents' answers about their trial's design (figures below).

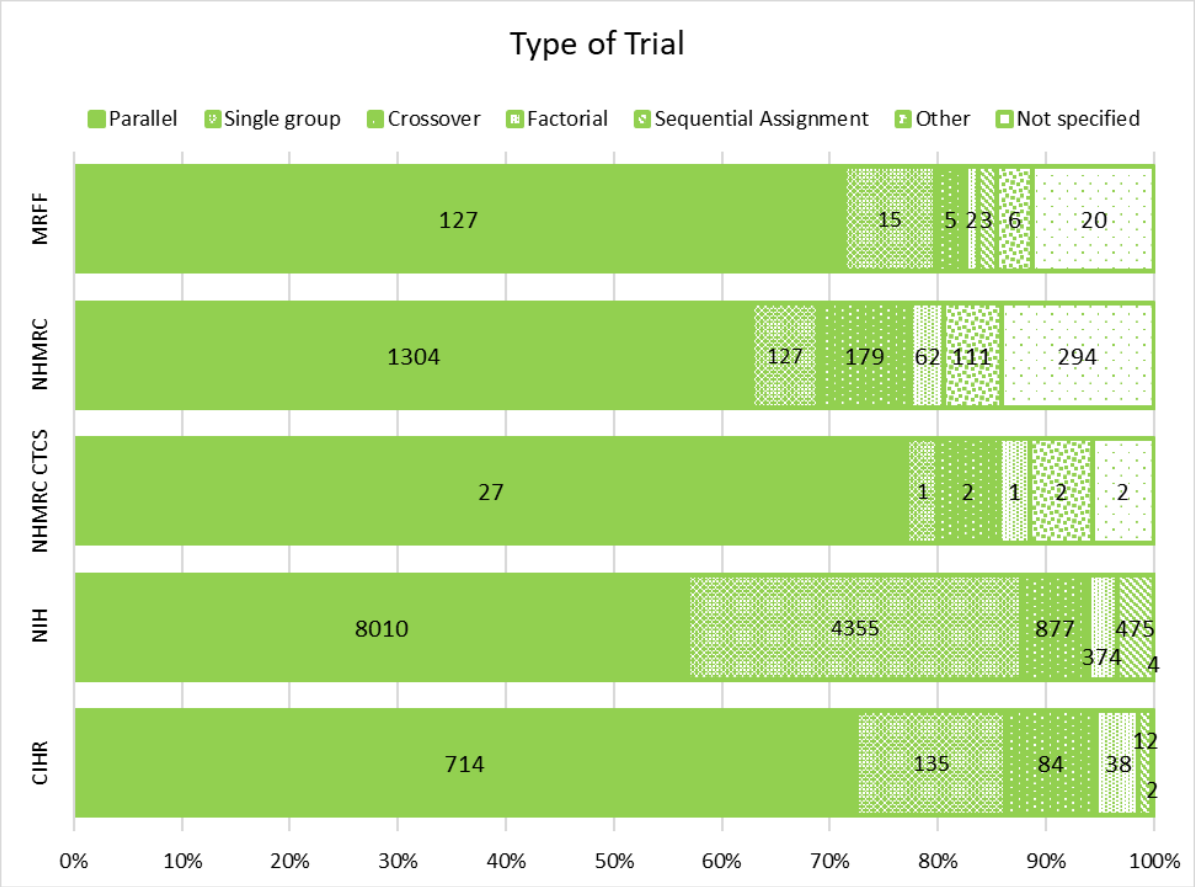


Figure 17 Desktop review: types of trial designs funded by the key funders

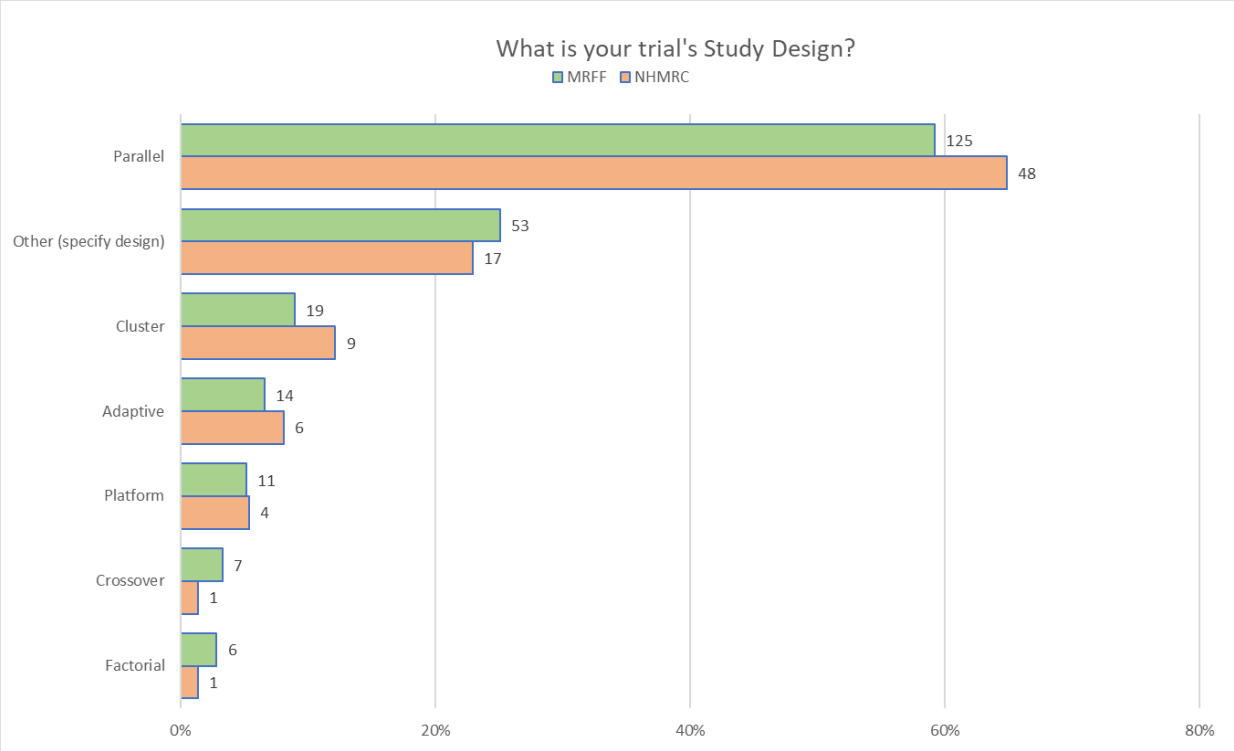


Figure 18 Survey data: types of trial designs whose CIs and EMCRs were funded by MRFF and NHMRC CTCS

The stakeholders' responses to the above data included: general observations about study designs that are – or are not – funded; and other, more general observations about the topic. The issues, comments or questions raised, included the following:

General observations about study designs that are/are not funded

- Not a lot of progressive trial designs are apparent here – adaptive, basket, umbrella, cluster trials
- MRFF sometimes has very targeted calls for research with short turnaround time. So the trial has to be ready "off the shelf", because there is not enough time to develop the idea, but a good platform or adaptive design requires a lot of time
- Trials seem forced to fit the narrow calls and some could be designed very differently to give a better understanding of the effect, but I suspect this does not happen because of the lack of lead time
- One would expect cluster trials for some of the studies we saw on the previous slide (behavioural, prevention type studies) – but there are fewer than one would think. Perhaps because people are still getting used to this methodology.
- Innovative design may not apply to all clinical areas (e.g. some neuro topics)
- Factorial trials seem to have decreased for some reason. But it is a really good design.
- Platform trials seem to be becoming popular
- It is good that some adaptive and platform trials got funded
- There are higher rates of funded platform and cluster trials than I was expecting
- I am not surprised by the factorial trials – there are very few indexed in Medline
- I am not surprised by the dominance of parallel trial since that is probably the easiest and most traditional way of performing clinical trials
- The number of trial designs other than parallel are probably a function of the patient population – numbers possible, ease of recruitment

- We should do more factorial trials – they are efficient. A lot of the efficiency in adaptive trials is that they are multifactorial. If a study is a multifactorial, it might as well be an adaptive platform trial.
- The number of single group trials is probably appropriate – these are good for studies first-in-patient

Other observations (technical, conceptual)

- There are limitations to the labels that are attached to studies in the registries – so this may not be that helpful
- Some applications will claim to be for innovative trials when they are not, in reality
- There is probably some redundancy between platform and factorial trials – there is some imprecision in terminology here
- It is difficult to identify the investigator grants that also support clinical trials activity
- There are probably a lot of little trials happening – that can lack power or the appropriate expertise/skill-set. Some way to help people to collaborate better would be helpful
- MRFF has a program that funds an initial stage, and if that is successful at the end of a year, it is reviewed and if all is well, the project gets more funding. It is a program to get pilot data to set up the collaborations

Stakeholder awareness of innovative trial designs

No data was presented as part of this question.

The stakeholders were aware of a large variety of innovative trial designs, with the largest number of stakeholders identifying adaptive and platform trials (8 each). (See Table, below).

Table 39 Stakeholder awareness of innovative trial designs

Trial design	Number of respondents
Adaptive	8
Platform	8
Cluster	4
Crossover	2
Investigator Grant	2
Stepped Wedged designs	2
Bayesian frameworks	1
Factorial	1
Hybrid Effectiveness Implementation	1
Parallel	1
Precision Medicine trial	1
Umbrella	1

Are there ways MRFF could better support use of innovative designs?
No data was presented as part of this question.

The stakeholders' responses to this question included both specific suggestions for support mechanisms, and general observations relevant to this question. The issues, comments and questions raised, were as follows:

Specific suggestions for support mechanisms

- Explicitly requesting these types of designs – e.g. through a dedicated round, or by scoring them differently
- MSAC [Medical Services Advisory Committee] deliberations that result in a reject decision or uncertainties could be channelled to MRFF funding calls – some have already been
- Adaptive trials have a long lead time because of their complexity. But the funding cycle is a 5-year cycle rather than longer-term
- Before a grant is submitted, $100-200k of planning money is needed – but finding those pots of money is not easy, compared to e.g. $10k pots of money and million-dollar sized pots of money
- If MRFF would like to fund adaptive trials, it should be focusing on conditions that are appropriate for this – those of highest importance for public health
- An iterative gate-keeping process, e.g. some (planning) money for the simulations, then a formal application process, then a 18-24 month period to setup the infrastructure. If the project is not set up at that stage – it ceases. This process would require more of a collaboration between the funder and the researcher team.
- NIHR have a system for funding these kinds of trials
- Equitable and transparent management is critical to the success of big adaptive platform trials – they require a governance structure in place, to decide what treatments will be evaluated, rather than leaving this decision to a small number of investigators who received the grant
- NHMRC funding averages ~2.5M dollars, so these are not likely adaptive trials, because those cost more or a lot more. A quarantined pot of funds for these types of projects might be helpful.

General observations

- Is there a reluctance to take on new approaches, e.g. adaptive trials, platform trials?
- Studies that use routine data sources would also have a different design
- The key is asking an important question – and then, using the best study design for answering it
- Registry studies could be another type of innovation – e.g. connecting the TGA data on adverse events and health insurance data and clinical outcomes, resulting in a single registry of all of this data in one place
- Adaptive trials were highlighted as valuable during the pandemic – they are 5-10x more efficient (cost-wise) per question answered than conventional trials – and this could probably increase to 20x more efficient

Population

Target Study size

Of all the funders considered, the Desktop Review showed that 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). This is somewhat larger than the entire set of NHMRC funded studies (15%, 310 trials) and the CIHR (13%, 126 trials).

Table 40 Target size of the trial

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
<100	36	20%	616	30%	2	6%	8541	61%	395	40%
100-299	57	32%	676	33%	8	23%	3010	21%	268	27%
300-999	58	33%	475	23%	11	31%	1723	12%	193	20%
>1000	28	16%	310	15%	14	40%	820	6%	126	13%
Total	**179**		**2077**		**35**		**14094**		**982**	

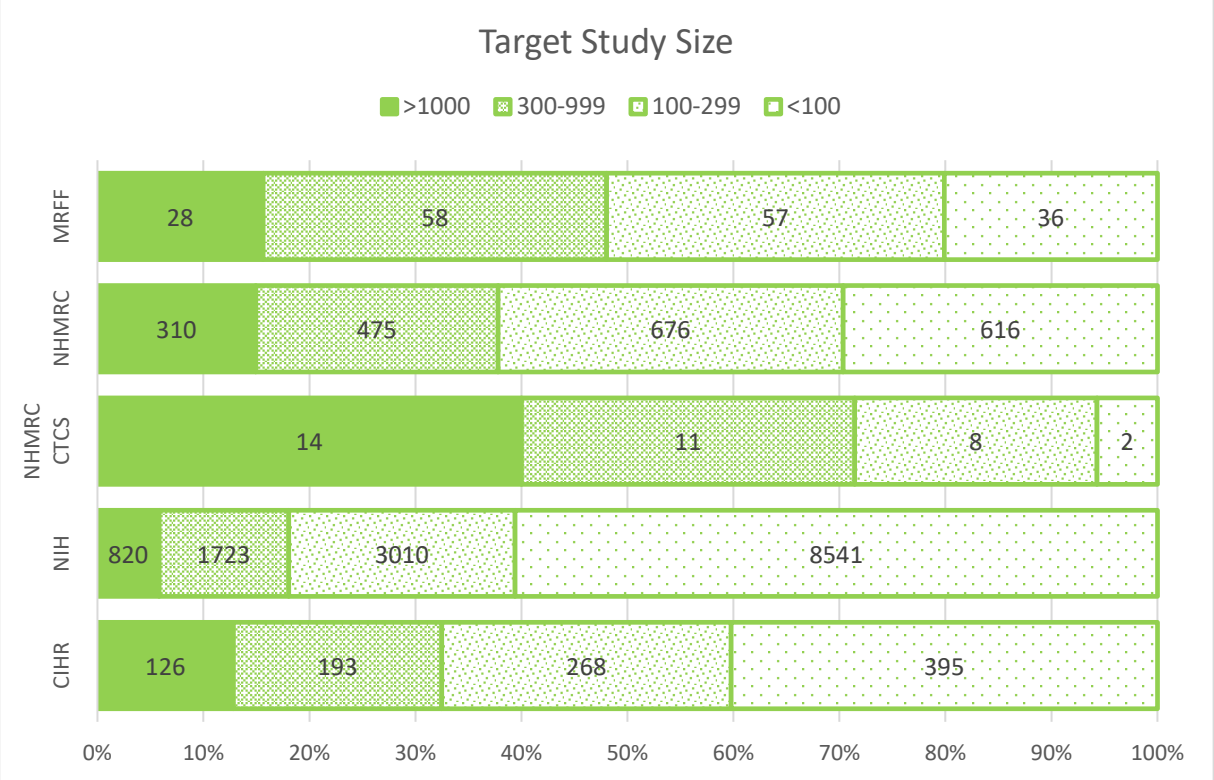


Figure 19 Target size of the trial

Stakeholder comments on study sizes

The stakeholders were presented two figures as part of answering this question: first, a cropped version of the full figure, presenting MRFF data only; second, the full figure, showing MRFF in comparison to other funders. The figures are reproduced below.

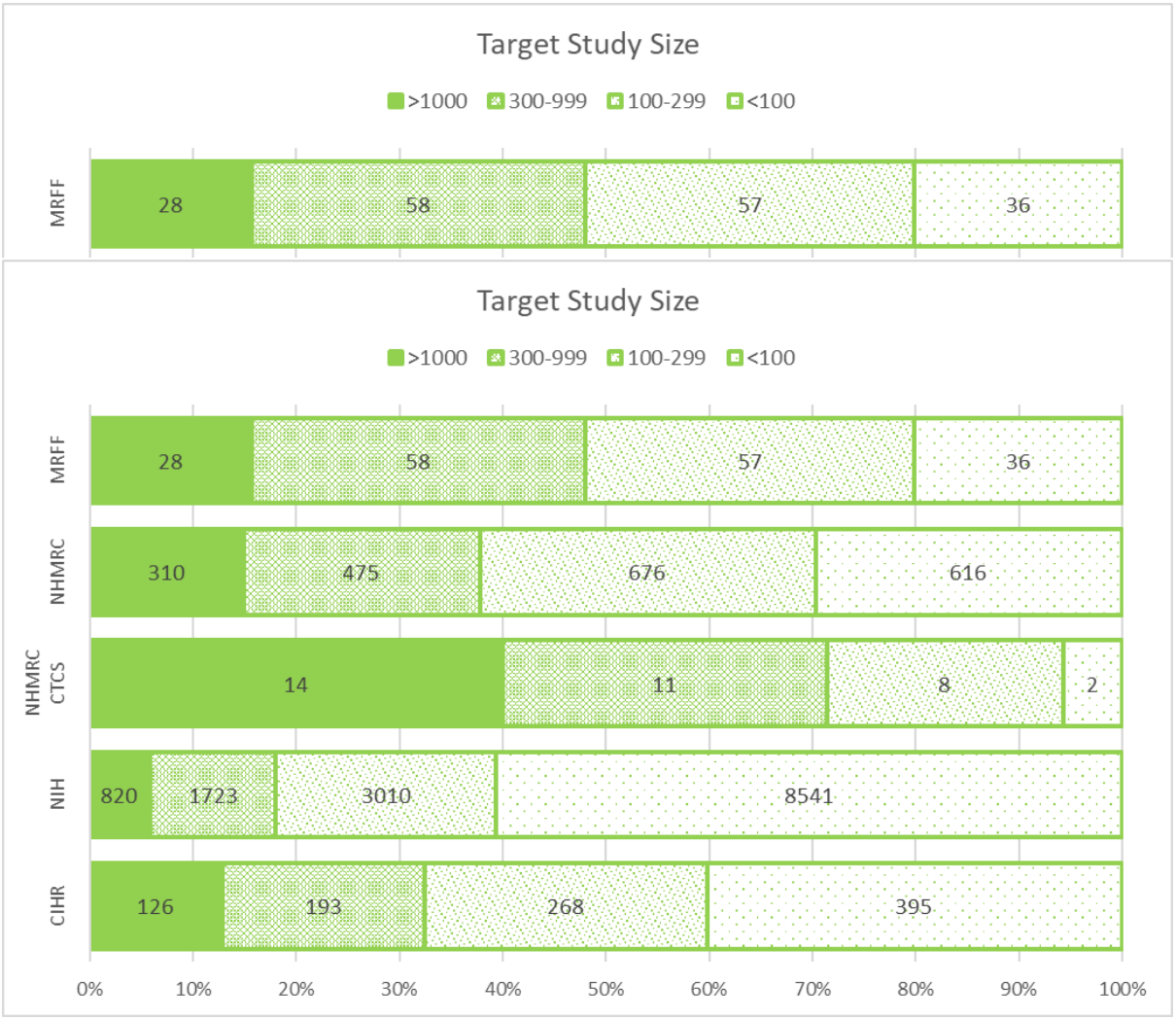


Figure 20 Data presented to stakeholders on study sizes

The stakeholders' responses fell into two categories: observations about the sample sizes of the trials funded by individual funders or comparisons between funders; and explanations of the patterns observed in the presented data. The following issues, comments or questions were mentioned:

Observations about individual funders/comparisons between funders

- There is consistency between MRFF, NHMRC and CIHR (several stakeholders made this observation)
- The numbers are surprisingly similar [across funders]
- The pattern (across funders) looks essentially the same. CTCS is the only outlier – it seems to be funding larger trials
- Study size for NIH is quite small
- The number of smaller studies at CIHR is surprising
- I thought MRFF has funded more studies
- Canadians generally get things right, and it is interesting that it is a close match to the MRFF

Stakeholders' explanations of the patterns in the presented data

- NHMRC CTCS is probably skewed because of the cohort studies
- NIH trials probably not recruiting too many patients
- In Australia and NZ, clinical trials are getting smaller over time, shifting toward earlier stage trials (phase 1, 2) so this (pattern) is not surprising
- How many people you need in a trial depends on the hypothesis – so bigger is not necessarily better, a small trial may be appropriate
- The size depends on whether the trial is designed for superiority, equivalence or non-inferiority
- Sample size depends on the effect size and the uncertainty about it – strict number (alone) does not mean that much
- NIH trials include smaller pilot trials, and adaptive designs which do not need as many people
- NIH have a lot of different schemes, so there may be a greater likelihood of pilot studies being done, explaining the small sizes
- Phasing would be more interesting than study sizes
- Unless the trial is large, it is hard to get NHMRC funding
- NHMRC are mostly at least 300 – this is surprising, suggesting very few studies are being funded based on sample size factor
- Sample size alone does not take into account how many are needed to answer the question – when you need a large sample size, the study is looking for very small treatment effect. So important questions that may require smaller sizes may be left out.
- The phasing language (phase 2, 3) maps onto drug trials but not too well for non-pharmacological trials
- The sample size is interpretable in terms of whether it is intended to be practice-changing or not
- Larger trial size is needed for events that are rare

Age

The minimum age of study participants was specified by nearly all trials. The Desktop Review showed that there is no comparable difference between the MRFF-funded and the non-MRFF-funded studies.

Table 41 Minimum age of study participants

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
0-17 Years	42	24%	418	20%	7	20%	2142	15%	170	17%
18-64 Years	128	72%	1400	67%	24	69%	11156	79%	704	71%
65 Years and older	2	1%	87	4%	1	3%	266	2%	38	4%
Not Specified/No limit	6	3%	172	8%	3	9%	531	4%	73	7%
Total	**178**		**2077**		**35**		**14095**		**985**	

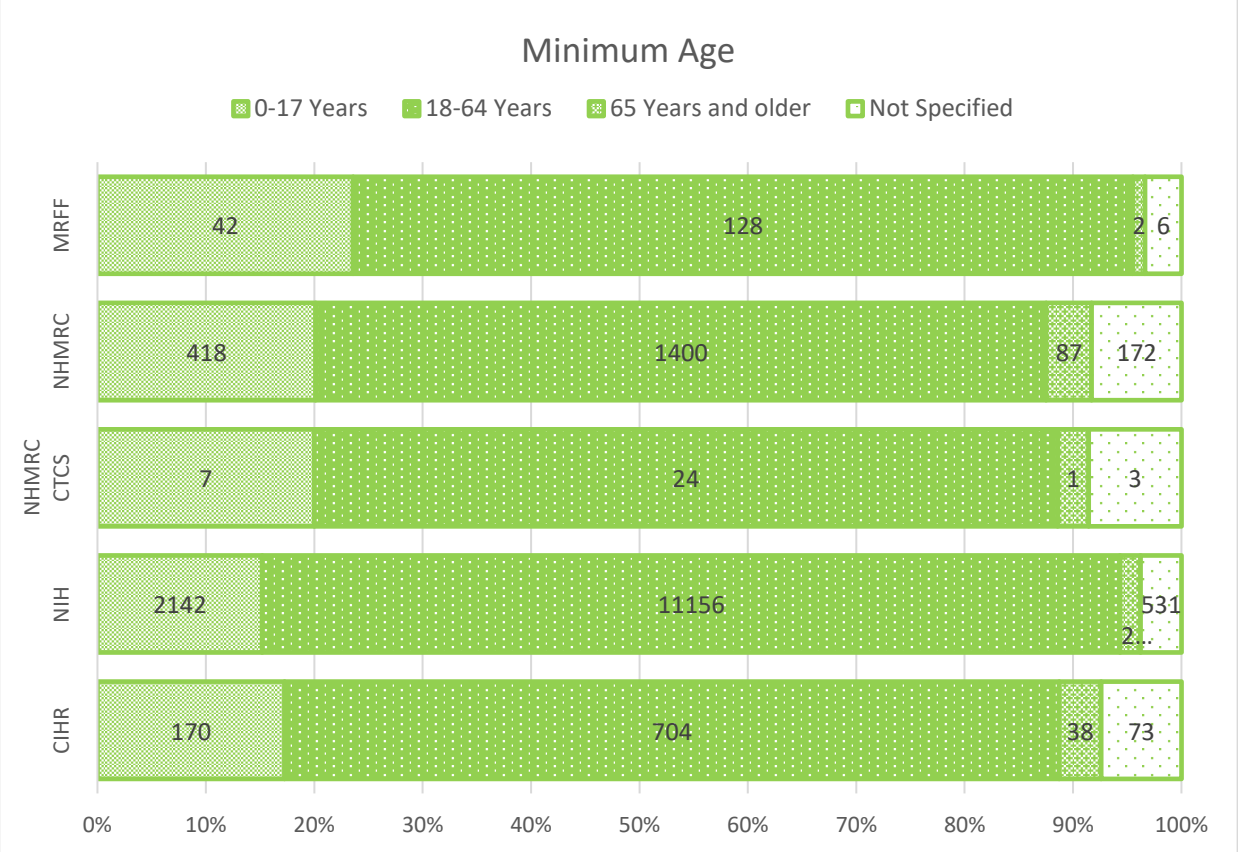


Figure 21 Minimum age of study participants

The trials frequently did not specify the maximum age of study participants, with more MRFF-funded trials not stating the maximum age (67%) than trials funded by comparable funders: NHMRC (55%), NHMRC CTCS (54%), NIH (53%), and CIHR (58%), according to the Desktop Review. This is a favourable characteristic because it implies that the MRFF studies may include a broader range of age groups. Furthermore, the MRFF funds only 6% in Paediatric age-group (0-17 years), which is comparable to the NIH, but lower than the NHMRC (10%), CTCS (20%) and CIHR (9%).

Table 42 Maximum age of trial participants

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
0-17 Years	11	6%	207	10%	7	20%	881	6%	91	9%
18-64 Years	26	15%	288	14%	4	11%	2662	19%	148	15%
65 Years and older	22	12%	448	22%	5	14%	3093	22%	177	18%
Not Specified/limit	119	67%	1134	55%	19	54%	7459	53%	569	58%
Total	**178**		**2077**		**35**		**14095**		**985**	

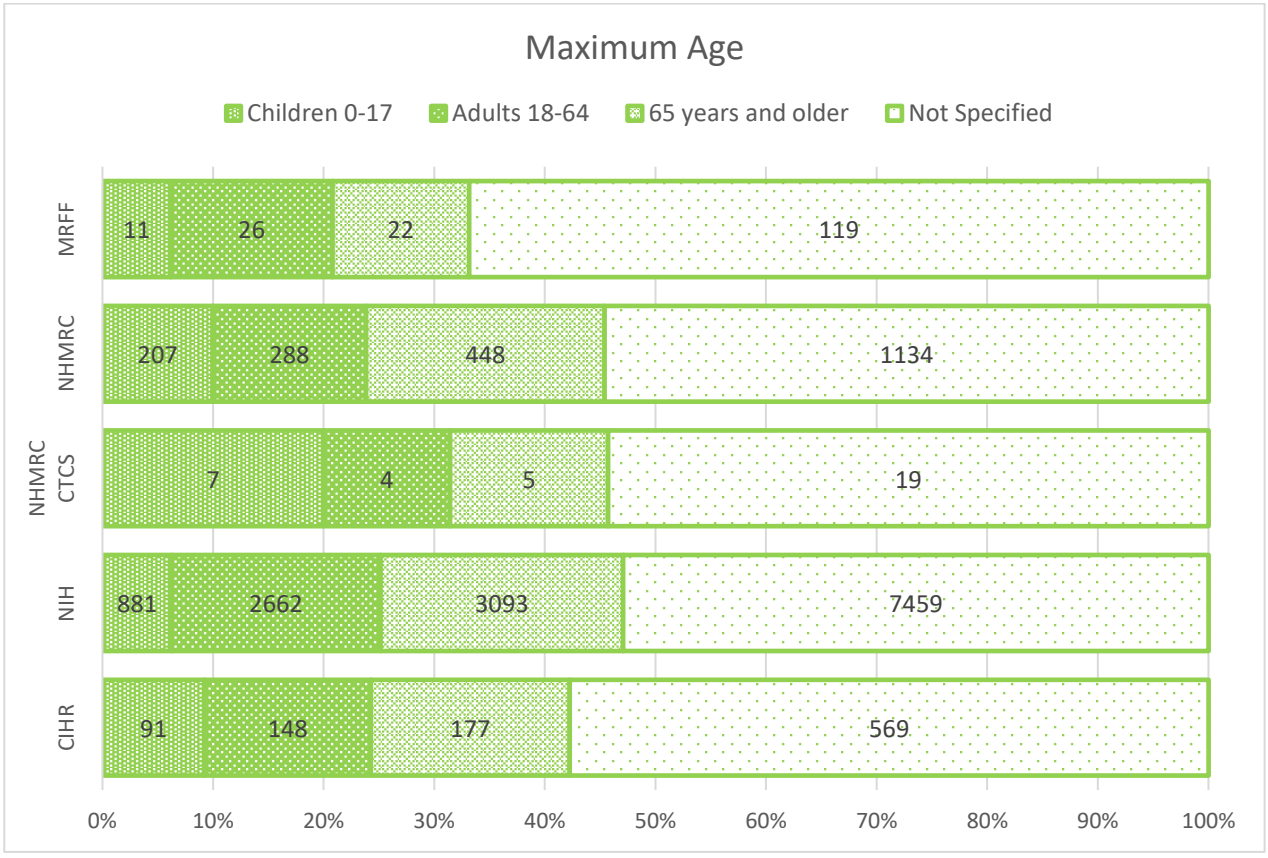


Figure 22 Maximum age of trial participants

Gender

The gender distribution of participants in MRFF-funded and trials funded by compared funders was comparable. Desktop Review found that >80% of both MRFF-funded and non-MRFF-funded studies were relevant to both men and women. For all funders, the proportion of female trials to male trials was larger. This is most likely due to reproductive studies, as supported by the number of studies in the Condition Code.

There was one participant in NIH whose gender was classified as 'not applicable'. All the other studies had no missing data and described the groups as 'Males,' 'Females,' or 'Males and females.' Therefore, the non-binary category was not included in the analysis.

Table 43 Gender of trial participants

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Males	5	3%	95	5%	0	0%	553	4%	44	4%
Females	23	13%	175	8%	3	9%	1401	10%	113	11%
Males & females	149	84%	1806	87%	32	91%	12140	86%	827	84%
Total	**177**		**2076**		**35**		**14094**		**984**	

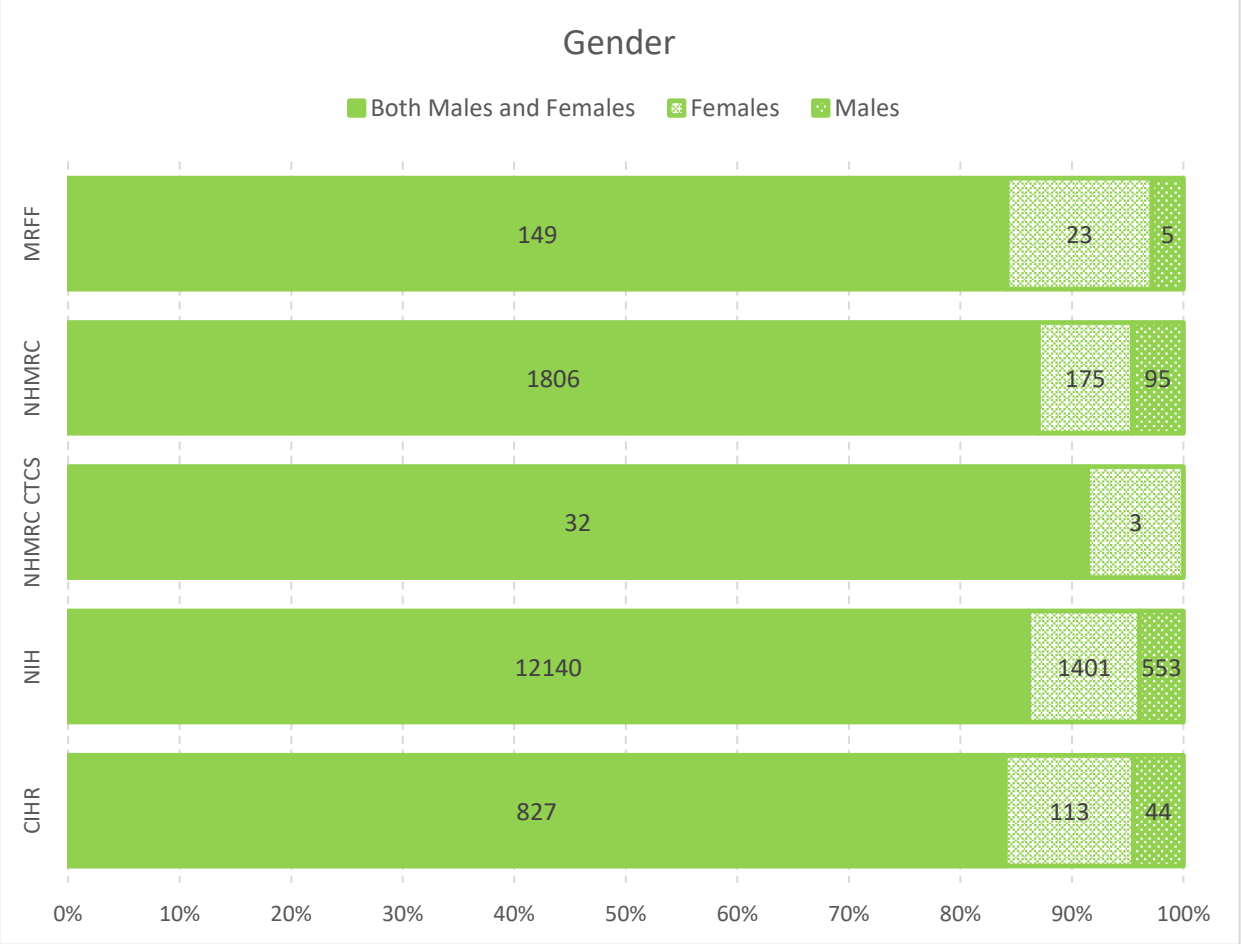


Figure 23 Gender of trial participants

Conditions Studied

The name(s) of the disease(s) or condition(s) researched in the clinical trial, or the focus of the clinical study, is the 'Condition'. The conditions studied were extracted from the clinical trials standard MeSH (Medical Subject Headings) keywords using an internal algorithm on the AACT website.

Desktop Review found that, in terms of conditions studied, the MRFF-funded and 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%). The MRFF funding of cancer is challenging to compare with other international funders because the funding could come through other streams and the large proportion of cancer-focused trials may be explained by cancer being one of the key areas of investment for MRFF.

Table 44 Condition code for the patients being treated, into which the trial is categorised

	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**	

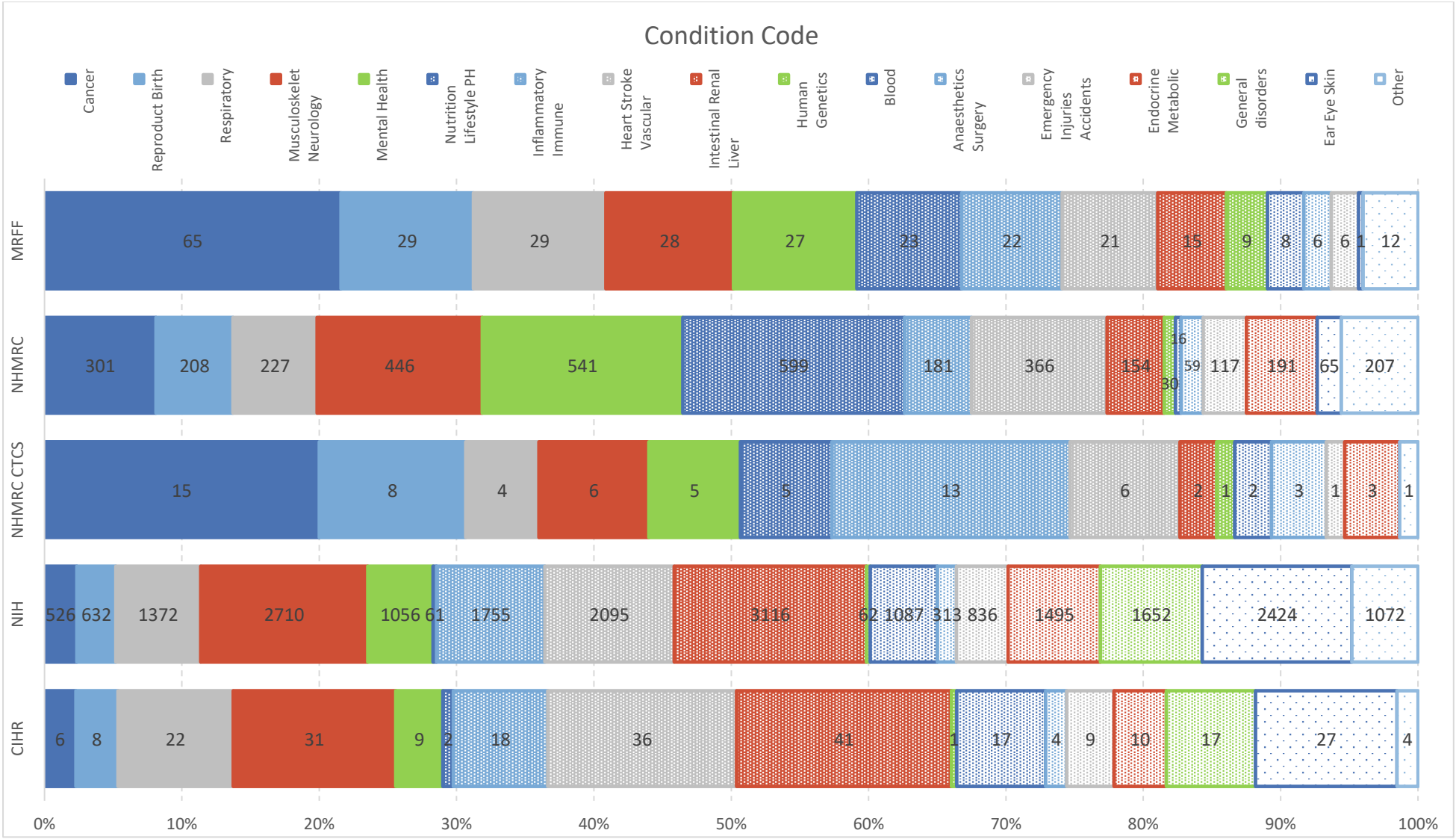


Figure 24 Condition code for the patients being treated, into which the trial is categorised

If your trial involved both Australian and non-Australian (overseas) research sites, what percentage (%) of your trial participants were/will be recruited within Australia?

The most common response – by 74% of MRFF respondents and 54% of NHMRC respondents to the survey – was that the trial involved only Australian (100% Australian) research sites.

Table 45 Percentage of Australian participants in your trial (international trials)

	MRFF (n=213)		NHMRC (n=74)	
100% Australia	158	74%	40	54%
75-99%	18	8%	12	16%
50-74%	14	7%	16	22%
25-49%	24	11%	6	8%
Total	**213**	**100%**	**74**	**100%**

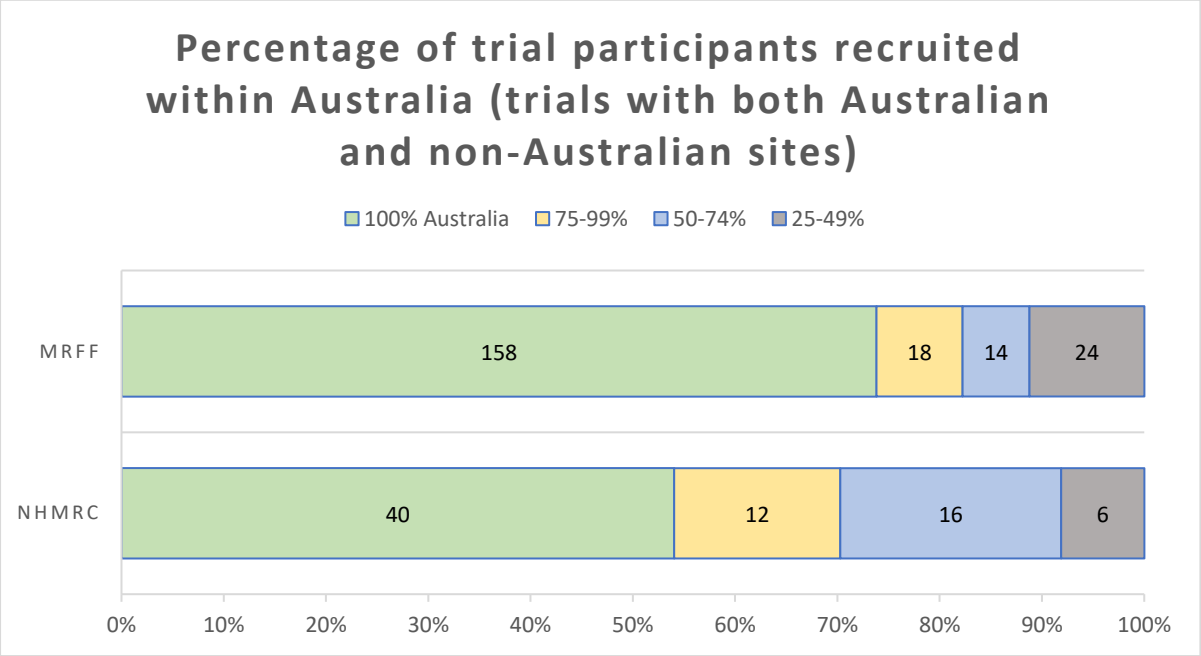


Figure 25 Percentage of Australian participants in your trial (international trials)

Are there ways that the MRFF clinical trial initiatives could better support (establish and/or participate in) multi-site studies and/or multi-national (international collaborations)?

The stakeholders were presented with information about the percentage of trial participants within Australia (survey data).

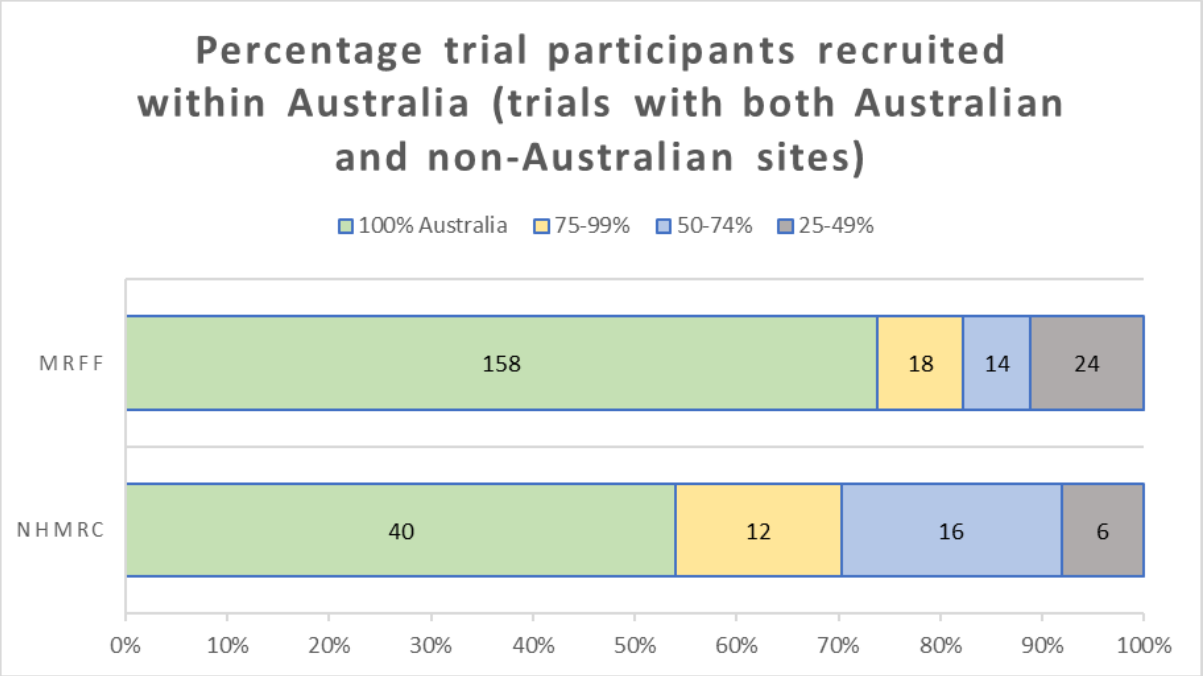


Figure 26 Percentage of Australian participants in your trial (international trials) - presented to stakeholders

In response to the above data, the stakeholders made suggestions about support arrangements, and made other relevant comments. The issues, comments or questions raised, included:

Suggestions for support arrangements

- NHMRC has an arrangement with the UK, where if a trial is funded in the UK, an Australian collaborator can apply to NHMRC for funding for an Australian site, if the trial is a good project – MRFF could look at this model. This would require lifting the 10% rule, which is currently a barrier
- Multi-site trials could be supported by allowing in the budgets more realistic amounts for site setup staffing
- The MRFF panels currently make the decisions whether the budget amount is appropriate with decisions varying considerably about what is or is not appropriate. It is inappropriate for the scientific review panel to be making these decisions – MRFF should take the budget decision away from the review panel
- Greater MRFF involvement in international trials could result in research that is more valid – this could be accomplished by relaxing the rules around international trials to encourage them.
- Multi-site studies improve generalisability of the results, but it is not certain whether a specific funding stream is required - it could be part of peer review/panel assessment

- Small countries (e.g. NZ) tend to be more open to this, as they recognise that they need to be a part of a global collaboration
- There are always human resource constraints – it is difficult to interest [disease area] trainees interested in research, because clinical practice is better paid. We need more paid clinician-researchers. We need better ways to address this in terms of both finances and protected time. MRFF could have practitioner-fellows and fund them appropriately.
- The MRFF should be seeking as much as possible, collaborations with as many sites as possible – this would have the benefit of creating national access to investigators, no matter where one is located
- The results are not surprising, because MRFF does not send money overseas – whereas the NHMRC does allow this.
- MRFF could start specific trial schemes requiring partnership with an overseas partner. NHMRC has a scheme like that, partnering with Singapore, US, and UK

Other relevant comments

- R&D tax incentive has led to a large growth in organisations setting up in Australia to do clinical work, in the last 10 years
- The NHMRC used to have a rule that money could not be paid to overseas site – that was a disincentive
- One Stop Shop is waiting on Ministerial approval at the moment – there is a role for government in helping with some of these issues
- For multi-national trials, getting the first site/country funded, makes it more likely to get the next one funded – but getting the first one is very challenging
- More recognition is needed, that big questions will need multiple funders
- Big multi-national studies answer important questions that cannot be answered in a single country
- Some population groups are excluded from studies, because it is too hard and too expensive

Do you see any role for the funders, such NHMRC and MRRF, or for the Departments of Health (State or Federal), to assist with these trial conduct issues? Have you seen examples of this elsewhere?
No data was presented as part of this question.

The stakeholders offered suggestions for ways that funders can assist with these trial conduct issues, and made other relevant comments, raising the following issues, comments or questions:

Suggestions for ways that funders can assist

- The MRFF and NHMRC can assist by establishing clinical trial networks, and funding them to recruit core staff (e.g. trial coordinators). This could also bypass University constraints, which mandate annual contracts, even if grants are funded for 5 years.
- The funders should remove the budget decisions from the review panels, and assign them to experts in clinical trial conduct. The panels should review the scientific quality, and possibly the appropriateness of staffing, but not the dollar amount.
- Many trialists feel they are better at recruitment than they actually are. Funders could assist here, e.g., around consumer education around clinical trials. They could educate the public to be more willing to become participants – that could be a role for the funders.
- MRFF and NHMRC can assist with setting up clinical trial units, but it may be more appropriate for the Department of Health to make the policy decision first [about the funding mechanism for those units], and MRFF and NHMRC could assist with the implementation of this

Other relevant comments

- CIHR has SPOR grants, which funded great initiatives – MRFF and NHMRC could look to this.
- The MTPConnect is a great programme for workforce development, as well as the funding to support the clinical trials networks

Does your trial include participants from any of the following [vulnerable] populations?

In response to this survey question, the MRFF investigators reported involving, most commonly, Australians from regional/rural/remote areas (59%), and culturally and linguistically diverse populations (53%).

NHMRC investigators reported involving most commonly, Australians from regional/rural/remote areas (42%) and children/young people (38%).

Table 46 Does your trial include participants from any of the following [vulnerable] populations?

	MRFF (n=193)		NHMRC (n=69)	
Women who are pregnant and the developing foetus	19	10%	17	25%
Children/young people	46	24%	26	38%
Aboriginal and/or Torres Strait Islander people	80	41%	23	33%
Culturally and Linguistically diverse populations	102	53%	25	36%
Regional, rural, remote Australians	114	59%	29	42%
People in dependent or unequal relationships	41	21%	9	13%
People highly dependent on medical care who may not be able to give consent	25	13%	10	14%
People with cognitive impairment, intellectual disability, or mental illness	45	23%	17	25%
People who may be involved in illegal activities	13	7%	8	12%
People who live in other countries	21	11%	21	30%

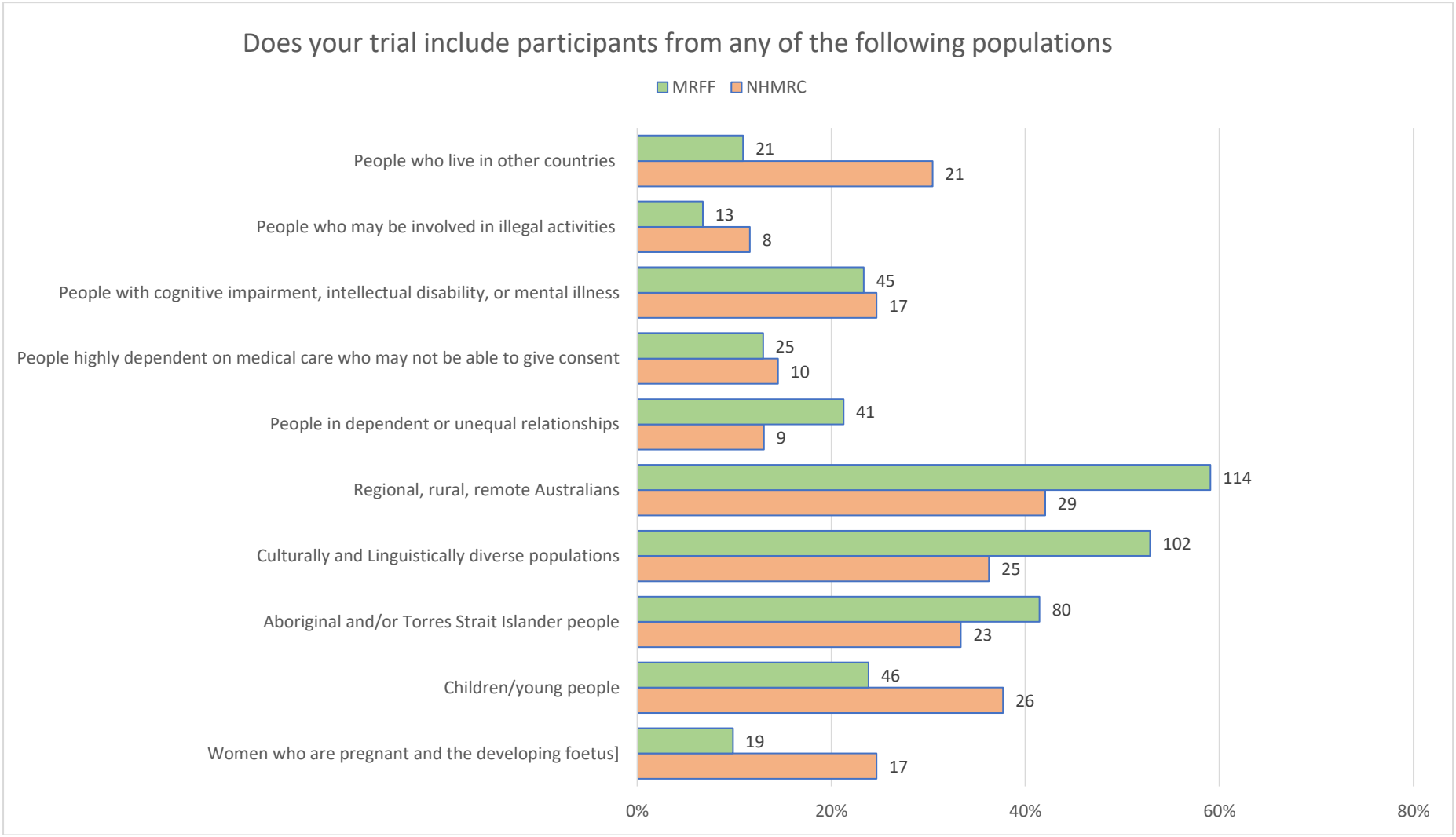


Figure 27 Does your trial include participants from any of the following [vulnerable] populations?

Intervention

Trial purpose

In terms of the trial purpose, the Desktop Review found that similar proportion of trials aimed to evaluate treatment, education/counselling/training, and diagnostic interventions across funders. The MRFF-funded trials had a higher number of treatment-focused research (67%) compared to the trials funded by the NHMRC (56%), NHMRC CTCS (64%), NIH (53%), and CIHR (52%). MRFF-funded research was slightly less prevention-focused (20%) than non-MRFF: NHMRC (23%), NHMRC CTCS (30%), NIH (14%), and CIHR (22%).

Table 47 Trial purpose classified in 5 categories

Trial Purpose	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Treatment	119	67%	1159	56%	21	64%	7460	53%	493	52%
Prevention	35	20%	472	23%	10	30%	2007	14%	207	22%
Educational/counselling/ training	9	5%	188	9%	2	6%	778	6%	3	0%
Diagnosis	4	2%	75	4%	0	0%	604	4%	28	3%
Other/Not specified	11	6%	183	9%	2	6%	3246	23%	226	24%
Total	**175**		**2077**		**35**		**14095**		**957**	

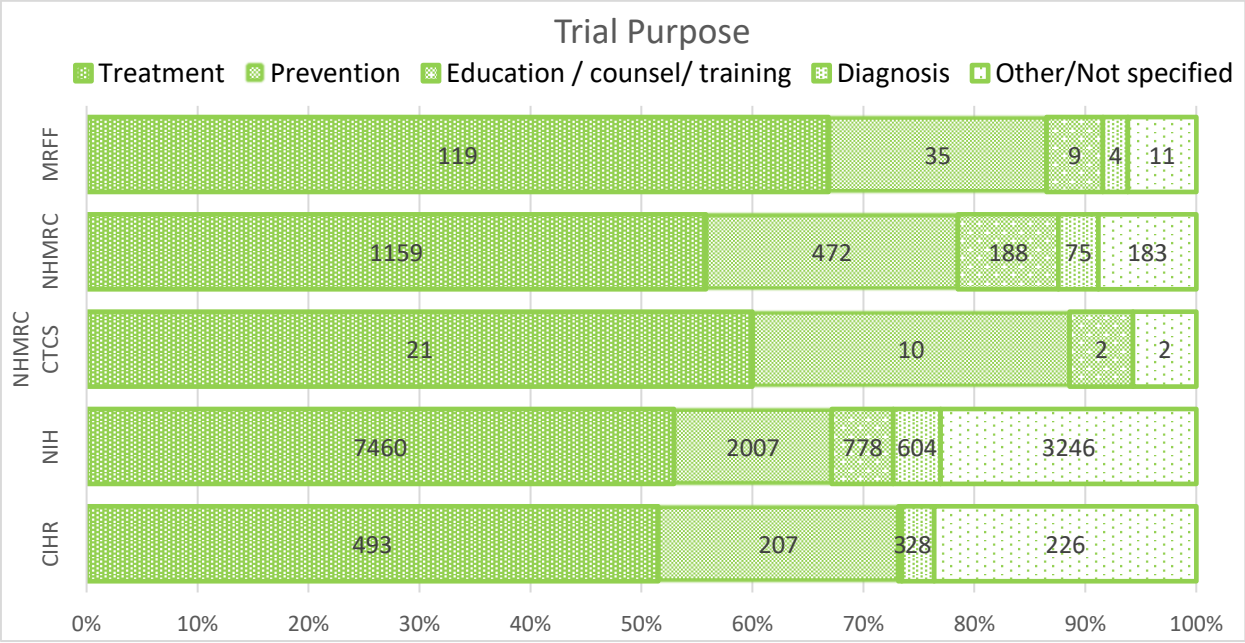


Figure 28 Trial purpose classified in 5 categories

Interventions Studied

We used the registries' intervention code to classify the trials. Because some trials had more than one intervention code assigned, there are more intervention codes than the total number of studies registered. The variables "non", "not applicable", "other observations", "blank", and exclusively the CIHR: dietary supplements (n=104) and combo product were grouped in a single category called "All Other".

The Desktop Review found that the greatest proportion of trials in preventative medicine (44%) was funded by the NHMRC; the proportion of trials in this category for the remaining funders – including the MRFF – was generally similar, ranging from 22% (NHMRC CTCS) to 30% (CIHR). Studies evaluating treatments comprised 61% of the trials funded by the MRFF, which is towards the upper end of all compared funders, whose funding of treatment trials ranged from 40% (NHMRC) and 70% (NHMRC CTCS). Few trials funded by the Australian funders were in the 'other' category – 10% by the MRFF, 8% by NHMRC CTCS specifically and 16% by the NHMRC overall; this was comparable to CIHR (10%) but lower than for the NIH (34%).

Table 48 Intervention code for the treatments used in the trial

		MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
		N	%	N	%	N	%	N	%	N	%
Preventative Medicine	Behaviour	24	8%	426	14%	2	3%	4462	22%	493	29%
	Diagnosis/Prognosis	8	3%	75	3%	1	2%	145	1%	13	1%
	Early detect/ Screening	8	3%	128	4%	3	5%				
	Lifestyle	17	6%	248	8%	1	2%	329	2%		
	Prevention	26	9%	419	14%	6	10%				
Subtotal: Preventative Medicine		***83***	***29%***	***1296***	***44%***	***13***	***22%***	***4936***	***25%***	***506***	***30%***
Treatment	Devices	12	4%	155	5%	4	7%	1101	5%	110	6%
	Drugs	117	41%	389	13%	23	39%	5902	29%	419	24%
	Other	39	14%	594	20%	13	22%	60		375	22%
	Surgery	6	2%	45	2%	1	2%	1285	6%	138	8%
Subtotal: Treatment		***174***	***61%***	***1183***	***40%***	***41***	***70%***	***8348***	***41%***	***1042***	***60%***
Other	Rehabilitation	8	3%	176	6%	2	3%				
	Biological	9	3%			2	3%	1909	9%	1	
	All other	10	4%	293	10%	1	2%	5079	25%	174	10%
Subtotal: Other		***27***	***10%***	***469***	***16%***	***5***	***8%***	***6988***	***34%***	***175***	***10%***
TOTAL		**284**	**100%**	**2948**	**100%**	**59**	**100%**	**20272**	**100%**	**1723**	**100%**

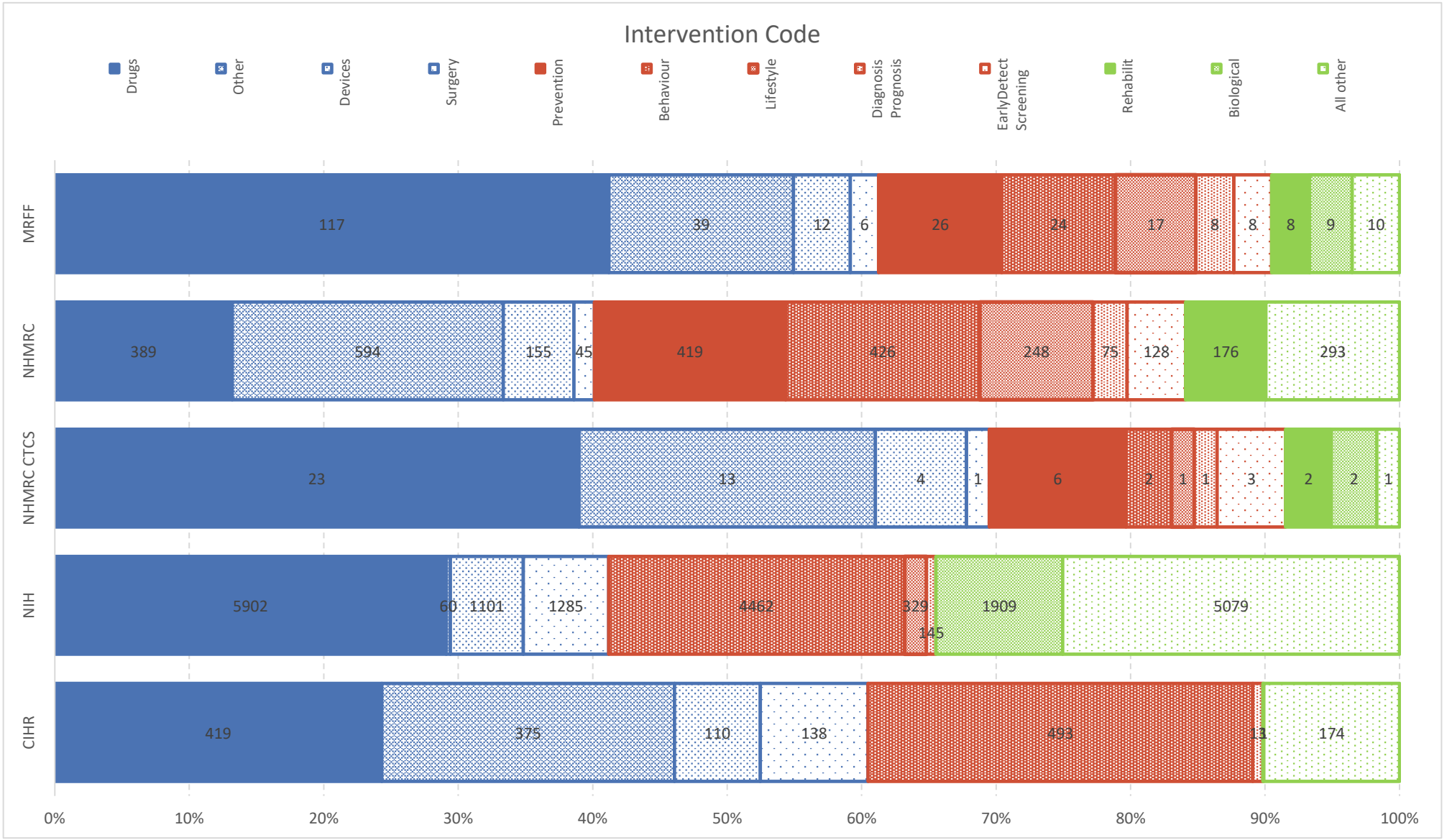


Figure 29 Intervention Code

Stakeholder comments on types of interventions studied

The stakeholders were presented a figure showing the types of interventions evaluated by MRFF-funded trials and by other, similar funders. (Figure below)

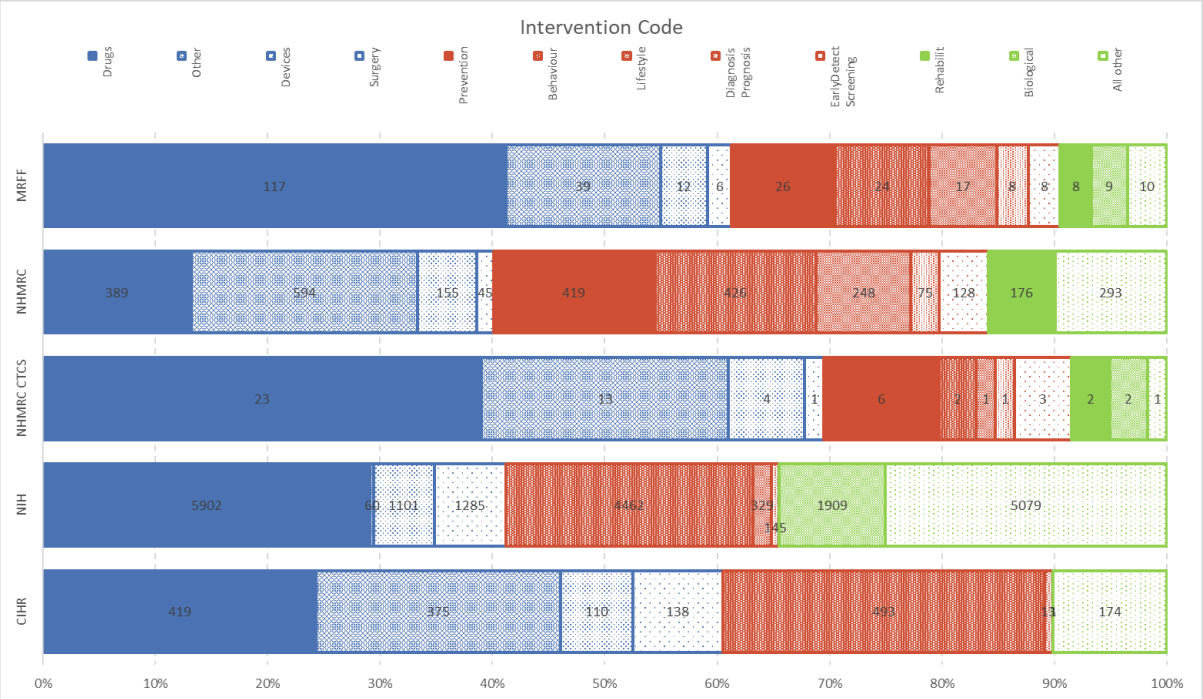


Figure 30 Stakeholder comments on the interventions studied

In response to the above data, the stakeholders shared their observations about the studies of interventions funded individual funders or made comparisons between funders; made general observations about the types of interventions whose studies are – or are not – funded; or made other relevant observations. The issues, comments or questions raised under each category, are as follows:

Observations about individual funders/comparisons between funders

- Australian schemes are looking more at public funding health
- MRFF has been very focused on trying to commercialise academic activity – drugs and interventions that might make money. Behavioural and lifestyle intervention has been sidelined by the MRFF in favour of drugs and devices.
- Canadians and Americans fund a lot more in the prevention area
- Australians fund more drugs than do other funders
- CIHR and NIH seem to have a really high number of behavioural trials – is this a true effect, or an artefact of how they classify them? E.g. Australia classifies 'behavioural' as 'other intervention' whilst NIH and CIHR specifically call it 'behavioural'?
- MRFF has more focus on drugs, whilst NHMRC is more equally divided
- Most of the American trials are on drugs
- Very few surgical trials – but more at NIH and CIHR than Australia
- It is interesting that the distribution of NHMRC CTCS is similar to MRFF
- MRFF is still on the learning curve for what [topics] to commission

General observations about areas that are/are not funded

- Not much funding goes to prevention research – that is unfortunate; nobody fully funds early detection and screening
- There is a big bias in favour of drugs
- Therapeutic devices are a fairly small group
- This makes sense since clinical trials are mostly focused on drugs, so you would expect that to be the majority of studies
- It is a good thing that multiple categories are funded
- There seems to be a bias towards drug trials, when there are many untested interventions used in routine clinical practice, surgery, physiotherapy, allied health, etc.
- It would be good to see more prevention and less treatment – prevention costs a lot of money, but treatment costs even more

Other observations (technical, conceptual)

- There are differences in how the clinical trial platforms categorise different types of interventions; and it is worth bearing in mind that these categorisations have also changed over time [interviewee was addressing the different intervention codes used by different clinical trial registries – e.g. ANZCTR, clinicaltrials.gov, etc.]
- How would a trial which combines e.g. a drug and a diagnostic be categorised?
- Clinicaltrials.gov is the simplest registry to get a trial up and start collecting pilot data for a grant [application]
- We do not really know what 'biological' is
- Rehabilitation may also be classified as 'physio'
- Pharmaceutical companies should be funding drug trials – so presumably these are "public good" drug trials, for drugs that are inexpensive or drugs that are being tested for a new use (other than one they are currently used for)?

Does your trial respond to an area of unmet need by addressing the following?

Most commonly, MRFF respondents to the survey stated that their trial addressed 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 NHMRC-funded trials, most commonly, the trial addressed 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 49 Does your trial respond to an area of unmet need?

	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%

Respondents who indicated "other" as their response, provided one or more of the following examples regarding their study (NHMRC and MRFF responses have been amalgamated to prevent reidentification):

- Adverse events of existing therapies
- Existing treatments not accessed by the patients
- Extension of existing approaches to treatment or prevention
- Implementation
- Improves outcomes
- Lack of long-term evidence for treatment or prevention
- Lack of RCT evidence / outdated evidence
- Lack of standard practice
- Limited or non-existent prevention options
- Limited treatment options
- Not a trial
- Public health issue
- Quality of life in a specific patient population
- Risk minimisation
- Risk-benefit
- Safety
- Targets a specific population or disease subgroup
- Trial of a new treatment option
- Unclear answer

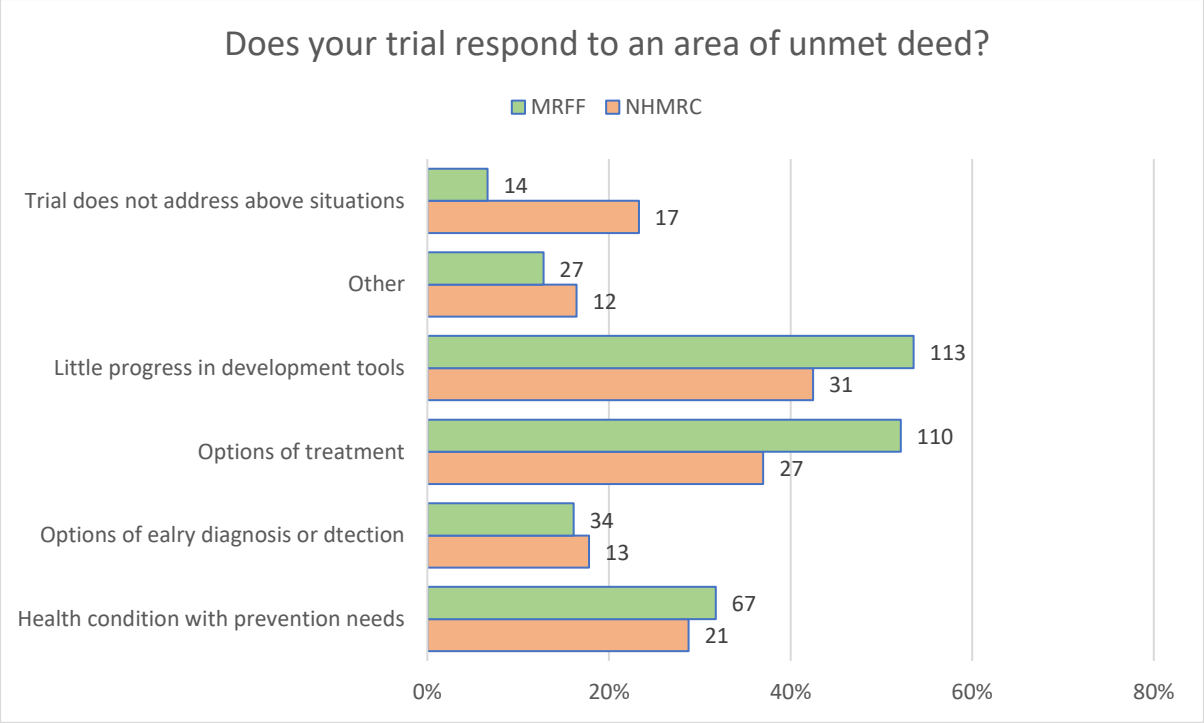


Figure 31 Does your trial respond to an area of unmet need?

Outcome

Does your trial's primary outcome come from a standardised outcome set (e.g. COMET, OMERACT, etc)?

Approximately 60% of respondents to the survey (61% of MRFF and 66% of NHMRC respondents) stated their trial's primary outcome did not come from a standardised outcome set.

Table 50 Does your trial's primary outcome come from a 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%**

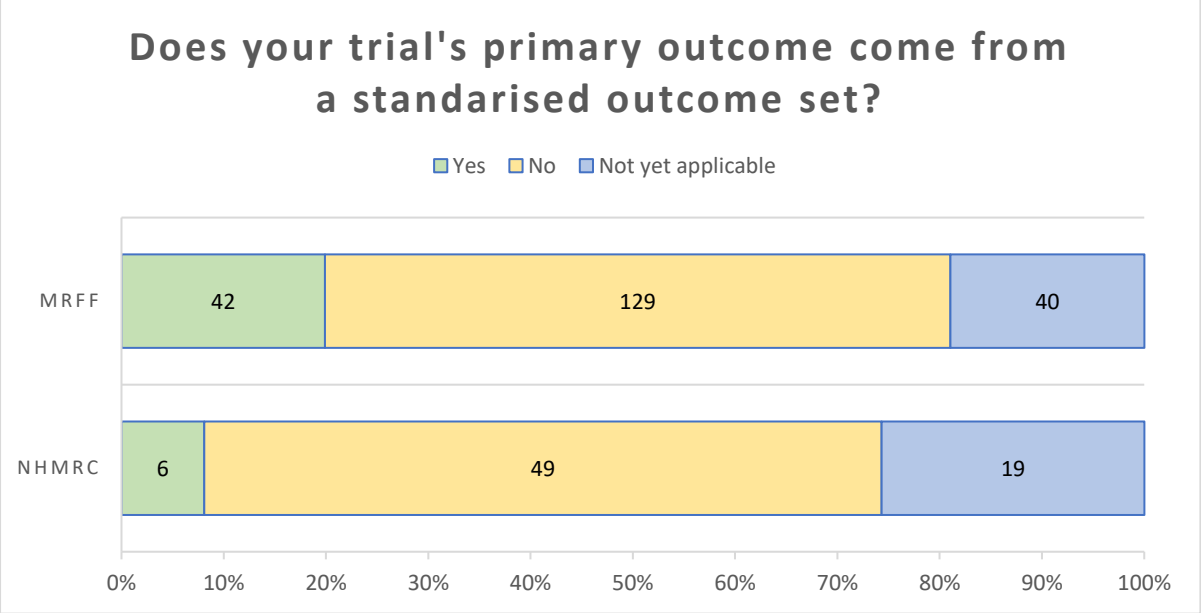


Figure 32 Does your trial's primary outcome come from a standardised outcome set

Flaws identified in the trial design (post-study collection)

Did you experience any of the following difficulties at the post-data collection stage: flaws identified in the trial 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 are not yet applicable according to the survey respondents.

Table 51 Did you experience any of the following difficulties at the post-data collection stage: flaws identified in the trial design

	MRFF (n=209)		NHMRC (n=71)	
Yes	2	1%		
No	44	21%	8	11%
Not yet applicable	163	78%	63	89%
Total	**209**	**100%**	**71**	**100%**

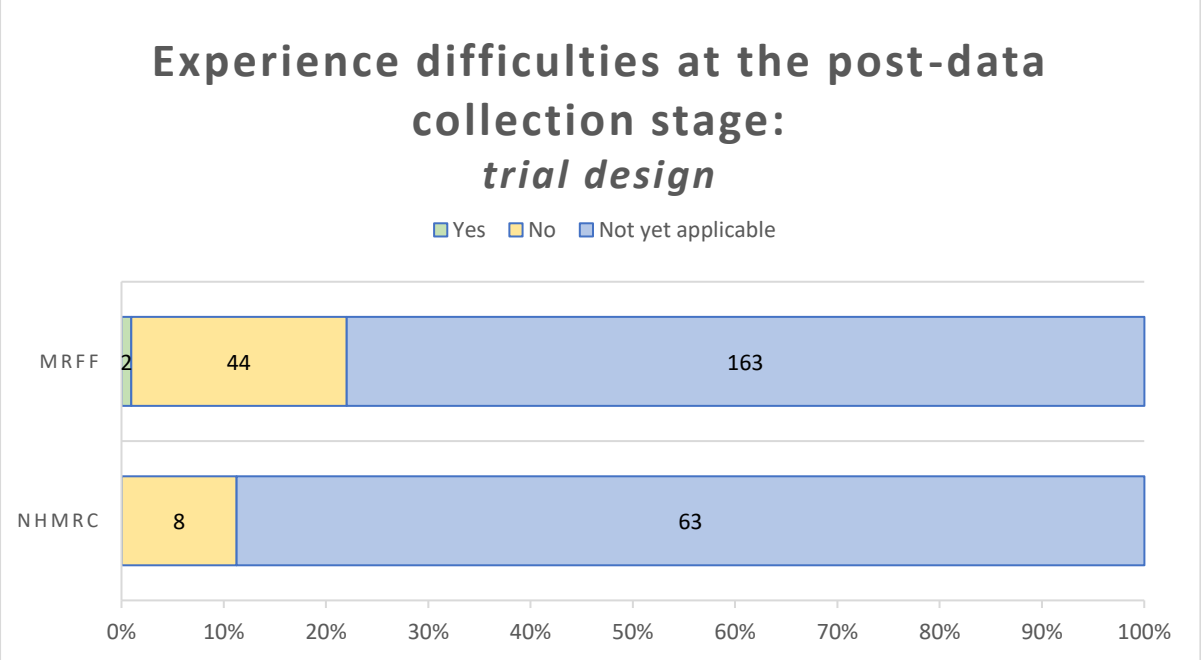


Figure 33 Did you experience any of the following difficulties at the post-data collection stage: flaws identified in the trial design

1.7. Data – Detailed results

Data linkage

Was using routinely collected data considered during trial planning?

Nearly the same proportion of survey respondents – 74% for MRFF and 71% for NHMRC – reported that they did not use routinely collected data during the planning of their trials.

Table 52 Was using routinely collected data considered during trial planning?

	MRFF (n=114)		NHMRC (n=21)	
Yes	30	26%	6	29%
No	84	74%	15	71%
Total	**114**	**100%**	**21**	**100%**

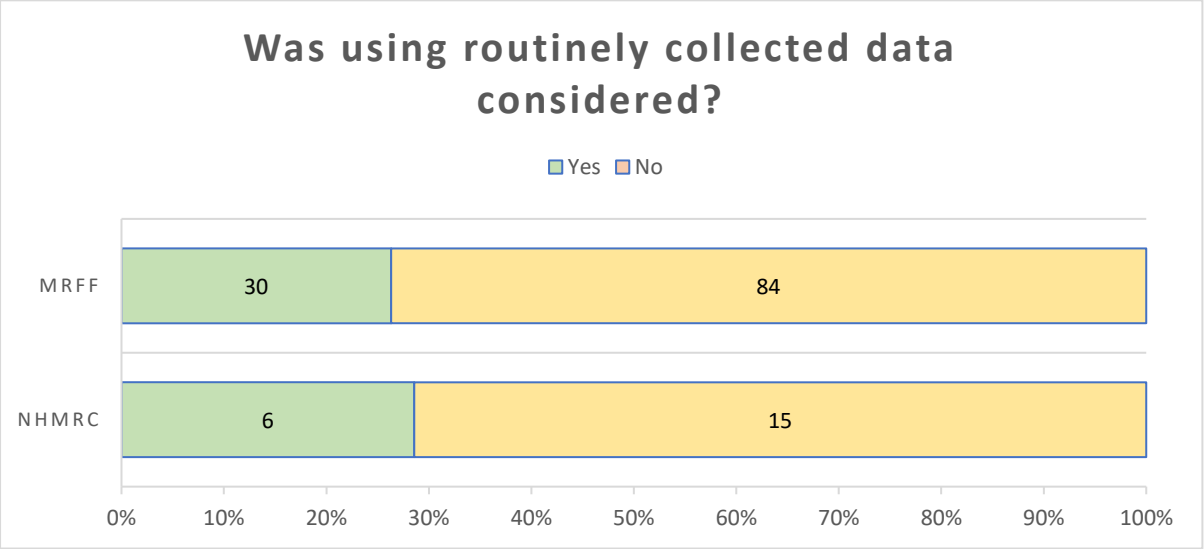


Figure 34 Was using routinely collected data considered during trial planning?

Does your trial utilise routinely collected data (e.g. PBS/MBS/death registry/ hospitalisation/Practice Management Software)?

More commonly, the MRFF respondents to the survey reported *not* using routinely collected data (54%). For the NHMRC respondents, it was more common to *use* routinely collected data (71% reported using it).

Table 53 Does your trial utilise routinely collected data

	MRFF (n=210)		NHMRC (n=71)	
Yes	96	46%	52	71%
No	114	54%	21	29%
Total	**210**	**100%**	**71**	**100%**

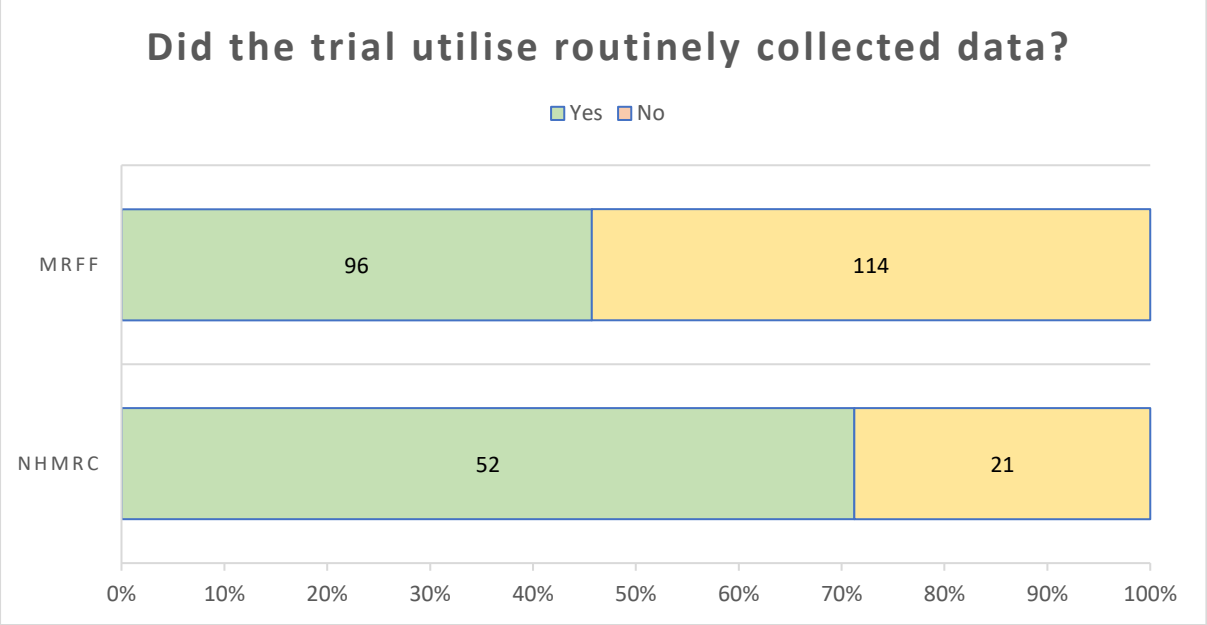


Figure 35 Does your trial utilise routinely collected data

Why did you not utilise routinely collected data even though it was considered?

27 of 29 MRFF investigators who considered but did not use routinely collected data responded to this question. The most common reason cited was time/cost (n=4).

Table 54 Why did you not utilise routinely collected data even though it was considered? - MRFF responses

Reason (27 respondents)	N	Sample quote/s
Time or cost involved in accessing prohibitive/ would delay	4	"Always too difficult and time-consuming to get approval for this in advance - too much else to do. Because it is not absolutely necessary, and we didn't have a strong justification for it, and it was an extra participant burden, we didn't do it." "costs and delays for "ethics" approvals would extend trial by 1-2 years."
Too difficult	3	"Too difficult to obtain consents - we thought the process would be too much and may further affect recruitment"
Still considering	2	"We haven't commenced the trial so we are still considering this option"
No routinely collected data fit for purpose	1	"[Country]* is the only country globally that may have some relevant population data. Under separate cover, we have recently established a collaboration to access [Country's] population health data. The potential population health data would not have precluded the need for a dedicated clinical trial."
Did use 'routinely 'collected data (but said no to Q24)	7	"We did use it"

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

6 of 6 NHMRC investigators who considered but did not use routinely collected data responded to this question. The most common reason cited is the absence of routinely collected data that was fit for purpose (n=4).

Table 55 Why did you not utilise routinely collected data even though it was considered? - NHMRC responses

Reason (6 respondents)	N	Sample quote/s
No routinely collected data fit for purpose	4	"We want data about the participants regular care at an individual level" "It misses the majority of people with the condition, as they do not routinely or consistently present to health services"
Time or cost involved in accessing prohibitive/ would delay	1	"Delays with data linkage"
Still considering	1	"We are actively investigating this and it would provide complementary data."

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Accessing routinely collected data (e.g. PBS/MBS/Death registry)

Approximately one-half (47%) of MRFF respondents to the survey did not experience challenges on account of accessing routinely collected data, although for 43% this was not yet applicable.

For the NHMRC respondents, most commonly, this issue was not yet applicable, although a notable proportion (30%) stated this was not a challenge for them.

Table 56 Difficulties accessing routinely collected data

	MRFF (n=213)		NHMRC (n=74)	
Yes	22	10%	9	12%
No	100	47%	22	30%
Not yet applicable	91	43%	43	58%
Total	**213**	**100%**	**74**	**100%**

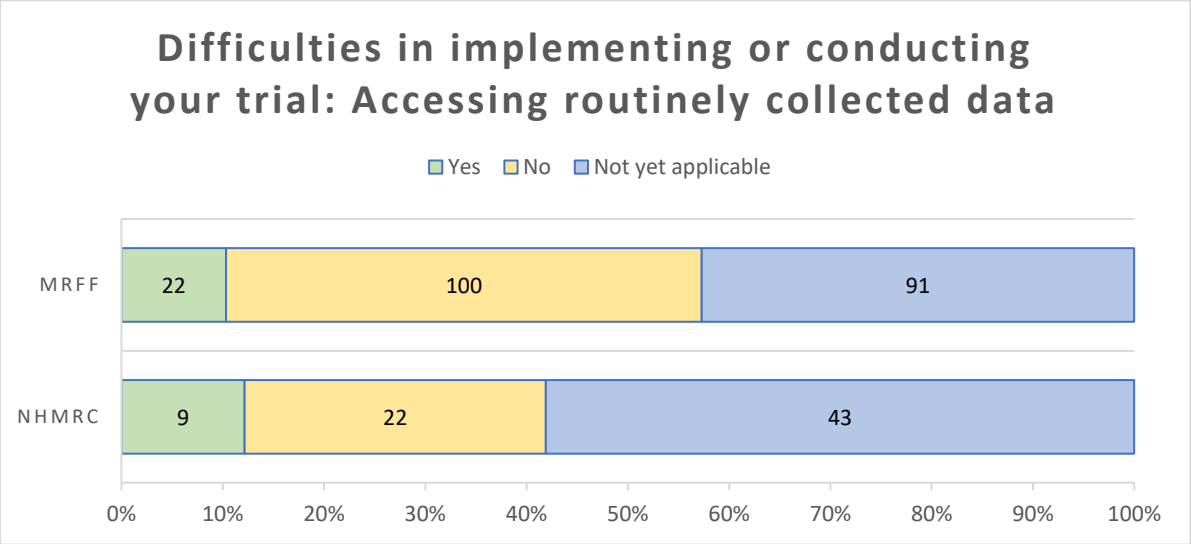


Figure 36 Difficulties accessing routinely collected data

22 MRFF respondents provided free-text responses which cited, in aggregate, 29 issues. Most commonly, these mentioned approval delays (n=17) and consent-related delays (n=9).

Table 57 Difficulties accessing routinely collected data - MRFF free-text responses

Responses (MRFF)	N respondents raising each issue (N respondents total = 22)	Sample quote(s)
Approval delays	17	"At the time of writing, the application process for this, which has gone through the PHRN, has taken more than 2 years and is still not yet completed/finalized, let alone data been provided. In contrast, the application process in New Zealand took less than a month to finalize and data are expected to be provided within a month of the final data request being submitted." "It took 4 years to gain approval. It is shameful how long it takes."
Consent delays	9	"There were complicated consenting processes that created a barrier for participants to come onto the general trial. There were also considerable delays in putting in place MBS and PBS agreements." "Challenges with delays in consent form approval from Services Australia, which led to delayed consent for MBS and PBS and has made it challenging to gain consent for linkage as some participants have now finished the trial." "Privacy lawyers for Services Australia requested multiple rounds of revisions to the Patient Information and Consent form that had been approved by our HREC. Time from first submission to approval to access MBS/PBS data by Services Australia was 12 months, and trial could not commence until approval in place." "That was most painful..... We did not have approval to consent until very recently. Our economic evaluation will not be an accurate measure of all resources used during the trial"
Minimal impact	1	"Minimal impact so far."
Unable to collect data	1	"Unable to collect data - influenced trial recruitment"
Eliminated this from the study	1	"Didn't do this in the end"
Grand Total	**29**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

9 NHMRC respondents provided free-text responses which cited, in aggregate, 10 issues. Most commonly (n=8), these mentioned approval delays.

Table 58 Difficulties accessing routinely collected data - NHMRC free-text responses

Responses (NHMRC)	N respondents raising each issue (N respondents total = 4)	Sample quote(s)
Approval delays	8	"Getting all of the agreements in place to work across multiple jurisdictions and international borders has been a heavy workload" "Increased limitations placed on access of research personnel to confidential patient data (even when research personnel are clinically trained) due to employment by a research institution rather than the health service is complicating data retrieval"
Cost	1	"Laborious process, cost"
Unclear answer	1	
Grand Total	**10**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Individual patient data (IPD)

Do you intend to make, or have you made deidentified individual participant data collected during the trial available to other researchers?

The majority of MRFF-funded trials (65%) and NHMRC-funded trials (72%) have made available – or intend to make available – individual participant data available to other researchers, according to survey respondents.

Table 59 Intention to make IPD available

	MRFF (n=208)		NHMRC (n=69)	
Yes	135	65%	50	72%
No	73	35%	19	28%
Total	**208**	**100%**	**69**	**100%**

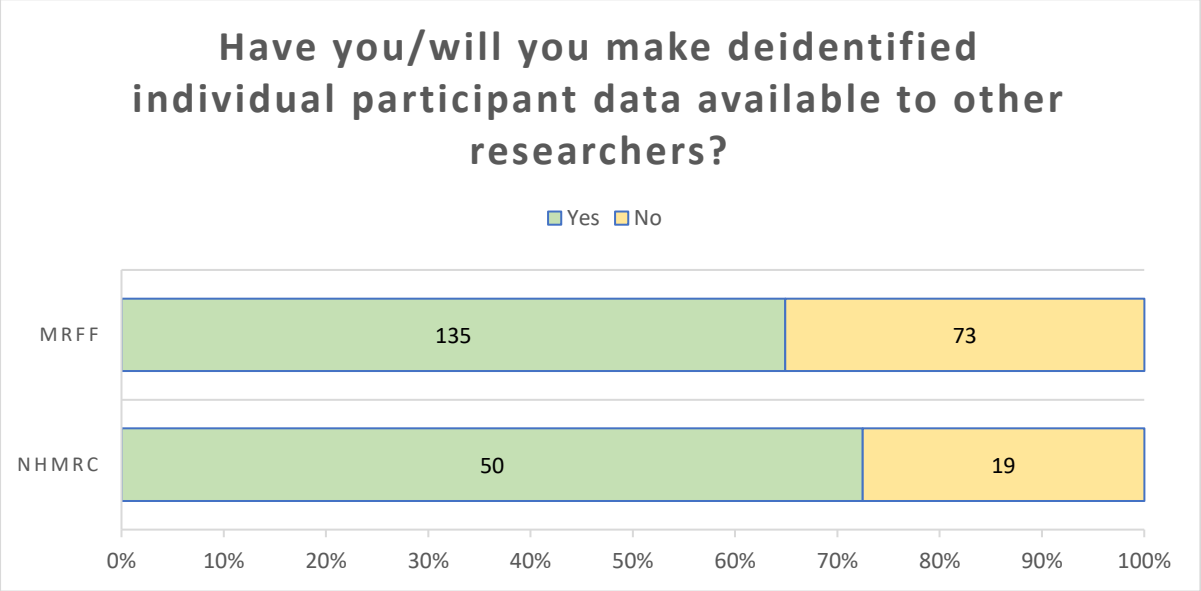


Figure 37 Intention to make IPD available

Individual patient data availability statement in the clinical trial registry record

Desktop Review found that the MRFF-funded trials had the highest data availability statements, with 33%, followed by the NHMRC CTCS (31%). This was significantly higher than the NHMRC (11%), NIH (16%), and CIHR (6%). Reasons for this include lack of patient consent (for example, in a retrospective study), confidentiality, legislation, the availability of or willingness to provide aggregate data, not considering this in the ethics application, not providing any reasons, and other factors were cited.

Table 60 Availability of Individual Patient Data - Desktop Review

	MRFF		NHMRC		NHMRC CTCS		NIH (Post Califf)		CIHR	
	N	%	N	%	N	%	N	%	N	%
Yes	58	33%	234	11%	11	31%	2215	16%	59	6%
No	99	56%	640	31%	19	54%	4131	29%	287	29%
Undecided	6	3%	5	0%	1	3%	596	4%	58	6%
Not Applicable	15	8%	1198	58%	4	11%	7153	51%	581	59%
Total	**178**		**2077**		**35**		**14095**		**985**	

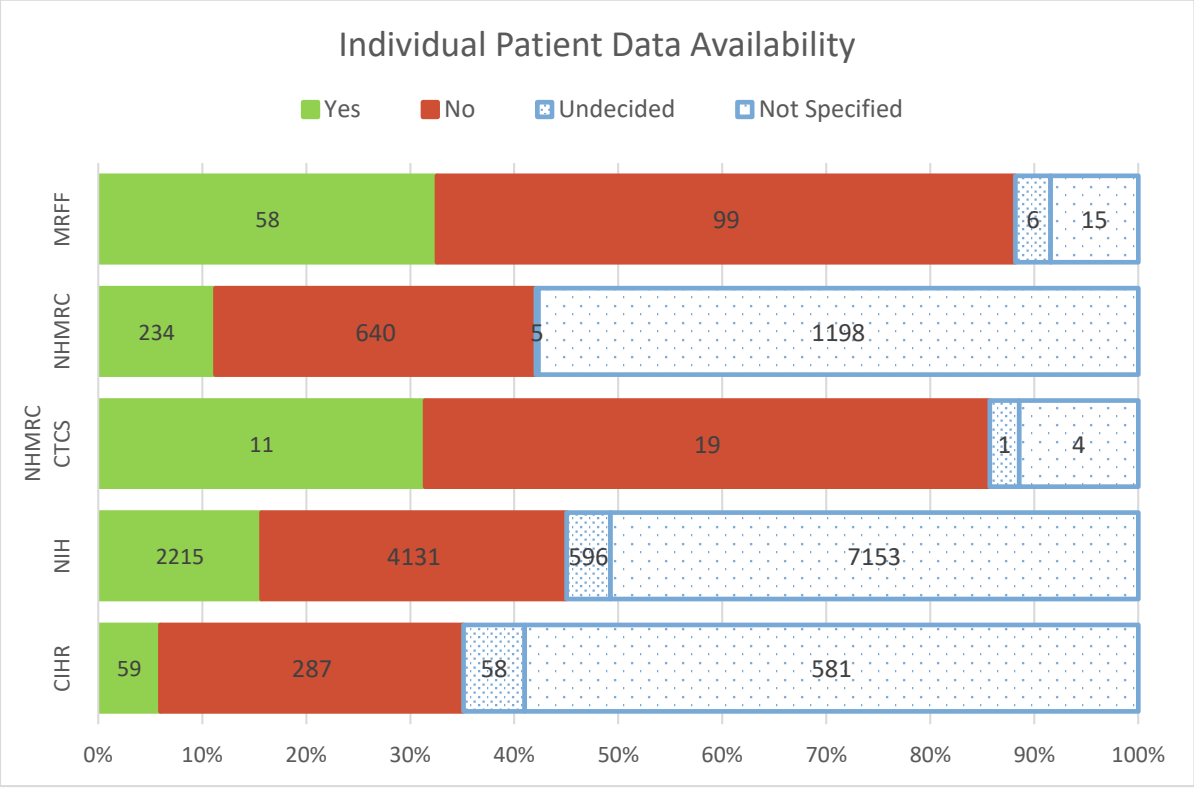


Figure 38 Availability of Individual Patient Data - Desktop Review

How will or how has de-identified individual participant data been made available?

Among MRFF-funded researchers, most commonly, the trialists intended to make individual participant data available on request (n=69) or through depositing the data in a repository, database or a platform (n=21).

Table 61 How will or how has de-identified individual participant data been made available - free-text responses MRFF

Response	N respondents (total = 237)	Sample quote
No answer provided (blank)	109	
On request	69	"by contacting the principal investigator and requesting access" "By application to the trial steering committee"
Deposited in a repository / database / platform	21	"Online services for long term public storage (and access) of data" "Deidentified data will be available through Open Science Framework."
Unsure/undecided at present	15	"To be determined"
Other	14	"Sometimes data is used by other researchers within our clinic. Data is always stored in a de-identified form." "Summaries to participants, media, community presentations" "Meta-analysis of individual patient data/pooled analyses with similar studies (using completely de-identified data only)"
In publications	7	"publication and supplementary information" "In publication"
Time period indicated	2	"12 months" "7 years"
Grand Total	**237**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Among NHMRC-funded researchers, most commonly, the trialists intended to make individual participant data available on request (n=21) or through depositing the data in a repository, database or a platform (n=12).

Table 62 How will or how has de-identified individual participant data been made available - free-text responses NHMRC

Response	N respondents (total=82)	Sample quote
No answer provided (blank)	35	
On request	21	"management committee will consider all requests for data sharing"
Deposited in a repository / database / platform	12	"public data repository" "Standardized repository protected by username and password and following the regulations for data sharing" "international "bio" bank, university data repository"
Unsure/undecided at present	7	"Not yet decided"
Not applicable	3	"N/A"
Data sharing/data transfer agreement	2	"Data transfer agreement"
In publications	1	"Tabulated in final publications."
Other	1	"use of a case record number"
Grand Total	**82**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Why will de-identified individual participant data not be made available to other researchers?

Among the MRFF respondents to the survey, the most common reasons for *not* making individual participant data available to other researchers, 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).

Table 63 Why will de-identified individual participant data not be made available to other researchers? - MRFF

Response	N respondents (total=237)	Sample quote
No answer provided (blank)	169	
Ethics approval/consent does not cover/allow this	17	"Ethics approvals are not in place"
May be considered under specific circumstances	14	"researchers from the study sites will be able to request de-identified data but not those from outside until the trial has been published"
Decision about this not made yet	8	"This has not been determined yet."
Other	8	"not a clinical trial" "not necessary" "Deidentified data will only be available to the researchers named on the grant application at this stage." "Samples collected during the trial will be available to our investigator team for exploratory testing"
Sensitive data	7	"Due to the sensitive nature of medical data collected"
Potential for identification/difficult to deidentify	5	"Case numbers are small [total N indicated]. Data is potentially identifiable."
No interest/requests yet	5	"There has been no recognised interest"
Study not yet completed / not appropriate at this stage	2	"ongoing phases of this study"
Not applicable	2	"Not currently applicable"
Grand Total	**237**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Very few responses were provided by the NHMRC respondents, to clarify their reasons for *not* making individual participant data available to other researchers. Most commonly, lack of permission to release (n=3), inappropriateness at this stage or incompleteness of the study (n=3) or other reason (n=3) were cited.

Table 64 Why will de-identified individual participant data not be made available to other researchers? - NHMRC

Response	N respondents (total=82)	Sample quote
No answer provided (blank)	66	
Other	3	"we will not have de-identified IPD for all jurisdictions"
Study not yet completed / not appropriate at this stage	3	"trial not complete yet"
Not permitted to release	3	"We do not have Ethics or participant permission to do so."
Not applicable	2	"NA as yet."
May be considered under specific circumstances	2	"This would be considered by the Trial Steering Committee in the right circumstances, but not contributing to a public repository"
Sensitive data	2	"The collected information is sensitive and from a vulnerable population"
Unsure / don't know	1	"You need to give don't know as a choice"
Grand Total	**82**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Stakeholder Comments on intent to make IPD available

The stakeholders were presented with survey data on intention to make data available. (Figure below).

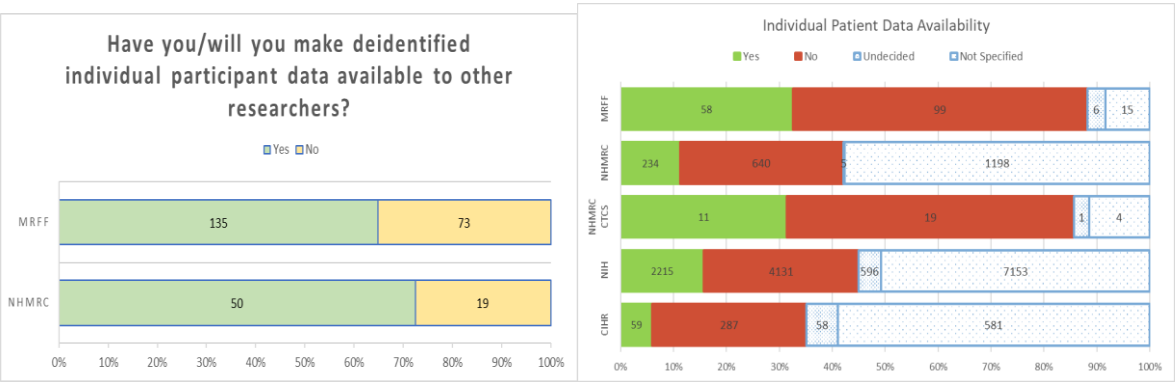


Figure 39 Data on intention to make individual patient data available presented to stakeholders

In response to the above data, the stakeholders raised the following issues:

Data availability / sharing

- Consent forms need to be standardised to allow use by other researchers – surveys show this is the public expectation of what will happen
- One of the barriers to sharing is the perception that this somehow violates ethics or patient privacy
- Ethics should not be a limitation or barrier towards data sharing
- It is possible that those who say they cannot, have not been shown how to do this – there is no instruction manual telling them what to do at each stage of the research lifecycle to share data ethically and in compliance with privacy principles
- These are human beings whose data is being used
- Some of this may depend on the nature of the collected data – e.g. it is not clear how one would share data from a pharmacokinetic study
- Some of the issues around sharing depend on what the ethics committee agreed to
- Availability of deidentified data depends on its purpose. We should be reducing waste and duplication of effort. This may help to do that.
- I have had some success to obtain data. I do not know if it is still a problem.
- It used to be the case that negative results were hidden – open science is a good approach for addressing this issue

1.8. Public availability – Detailed results

Protocol

Protocol availability

The availability of the protocol was difficult to interpret because just a few studies reported that they made the protocol available. This may be due to the age of the data set: whilst the MRFF-funded trials are from the previous 5 years and the NHMRC CTCS-funded studies cover the period from 2019 onwards (both coinciding with the greater prominence of the Open Science movement), NIH-funded studies cover the period since the analysis by Califf et al (2012 onwards) and the other funders cover a longer time period, which precedes the Open Science movement. Only NHMRC and NHMRC CTCS provided a "Not specified" option, therefore, for other funders, this column was calculated by subtracting the yes and no categories from the total number of studies in each data set.

Desktop Review showed that, apart from NHMRC CTCS (23%), the protocol availability for MRFF-funded studies was slightly higher (22%) than for non-MRFF-funded studies. The NHMRC CTCS study set had a small sample size, making comparison difficult. All funders, including the MRFF, have potential for improvement in terms of protocol availability.

Table 65 Protocol availability statement

	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**	

Stakeholder comments on protocol availability

The stakeholders were presented with data on intention to make protocol publicly available. (figure below).

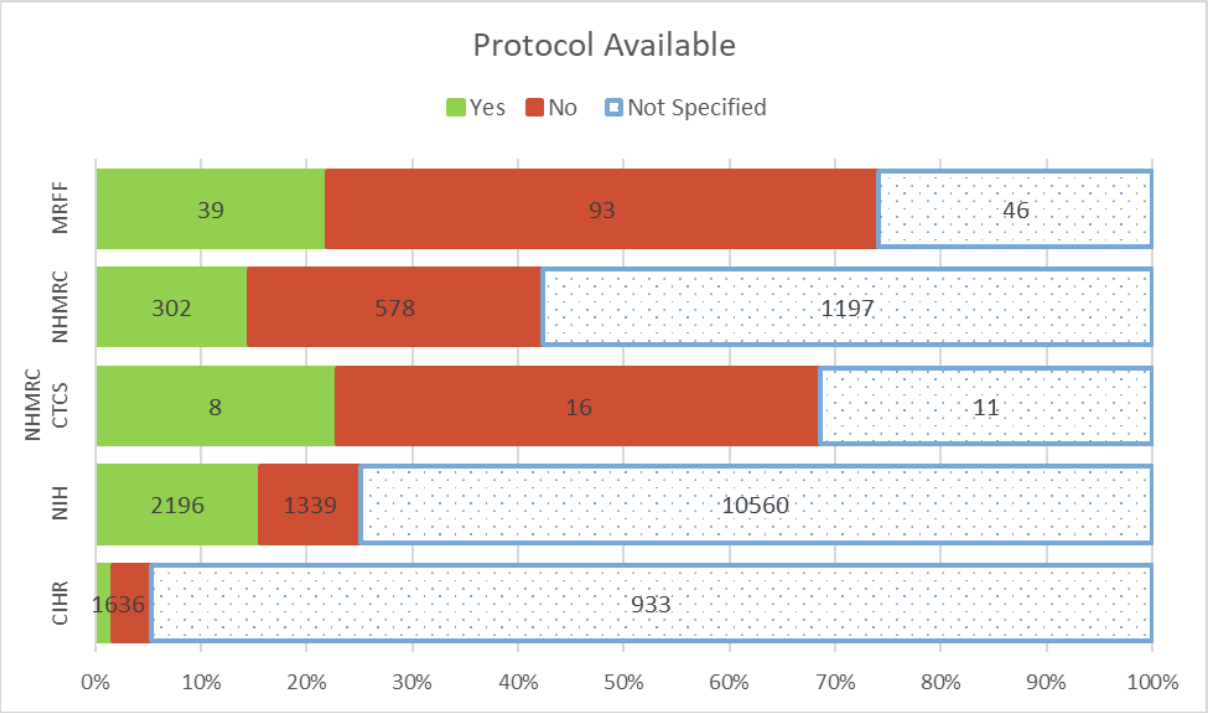


Figure 40 Protocol availability - data presented to stakeholders

In response to the above data, the stakeholders raised the following issues:

Protocols

- There are different senses of the word 'protocol' – the published protocol and the 'trial protocol'. The latter has more detail in it about how you actually do the trial, and people may not want this to be public (e.g. drug packaging information)
- I thought these days everyone publishes a protocol
- Very few published protocols are available in Medline specifically for factorial trials, which is surprising since the Trials journal welcomes them
- Protocol availability should be mandated and could be enforced when the researcher gets the funding – the trial should be registered before the funding is released. There could be an opt-out approach, if a reason is provided.
- If a study has only recently been funded, the investigators would not have yet published a protocol
- Some protocols (e.g. the RECOVERY trial in the UK) are made available on the trial's dedicated website – it is available but not published
- Having a protocol available is good, and imperative to know whether the results reported are trustworthy

Study results availability

Has your trial completed data collection for the main outcomes?

The vast majority of survey respondents – 89% for MRFF and 97% for NHMRC – have *not* completed data collection for the main outcomes.

Table 66 Has your trial completed data collection for the main outcomes?

	MRFF (n=210)		NHMRC (n=73)	
Yes	24	11%	2	3%
No	186	89%	71	97%
Total	**210**	**100%**	**73**	**100%**

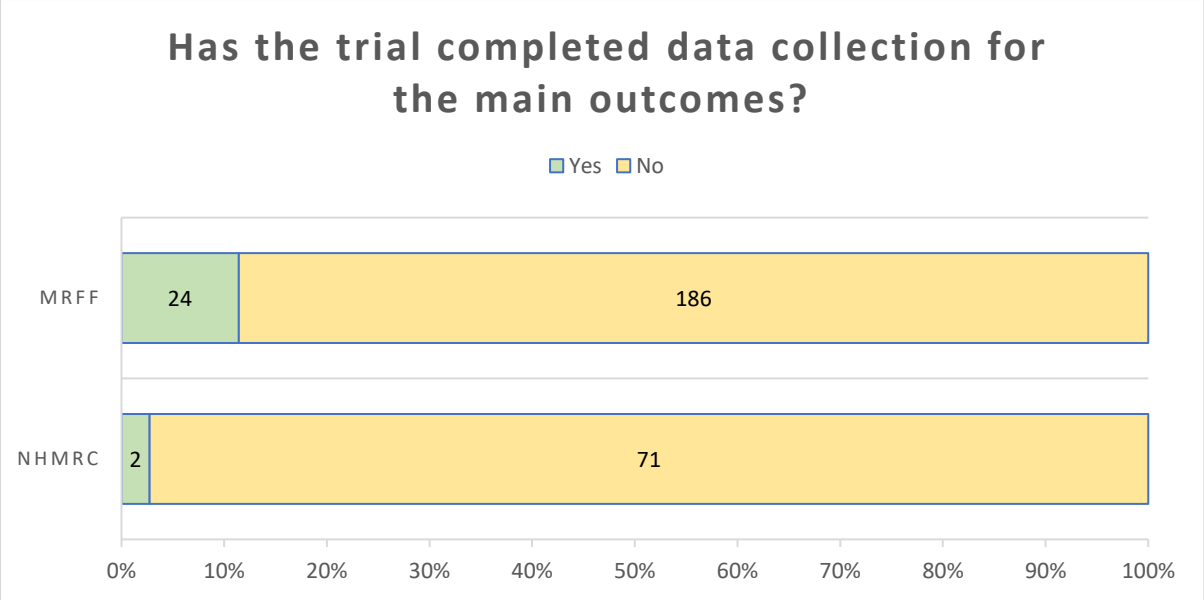


Figure 41 Has your trial completed data collection for the main outcomes?

Challenges around the dissemination of results (e.g. via publications, preprints, uploading results to clinical trial registries, etc.)

For the majority of both MRFF-funded trials (84%) and NHMRC-funded trials (93%), difficulties pertaining to the dissemination of results were not yet applicable, according to the survey respondents.

Table 67 Challenges around the dissemination of results

	MRFF (n=209)		NHMRC (n=71)	
Yes	3	1%	1	1%
No	30	14%	4	6%
Not yet applicable	176	84%	66	93%
Total	**209**	**100%**	**71**	**100%**

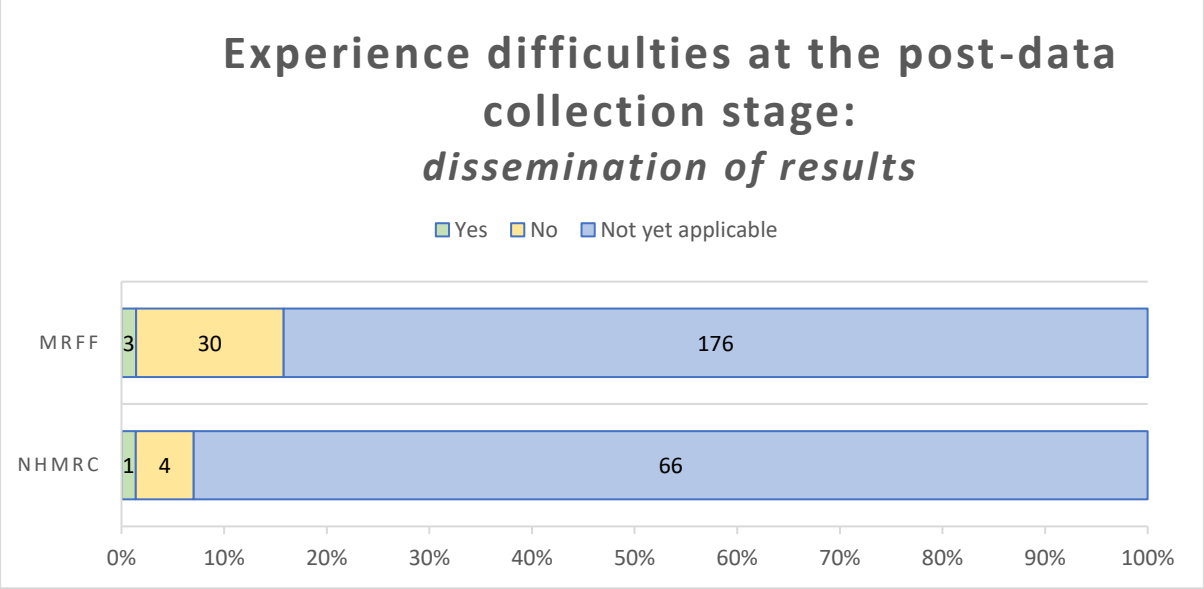


Figure 42 Challenges around the dissemination of results

How long (in months) after you finish data collection do you anticipate it will take to make the results available for others to view? [for those who answered yes to above]

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 with an NHMRC grant was 9.6 months (SD=6.7 months, n=66). Both were positively skewed, meaning that more researchers were estimating a shorter time to make the results available.

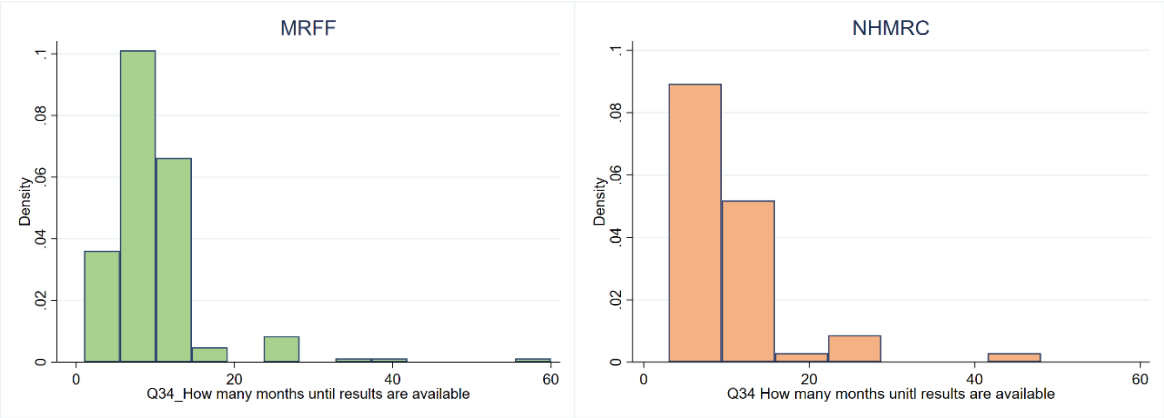


Figure 43 Estimated time (in months) to available results after finish of data collection, researchers with (a) MRFF grant (b) NHMRC grant

Where do you plan to make the results of your trial available?

Most commonly, MRFF respondents to the survey planned to make their trial results available via academic journals (87%) and at conferences or professional meetings (82%).

Most commonly, NHMRC respondents planned to make their trial results available via academic journals (98%) and at conferences or professional meetings (91%).

Table 68 Where do you plan to make the results of your trial available?

	MRFF (228 respondents)		NHMRC (77 respondents)	
Other	13	8%	11	20%
Trial registry	76	47%	31	55%
Conference/ professional meeting	134	82%	51	91%
Preprint server	27	17%	15	27%
Academic journal	142	87%	55	98%

Similar responses were provided by the MRFF and NHMRC respondents who selected the "other" category. Examples provided, included:

- Consumer/community organisations
- Patient/Disease-area specific organisations/bodies
- Industry forums
- Newsletters
- Partner organisations
- Policy documents/briefs
- Press
- Public summaries
- Social media
- Research repository
- Trial website
- Via guidelines (national, clinical, for patient care)

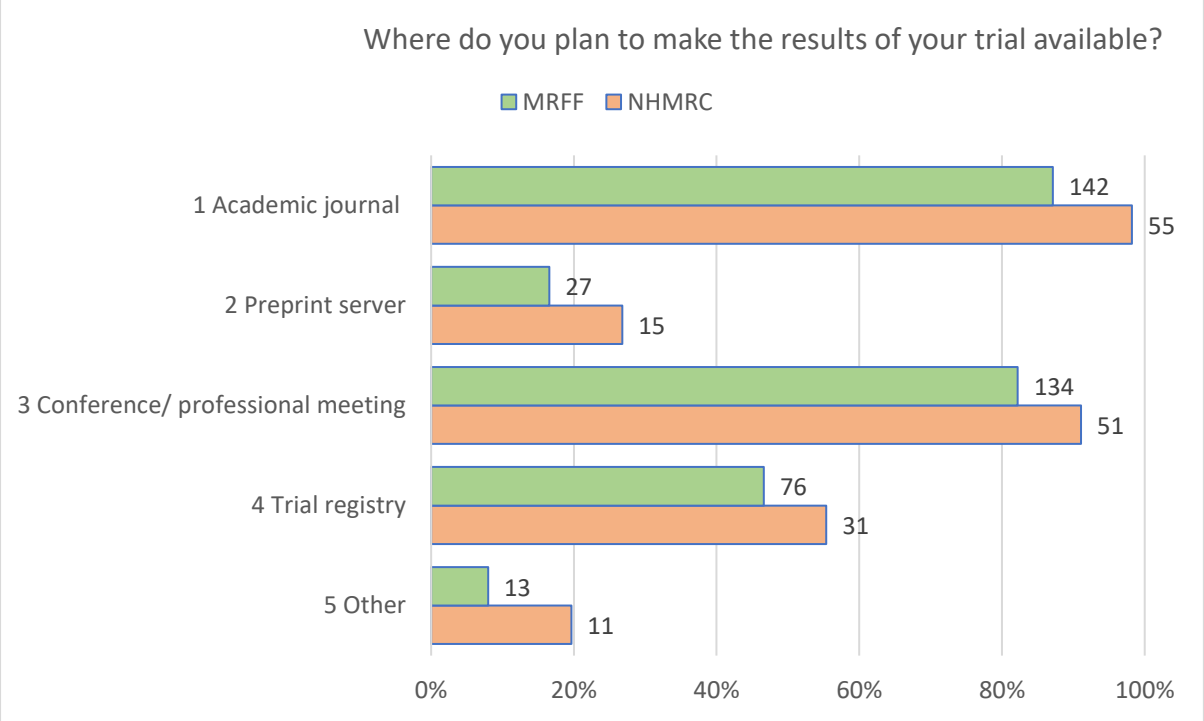


Figure 44 Where do you plan to make the results of your trial available?

Are the results currently available through the following channels?

Very few answers were provided to this question in the survey – thus the results need to be interpreted with considerable caution.

Academic journal

The majority of MRFF respondents (67%, n=16) and all of NHMRC respondents (100%, n=2) stated that the results are currently *not* available through an academic journal.

Table 69 Are the results currently available through the following channels?

	MRFF (n=24)		NHMRC (n=2)	
Yes	7	29%		
No	16	67%	2	100%
Not yet applicable	1	4%		
Total	**24**	**100%**	**2**	**100%**

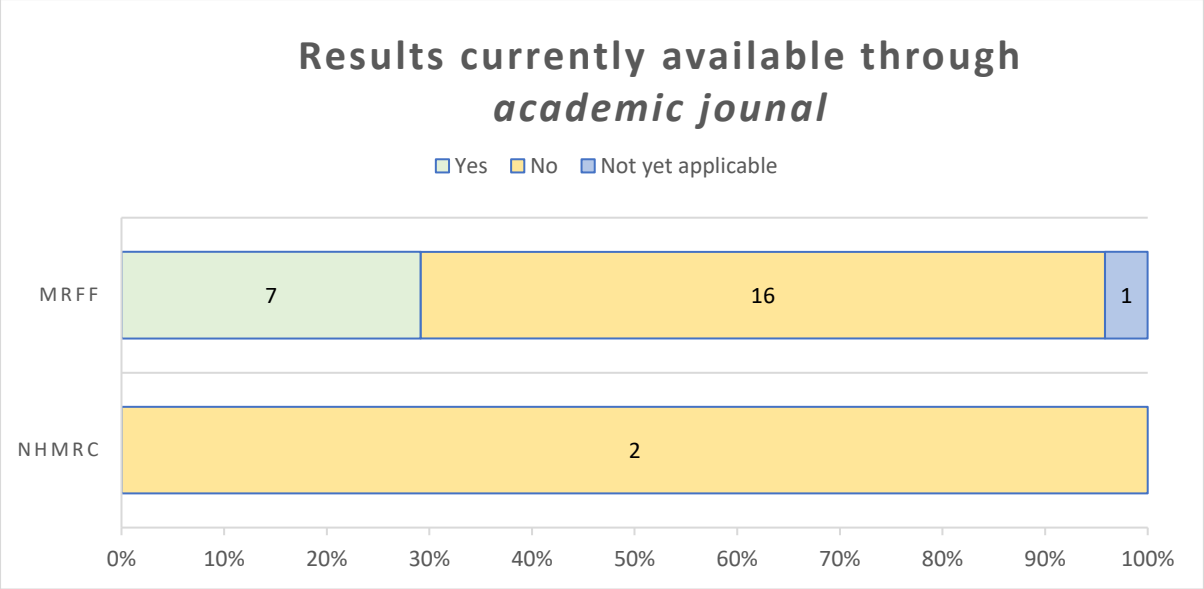


Figure 45 Are the results currently available through the following channels?

Preprint server (e.g. medRxiv)

For the majority of MRFF respondents to the survey, dissemination of trial results via a preprint server was not yet applicable (71%, n=17); all of NHMRC respondents (100%, n=2) stated that the results are not currently available through a preprint server.

Table 70 Are the results currently available through the following channels? Preprints.

	MRFF (n=24)		NHMRC (n=2)	
Yes				
No	7	29%	2	100%
Not yet applicable	17	71%		
Total	**24**	**100%**	**2**	**100%**

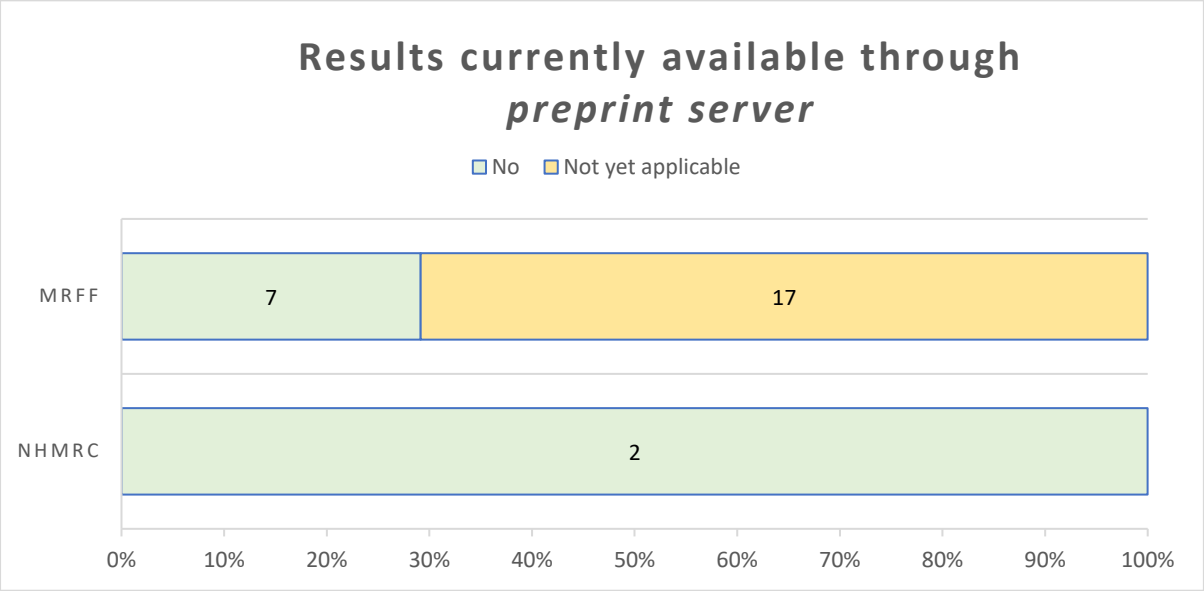


Figure 46 Are the results currently available through the following channels? Preprints.

Conference presentation or abstract

For the majority of MRFF respondents to the survey, results have been made available via a conference presentation or abstract (67%, n=16); no results are available through this avenue for NHMRC respondents (n=2, 100%).

Table 71 Are the results currently available through the following channels? Conference.

	MRFF (n=24)		NHMRC (n=2)	
Yes	16	67%		
No	7	29%	2	100%
Not yet applicable	1	4%		
Total	**24**	**100%**	**2**	**100%**

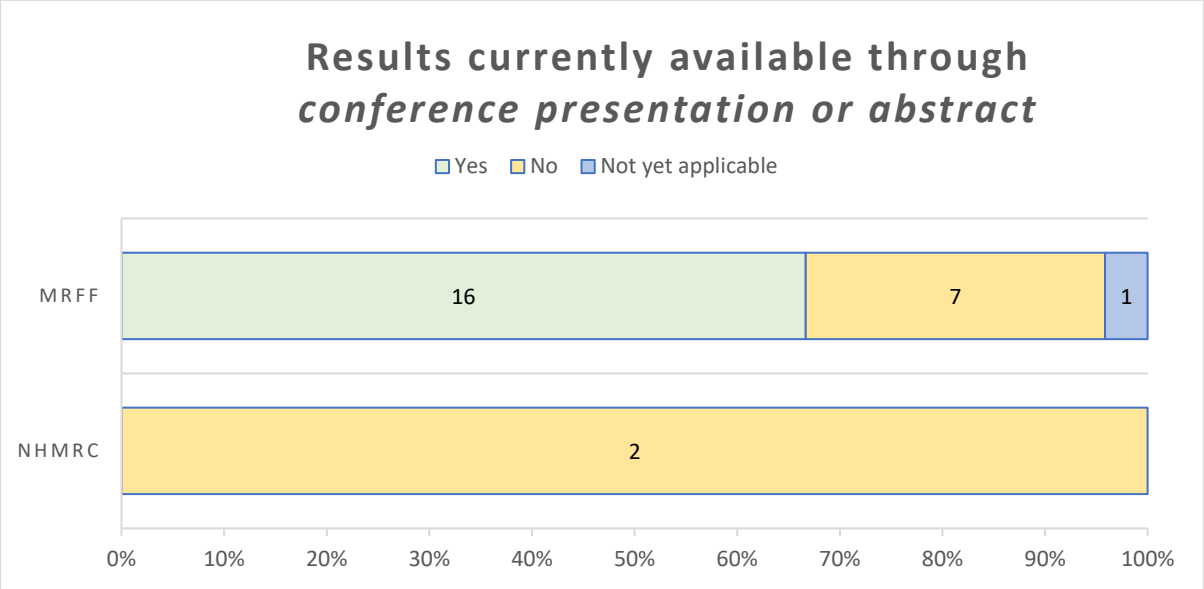


Figure 47 Are the results currently available through the following channels? Conference.

Trial registry (e.g. ClinicalTrials.gov)

For the majority of MRFF-funded survey respondents (n=13, 54%), results have not been made available via a clinical trial registry. For one half (n=1, 50%) of the NHMRC respondents, the results have not been made so available; for the other half (n=1, 50%), this was not yet applicable.

Table 72 Are the results currently available through the following channels? Registry.

	MRFF (n=24)		NHMRC (n=2)	
Yes	8	33%		
No	13	54%	1	50%
Not yet applicable	3	13%	1	50%
Total	**24**	**100%**	**2**	**100%**

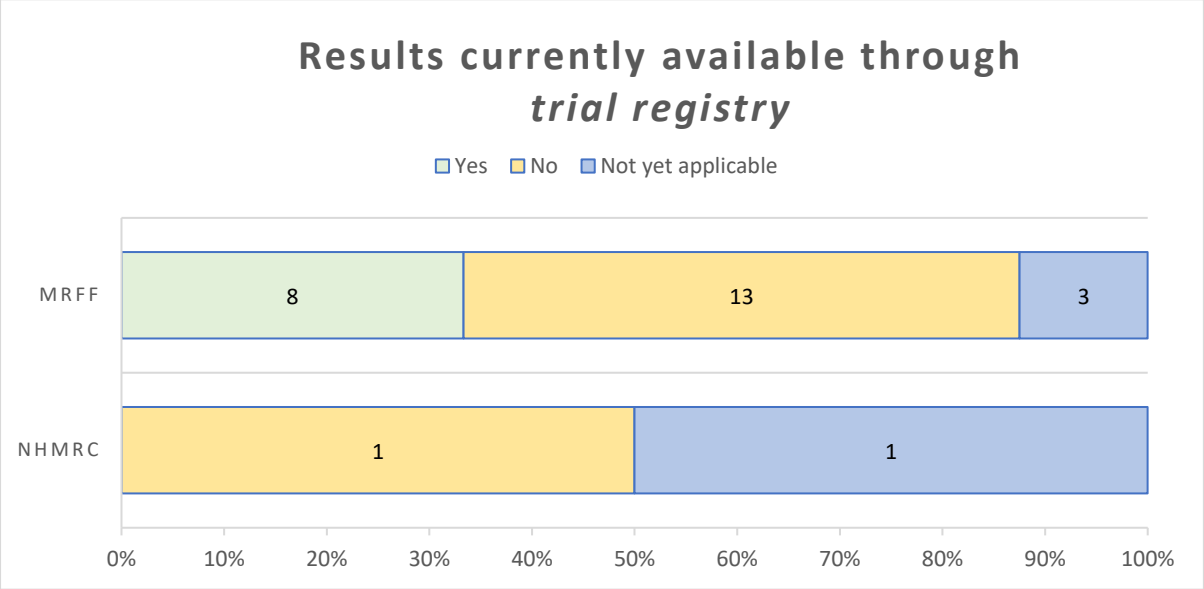


Figure 48 Are the results currently available through the following channels? Registry.

Other (please describe)

For the majority of MRFF-funded survey respondents, other means of making results available were not yet applicable (n=15, 68%). For one half (n=1, 50%) of the NHMRC respondents, the results have not been made available; for the other half (n=1, 50%), this was not yet applicable.

Table 73 Are the results currently available through the following channels? "Other."

	MRFF (n=24)		NHMRC (n=2)	
Yes	3	14%		
No	4	18%	1	50%
Not yet applicable	15	68%	1	50%
Total	**22**	**100%**	**2**	**100%**

As only 6 respondents in aggregate (MRFF and NHMRC) provided additional detail, their responses have been amalgamated to preserve anonymity. The examples provided, include:

- Conferences
- Dissemination to peak bodies and the TGA
- Incorporation into guidelines
- Policy briefs
- Reports to industry
- Via trial's website

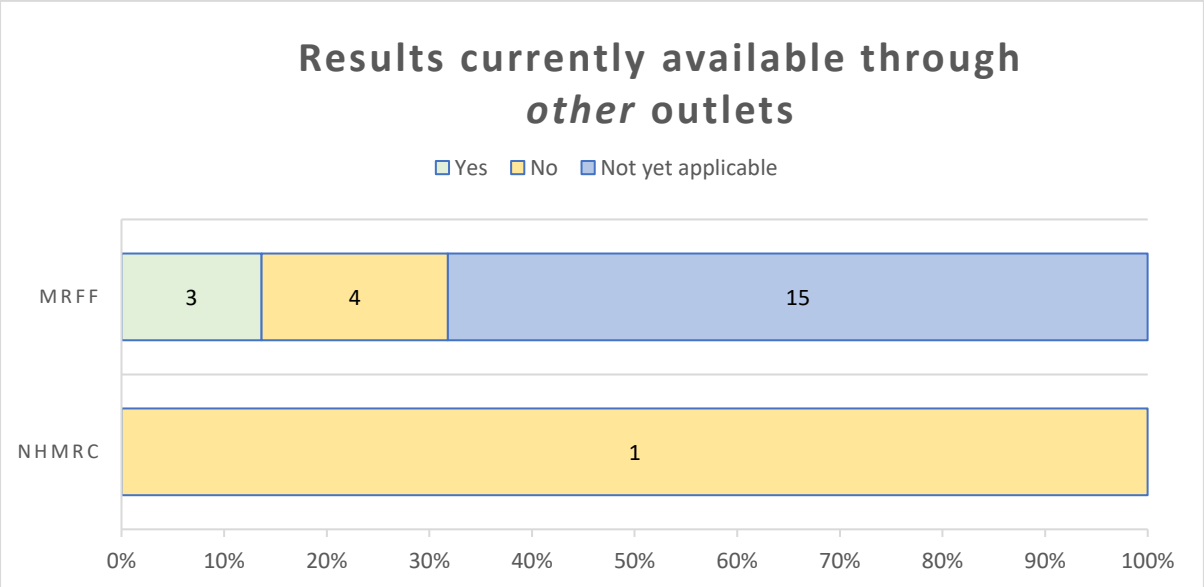


Figure 49 Are the results currently available through the following channels? "Other."

Please give the citation or website link for the channels identified above

6 MRFF respondents to the survey answered yes to the completed data collection question, and yes to results currently available in academic journal. Of those, 6 provided citations for the publication.

15 MRFF respondents said yes to the completed data collection question and yes to results currently available in conference presentation or abstract. Of those, 13 provided an identifiable link or other information indicating the conference or a meeting at which the results were presented.

7 MRFF respondents said yes to the completed data collection question and yes to results currently available in trial registry. Of those, 4 provided a specific link to a registry entry.

No (0) responses were provided by the NHMRC investigators for this question. It is worth noting, however, that only 2 NHMRC respondents indicated that trials had completed data collection for main outcome.

DETAILED RESULTS SECTION 2 – STUDY IMPACTS

2.1. Impacts – Detailed results

Healthcare impacts

What do you believe has been, or will be the main impact of your trial?

Among the MRFF respondents to the survey, the most common impact was a new treatment or intervention (63 responses) or change/improvement in practice (37 responses).

Table 74 What do you believe has been, or will be the main impact of your trial? MRFF respondents.

Response	N respondents (total=237)	Sample quote
New treatment/ Intervention	63	"Identify a new drug combination to improve treatment outcomes"
No answer provided	38	
Change/improvement in practice	37	"We hope to change clinical practice"
Not yet available/trial not finished	19	"too early to comment"
Improved health/well-being of patients	17	"If successful, a major impact on quality of life and outcomes for [condition*]"
Other	14	"evidence-based program" "it has already formed the basis of another trial" "increased ongoing adoption of evidence-based health-enabling policy"
Inform recommendation policy / guideline	11	"Changing international guidelines"
New/improved model of care	10	"Change the model of care for people with [disease] in Australia."
New test/diagnostic	6	"change method in which advanced [disease] is identified within primary practice"
Understanding of the disease/condition	5	"A greater understanding of the disease we are studying."
Harms/Adverse events	4	"reduced toxicity of therapy while maintaining efficacy"
Screening	2	"improved screening for [a specific type of] complications in [disease area]"
Risk factors/association	2	"Pragmatic [disease] risk factor screening and risk reduction delivered in primary care."
Collaboration/ engagement	2	"Improved collaborative research in [topic area], improved translation into practice, and ultimately, improved access to evidence based support in Australia."
Prevention of disease	2	"early prevention of [disease]"
Cost effectiveness evaluation	2	"Cost effectiveness evaluation of [intervention] as standard [disease area] care"
Improved capacity (research)	2	"Actually, capacity building: building capacity to conduct clinical trials in this research area.

		While we hope (and look forward to) positive trial outcomes, regardless of the findings, we have established new clinical trial sites (training staff, providing equipment etc) and trained researchers in clinical trial procedures. We can leverage of these developments to conduct bigger and better trials in the future."
New prevention approach/tool	1	"The results of this clinical trial could be used to develop evidence-based programs which are cost effective, broadly-applicable preventative approaches specifically aimed at enhancing [an area of] health and decreasing [a type of] incidence, conferring substantial social and economic impact."
Grand Total	**237**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

Among the NHMRC respondents, the most common impact was a new treatment or intervention (20 responses) or change/improvement in practice (19 responses).

Table 75 What do you believe has been, or will be the main impact of your trial? NHMRC respondents.

Response	N respondents (total=82)	Sample quote
No answer provided	20	
New treatment/intervention	19	"Will impact on [disease name*] treatment internationally"
Change/improvement in practice	13	"Provide evidence to support / refute current treatment practices"
Inform recommendation/policy/ guideline	10	"Guideline updates for first line use of [treatment] in [disease]"
Improved health/well-being of patients	8	"Improved outcome for patients"
Collaboration/engagement	3	"So far, collaboration and community engagement."
Risk factors/association	2	"This trial will determine whether [agent] use is linked with an increased risk for [condition]"
Understanding the condition/disease	2	"The findings of this study will determine why some individuals with [disease] (are programmed to) develop complications of their disease, while others do not, despite a similar duration of diabetes, treatment intensity"
New prevention approach/tool	2	"Providing an additional treatment that is affordable, widely available and safe"
New test/diagnostic	1	"Development of new test that could impact on treatment selection"
New/improved model of care	1	" Change the standard care and improve the overall prognosis"
Cost effectiveness evaluation	1	"Aims to determine whether a [payment for intervention] is cost-effective at improving patient outcomes"
Grand Total	**82**	

(Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets].)

In which of the following ways have the trial findings been used to change healthcare?

For both the MRFF respondents (72%) and NHMRC respondents (74%) to the survey, the question was mostly inapplicable.

For MRFF respondents to whom the question applied, their trial findings have most commonly been presented to clinical or healthcare professionals (9%).

For NHMRC respondents to whom the question applied, their findings have most commonly been cited in clinical guidelines (10%).

Table 76 In which of the following ways have the trial findings been used to change healthcare?

	MRFF (n=196)		NHMRC (n=62)	
"Other" Types of examples provided: Study has not yet commenced; study still in progress; study will lead to change in practice; study formed the basis of another trial	3	2%	1	1%
Result in collaboration with Clinical Quality Registry	3	2%		0%
Establish Clinical Quality Registry		0%		0%
Changes in healthcare procedures	7	4%	1	1%
Cited in clinical guidelines	6	3%	7	10%
Establish new research collaborations	8	4%	1	1%
Facilitate project team on research	12	6%		0%
Included to Pharmaceutical Benefits advisory committee		0%		0%
Included to Medical services advisory committee		0%		0%
Included to regulator for device/drug	1	1%		0%
Results presented to clinical/health groups	17	9%	1	1%
N/A	139	72%	51	74%

Have there been any new health technologies or interventions (e.g. drug, diagnostic, technological or similar development) identified or validated through your trial?

For 10% of MRFF respondents and 11% of NHMRC respondents to the survey, 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.

Table 77 Have there been any new health technologies or interventions from 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%**

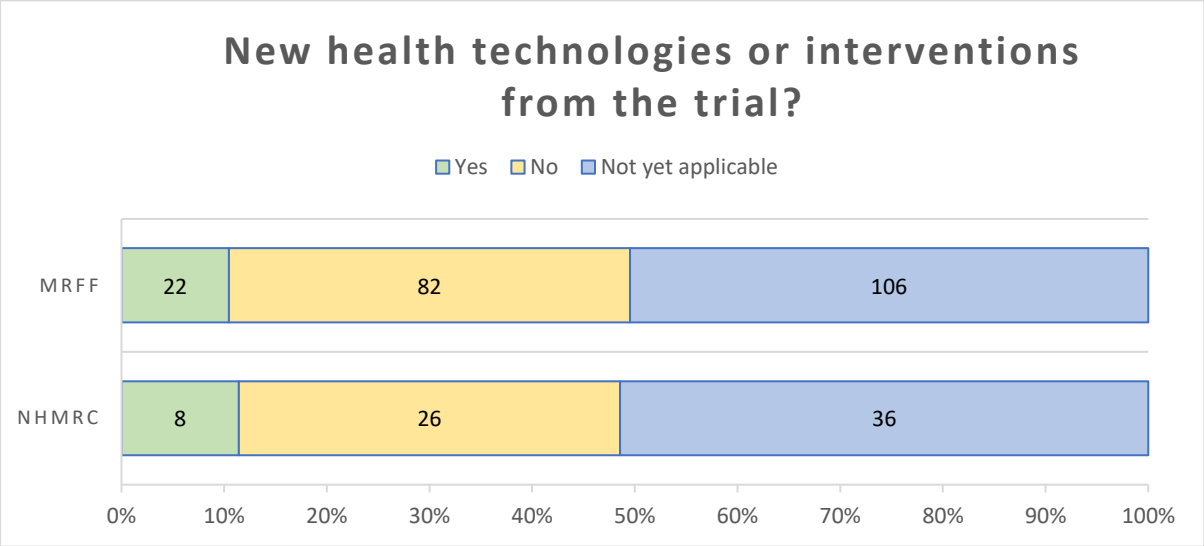


Figure 50 Have there been any new health technologies or interventions from your trial?

What are the details of these developments? [if answered yes to question above]

20 MRFF investigators identified new interventions or developments resulting from their trial. These included, most commonly, a new intervention (n=6).

Table 78 What are the details of these developments? MRFF respondents.

MRFF: Development identified (20 respondents)	N respondents
New intervention	6
New platform for treatment delivery	3
Other Types of examples provided: "benchmarking model"; adoption of outcome measure to a specific cultural background, with validity and reliability testing, and methods for this to be published.	2
New use of existing drug	2
Pilot evidence for a new intervention	2
Optimal intervention	1
Incorporation of a treatment in clinical guidelines	1
Verification of diagnostic measures	1
Combination therapy	1
New technology	1
Grand Total	**20**

7 NHMRC investigators identified new interventions or developments resulting from their trial. Most commonly, new intervention (n=2) or new drug selection process (n=2) were identified.

Table 79 What are the details of these developments? NHMRC respondents.

NHMRC: Development identified (7 respondents)	N respondents
New drug selection process	2
New intervention	2
New platform for treatment delivery	1
New risk prediction tool	1
Grand Total	**6**

Commercialisation

Have there been any commercialisation opportunities from your trial (e.g., opportunities to develop drugs, devices, other products or services with commercial partners)?

For 3% of MRFF respondents and 0% of NHMRC respondents to the survey, there were commercialisation opportunities arising from the trial. However, for 64% of MRFF respondents and 77% of NHMRC respondents, this was not the case.

Table 80 Have there been any commercialisation opportunities from your trial?

	MRFF (n=208)		NHMRC (n=71)	
Yes	6	3%		
No	133	64%	55	77%
Not yet applicable	69	33%	16	23%
Total	**208**	**100%**	**71**	**100%**

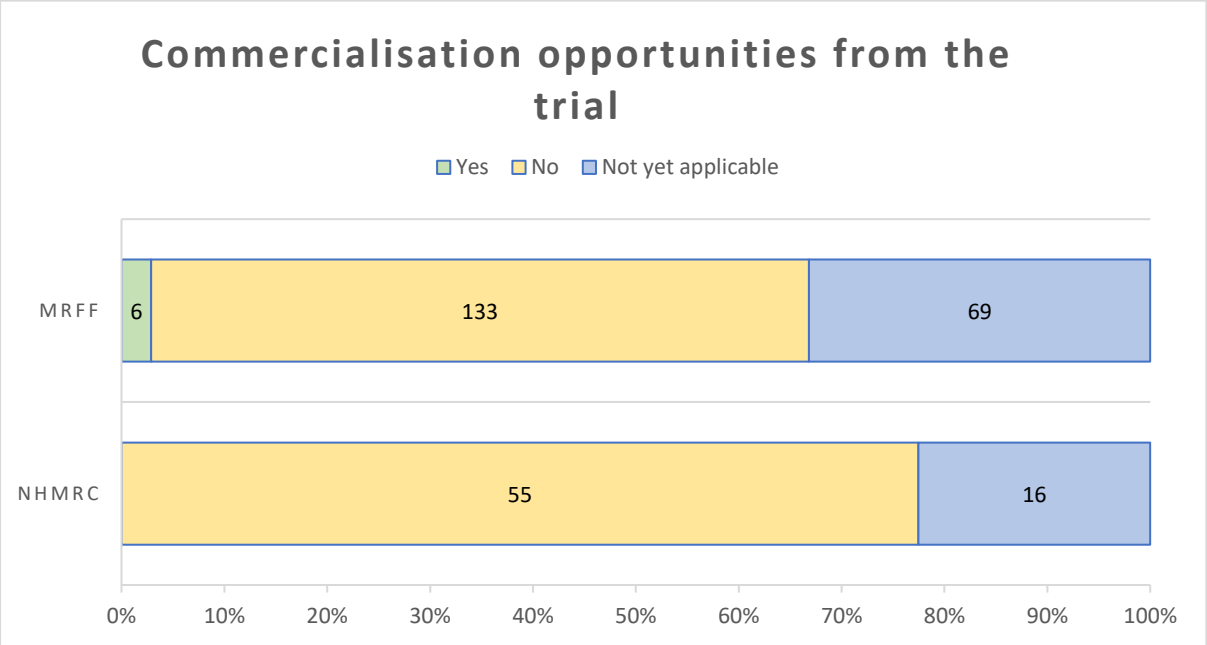


Figure 51 Have there been any commercialisation opportunities from your trial

What are the commercial opportunities? [if answered yes]

5 MRFF respondents to the survey provided an answer to this question. They identified (1 each):

- development of an app
- formulation of a new intervention
- use of trial data to licence a drug
- a spin-out company
- interest from a funder to pilot an adaptation of the trialled programme

No (zero) NHMRC respondents provided an answer to this question.

What, if any, difficulties or barriers to commercialisation have you experienced? [if answered yes]

5 MRFF respondents provided an answer to the question about identified difficulties or barriers to commercialisation. Issues identified included (1 each):

- absence of commercialisation advice specifically
- issues involving coordinating multiple collaborating organisations
- time and legal support
- challenges within a university
- challenges are “not applicable at this stage”

No (zero) NHMRC respondents provided an answer to this question.

DETAILED RESULTS SECTION 3 – STUDY CHALLENGES

3.1. Study Challenges – Detailed results

Design/setup

Agreement on protocol details

Coming to an agreement on protocol details was not a common challenge in implementing or conducting the trials – 88% of MRFF respondents, and 68% of NHMRC respondents to the survey, stated they did not experience this challenge.

Table 81 Agreement on protocol details

	MRFF (n=213)		NHMRC (n=74)	
Yes	18	8%	6	8%
No	188	88%	50	68%
Not yet applicable	7	3%	18	24%
Total	**213**	**100%**	**74**	**100%**

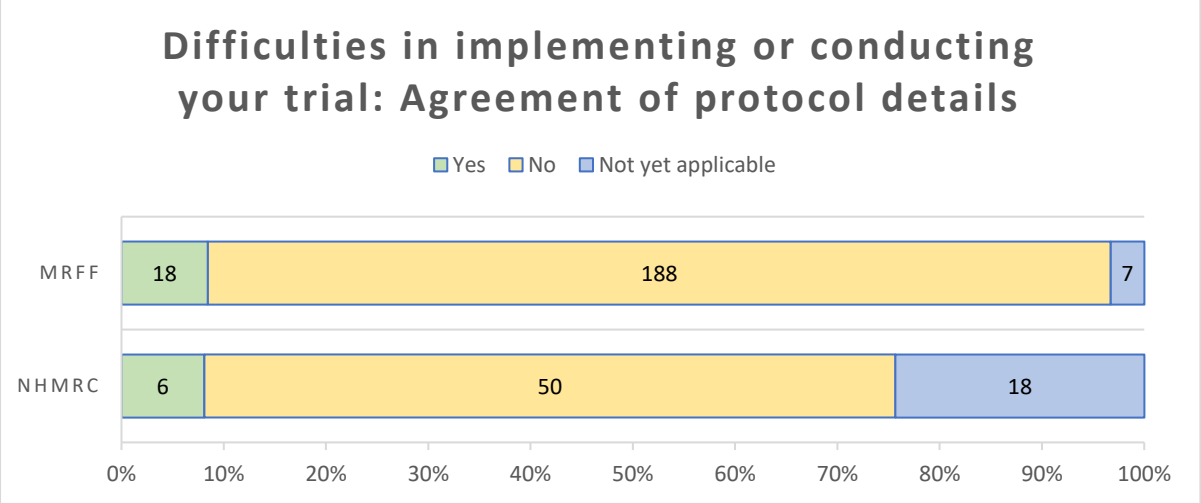


Figure 52 Agreement on protocol details

18 MRFF respondents provided free-text responses which cited, in aggregate, 20 issues. Most commonly, these mentioned delays (type not specified) (n=4) and changes in outcome measurement (n=3).

Table 82 Agreement on protocol details - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 18)	Sample quote(s)
Delay (type not specified)	4	"Slower than usual" "Delays"
Change in outcome measurements	3	"Changes regarding the outcomes measurements" "change in definitions of capturing data, how to test for [disease], exposure definitions changed throughout the study and then any change in the protocol meant an amendment"
Complexity of the trial	2	"The trial is complex. It required extensive simulations to inform. All up the protocol has been about 3 years in the development."
Change to patient recruitment process	2	"altered way patients were recruited to trial initially"
Reaching consensus among collaborators/ partners	2	"variations in clinical practice and standard of care in [disease area] meant that it took sometime to reach consensus on a research protocol which everyone was happy with"
Delay to study start	1	"Delay in starting study"
Delay to protocol publication	1	"Delayed publication of protocol"
Not applicable	1	
Delay to enable remote trial conduct	1	"Protocol had to be updated to enable remote trial conduct."
Site did not cooperate	1	"One participating health service changed mind and did not want to follow protocol (inclusion criteria related to [risk status in a population subgroup]). It had no overall impact because we have plenty of eligible participants at the other sites."
Change in drug supply	1	"Change in drug supply meant change in protocol"
Delay due to external reviews	1	"The company reviews took 2-3 months."
Grand Total	**20**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

5 NHMRC respondents provided free-text responses which cited, in aggregate, 5 issues. Most commonly mentioned were issues around reaching consensus among collaborators or partners (n=2).

Table 83 Agreement on protocol details - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 5)	Sample quote(s)
Reaching consensus among collaborators/ partners	2	"Multiple partners wanting inclusion of their project vs not overburdening participants. We are working on compromises"
Pilot findings resulted in a delay	1	[Population subgroup] trial results resulted in a [several] month pause in the trial. Lots of further discussions around our protocol before consensus was reached.
Change to patient recruitment process	1	"Recruitment time window is restrictive and there are good arguments in either direction to change it"
Not applicable	1	
Grand Total	**5**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Ethics approvals

Few respondents to the survey reported difficulties in implementing or conducting their trials due to difficulties related to ethics approvals: this was the case for 22% of MRFF respondents, and 16% of NHMRC respondents.

Table 84 Difficulties in implementing or conducting your trial: Ethics approvals

	MRFF (n=213)		NHMRC (n=74)	
Yes	46	22%	12	16%
No	158	74%	40	54%
Not yet applicable	9	4%	22	30%
Total	**213**	**100%**	**74**	**100%**

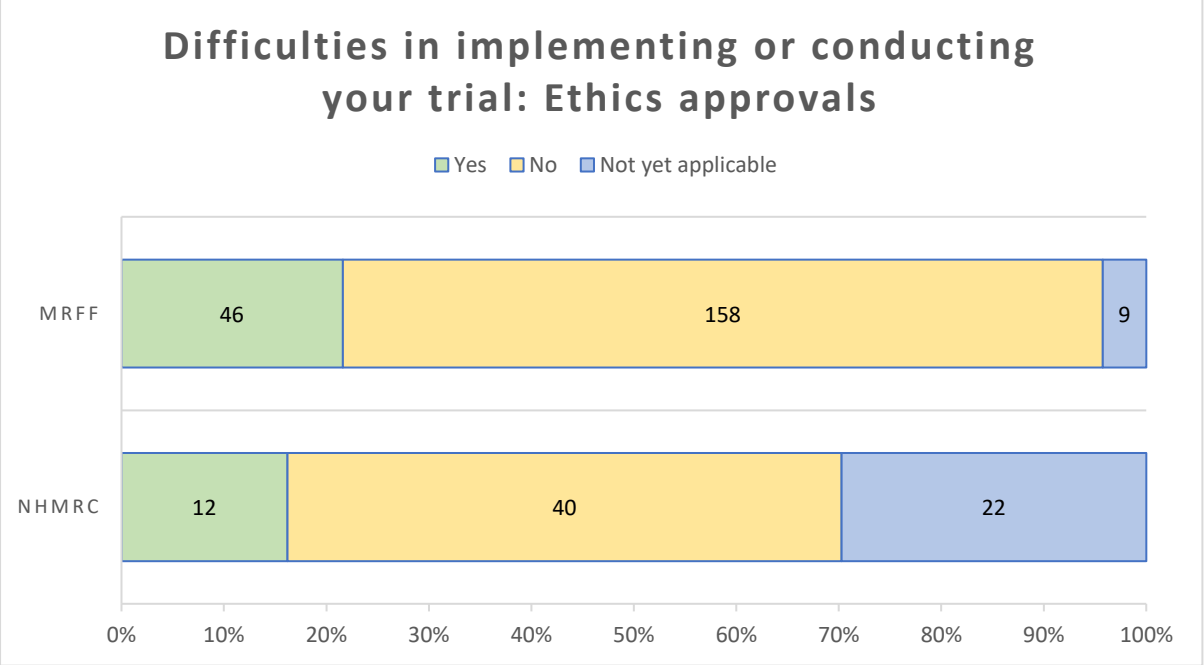


Figure 53 Difficulties in implementing or conducting your trial: Ethics approvals

45 MRFF respondents provided free-text responses which cited, in aggregate, 54 issues. Most commonly, these mentioned ethics approval delays (n=21) and multi-site approval delays (n=11).

Table 85 Difficulties in implementing or conducting your trial: Ethics approvals - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 45)	Sample quote(s)
Ethics approval delay	21	"Some delay with initial ethics but then subsequent delayed time to ethics approvals for amendments severely delayed the trial" "Delayed commencement due to prolonged HREC approval"
Multi-site approval delay	11	"a number of versions of the Protocol/Participant Information and Consent Form and multiple requested changes to documents" "No problem locally, but major delays interstate and internationally"
Recruitment delay	5	"Unable to recruit patients in some areas of Australia, due to existing legislation." "Delay in being able to commence recruitment"
Delay (unspecified or unclear)	4	"Delays really. Even with all the preparation in the world"
Governance approval delay	3	"Delay in governance at local sites" "Delay in trial progress due to ethics and governance approval processes"
Study start delay	3	"Significant delays in receiving approval. Feedback provided was at odds with experience of our team in doing research and working with [intervention]. Delayed onset of trial by several months."
COVID-related delay	2	"COVID shutdowns and travel restrictions, and other local conditions have consumed a lot of time from the approved period to conduct research."
Site activation/ initiation delay	2	"Delayed site initiation at multiple sites across multiple states"
Delay in reaching study design consensus	1	"disagreement around whether to apply for single trial, with two intervention arms, or as two separate trials. Disagreements between various groups including clinical trials team, ethics office, pharmacy etc"
Costs	1	"Significant time delays and added costs."
Community interest decreased	1	"Communities research appetite has also come down"
Grand Total	**54**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

11 NHMRC respondents provided free-text responses. Most commonly, these mentioned issues around multi-site approval or ethics approval delays.

Table 86 Difficulties in implementing or conducting your trial: Ethics approvals - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 11)	Sample quote(s)
Multi-site approval delay	7	"[Multiple] Nine sites, not all mutually recognising, all wanting minor variations in method, public facing docs etc - laborious and time consuming. We ended up prioritising potentially larger sites so that we could get started. Smaller sites still delayed" "We used the NMA process, however a number of our study sites do not participate in the NMA and submissions through non NMA ethics approvals have been onerous and prolonged duration between initial submission and approval."
Ethics approval delay	4	"Our trials required ethics approvals from a number of HRECs. Different committees requested different minor amendments to our protocols and processes, which caused a little further delay. In addition, there were associated time delays while waiting for each committee to approve the final project." "each local HREC at potential participating sites has additional specific needs. This has led to extensive, time consuming processes that has delayed site set-up and therefore trial recruitment"
Grand Total	**11**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Governance/Study Site Approvals/Contracts

The most common response to this survey question was yes – 53% of MRFF respondents and 35% of NHMRC respondents experienced difficulties in implementing or conducting their trials due to governance / study site approval / contract issues.

Table 87 Difficulties in implementing or conducting your trial: Governance/Study Site Approvals/Contract

	MRFF (n=213)		NHMRC (n=74)	
Yes	113	53%	26	35%
No	90	42%	24	32%
Not yet applicable	10	5%	24	32%
Total	**213**	**100%**	**74**	**100%**

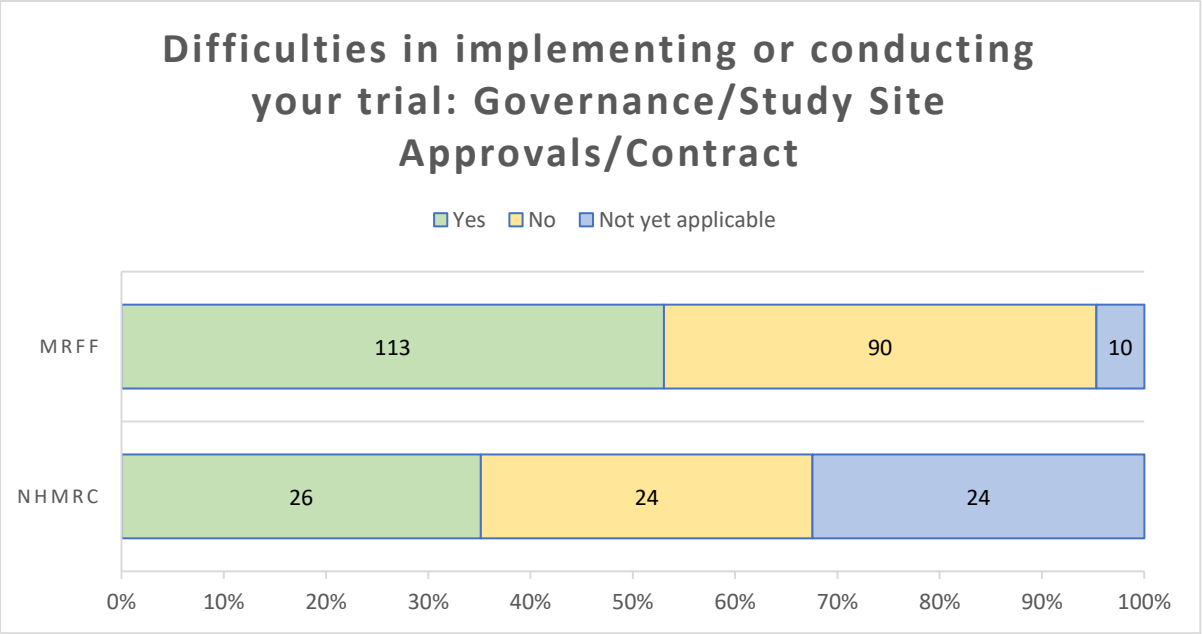


Figure 54 Difficulties in implementing or conducting your trial: Governance/Study Site Approvals/Contract

111 MRFF respondents provided free-text responses which cited, in aggregate, 140 issues. Most commonly, these mentioned contract execution (n=27) and governance delays (n=23).

Table 88 Difficulties in implementing or conducting your trial: Governance/Study Site Approvals/Contract - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 111)	Sample quote(s)
Contracts execution delay	27	"Complex structure with contracts to be signed between international and local sponsor and delays associated with receiving fully executed contract from international sponsor." "Contracts took 12 months to execute, significantly delaying the commencement of the trial." "Getting contracts and institutional approvals for the grant has been a major hurdle"
Governance delay	23	"Governance approval was our major barrier to activating sites and subsequent recruitment of participants." "Governance delays are extremely difficult where multiple sites are required. Ethics now is a centralised process and is efficient. Governance depends on multiple sites organisational requirements and differs with every site. it is very slow and sites were also closed during the pandemic and were slow to get back into the swing of research. We have opened [N indicated] sites and we have Ethics approval for [~2x as many] further sites across Australia that are awaiting governance still now >12 months waiting."
Delays (type unspecified)	23	"Fiddly long process"
Delay to study start/ completion	21	"Huge and severe. Delayed the trial commencement by 1 - 1.5 years"
Site start delay	11	"extreme delays precluded a major site joining in time" "delays in getting site approvals - especially at the University level - as complex negotiations needed to sort out indemnity and sponsorship"
Multi-institution agreement delay	10	"The [University Name]'s contract office is particularly slow at arranging Multi-Institutional or Service Agreements and this resulted in a delay in us receiving our necessary agreements and governance approval." "Delays in multiinstitute agreements and collaborative contracts due to legal to-ing and fro-ing"
Patient recruitment delay	7	"Delayed recruitment of participants" "Unable to recruit in certain jurisdictions, as no facility to enrol [specific patient group]"
Ethics delays	7	"delays because of ethics"

		"Multiple ethics applications required to conduct research over multiple sites."
Unclear answer	5	
Staff shortage/ availability	4	"staff shortages brought about by staff illness due to the pandemic." "Delays with agreements occurred due to staff shortages and high workload within [University's Research Office]. Impacts have been delays to site setup."
Not applicable	2	
Grand Total	**140**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

25 NHMRC survey respondents provided free-text responses which cited, in aggregate, 29 issues. Most commonly, these mentioned contract execution delays and governance delays.

Table 89 Difficulties in implementing or conducting your trial: Governance/Study Site Approvals/Contract - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 25)	Sample quote(s)
Contracts execution delay	9	"Delays in receiving the funding has led to delays in contracts being arranged, which has knock on effects on timelines." "These are incredibly slow at many sites, and reprosecute all of the same questions that ethics have already approved due to the NMA process. This means that contracts are often revised to adjust"
Governance delay	4	"Governance process in some jurisdictions is pain free, but in SA and WA it is laborious, unhelpful, incredibly slow and delays patients being able to participate in important clinical trials." "Variability in governance requirements. Just takes time and effort"
Delay to study start/ completion	3	"The trial was delayed and paused, waiting for clarity of restoration of normal hospital work practice, normalised patient medical and surgical services, and research practice."
Not applicable	3	
Unclear answer	2	
Delays (type unspecified)	2	"Slow."
Costs	2	"increased time spent on governance has negatively impacted the budget as we had to employ extra staff to manage the load"
Overseas approval delays	1	"international trials require country specific approvals. this is particular challenging in countries with weak regulatory systems"
Site start delay	1	"Delay starts for sites."
Patient recruitment	1	"Extension of timeframes that impact recruitment"
Multi-institution agreement	1	"Substantial delay in sign off of multi institution agreement delaying all other milestones"
Grand Total	**29**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Availability of trial materials (e.g. drugs, data collection instruments)

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

Table 90 Availability of trial materials

	MRFF (n=213)		NHMRC (n=74)	
Yes	52	24%	11	15%
No	143	67%	38	51%
Not yet applicable	18	8%	25	34%
Total	**213**	**100%**	**74**	**100%**

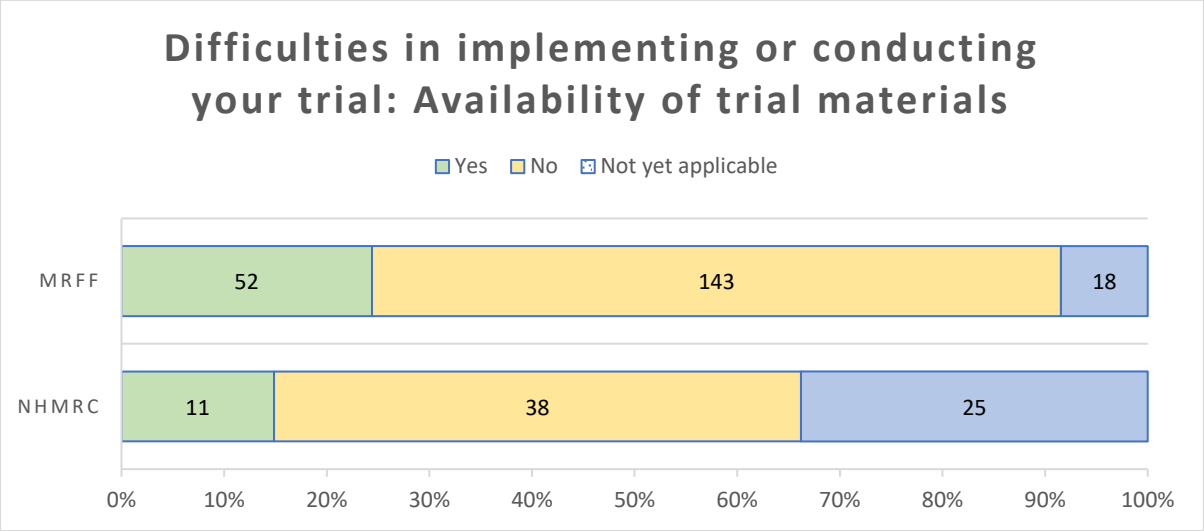


Figure 55 Availability of trial materials

52 MRFF respondents provided free-text responses which cited, in aggregate, 60 issues. Most commonly, these mentioned medication sourcing delays (N=24).

Table 91 Availability of trial materials - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 52)	Sample quote(s)
Medication sourcing delay	24	"Drug production and shipment delays [drug named] first due to the pandemic and then pending amendments to the site contracts to satisfaction of companies." "delay in drug and placebo packaging meant delay in trial commencement" "Difficulty in finding drug manufacturer (worldwide)."
Equipment sourcing delay	8	"Ordering clinical equipment (comes from [country 1 and country 2] - have to wait for arrival here, no stock in Aus)" "Shortage of reagents for clinical test that is part of the trial intervention resulted in long delays for intervention results for participants. Ultimately this may decrease the power of the trial. This was due to the pandemic"
Study consumables (type not specified) delay	6	"Severe. Had to negotiate with suppliers to re- establish supply" "Pandemic related delays in supply of IP from [country]"
Delay (type not specified)	3	"Substantial and continues to be."
Study commencement delay	3	"Delay in commencement of [study description]" "Delays meant study was not able to start prior to outbreak of COVID"
Recruitment delay	3	"The [regulator] has recently announced a global shortage of the [intervention]. This has slowed down recruitment and governance processes at sites where the drug is not available."
Unclear answer	3	
Study design change	2	"We were forced to design two 2-arm trials rather than a single 3-arm trial because of difficulty in obtaining [intervention] from our original supplier" "had to change from double-blind (with placebo) to open due to alternation in pharma business model and high costs of placebo"
Costs	2	"high cost of medications for clinical trials and placebo costs"
Biological materials delay	2	"Prolonged time for vaccine manufacture by [organisation]"
Not applicable	2	
Contracts delay	1	"Delays in getting the commercial contracts developed."
Study staffing challenges	1	"We needed to develop a website which was delayed due to low staffing during the pandemic."
Grand Total	**60**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

11 NHMRC respondents provided free-text responses which cited, in aggregate, 13 issues. Most commonly, these mentioned medication sourcing delay (n=3) and cost increase and medication distribution across sites (both n=2).

Table 92 Availability of trial materials - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 11)	Sample quote(s)
Medication sourcing delay	3	"company sourcing meds has changed provider several times based on price and availability (inflation, covid etc)"
Costs increased	2	"Medication quote once funding obtained was several times higher than the medication quote when the grant application went in, so this has caused issues with budget and delay in commencements while negotiations are ongoing."
Medication distribution across sites	2	"The approach to drug delivery has been challenging as different sites have different expectations" "There have been issues with trial medication distribution during the pandemic"
Unclear answer	2	
Unusuable trial materials	1	"Suspected contamination of study imported from [country]"
Biological materials delay	1	"No [specific type of biological material collection] was possible due to suspension of public [biological material] Bank activities (as a consequence of suspended hospital and donor/patient access)."
Equipment sourcing delay	1	"Delays in sourcing trial equipment due to supply chain challenges"
Not yet procured materials	1	"We're still trying to figure out which [source] to use to [obtain the material]"
Grand Total	**13**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Recruitment

Site recruitment or site setup

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

Table 93 Site recruitment or site setup

	MRFF (n=213)		NHMRC (n=74)	
Yes	87	41%	19	26%
No	103	48%	26	35%
Not yet applicable	23	11%	29	39%
Total	**213**	**100%**	**74**	**100%**

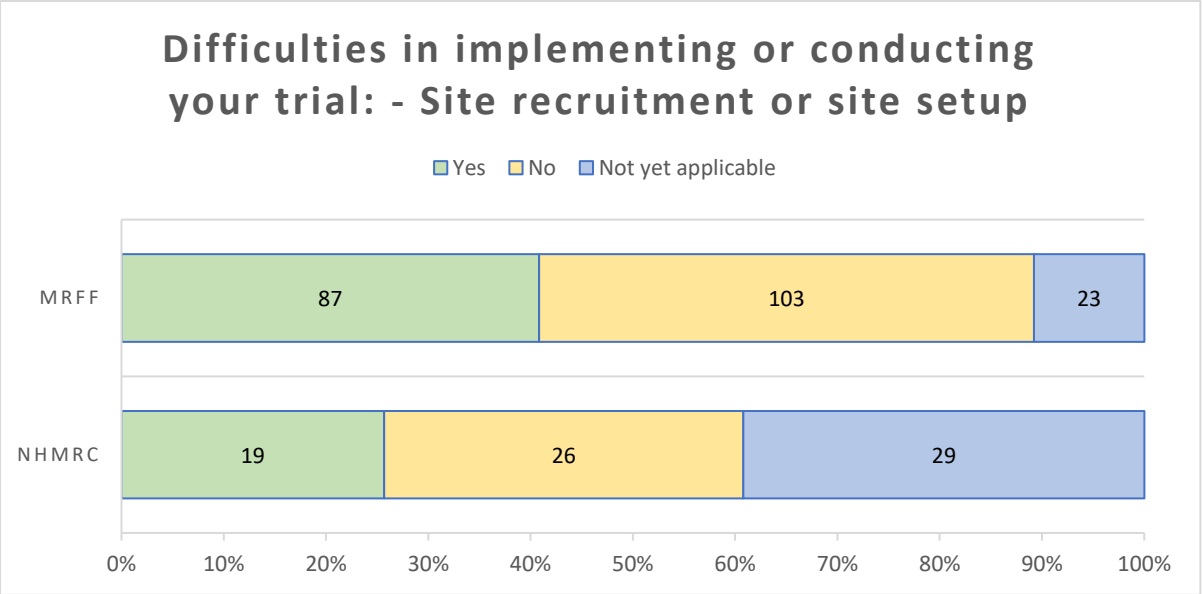


Figure 56 Site recruitment or site setup

85 MRFF respondents provided free-text responses which cited, in aggregate, 114 issues. Most commonly, these mentioned patient recruitment delays (n=28) and site setup delay (n=27).

Table 94 Site recruitment or site setup - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 85)	Sample quote(s)
Patient recruitment delay	29	"Delay in patient recruitment" "lengthy process delayed recruitment of first patient in NSW and Queensland" "Slower recruitment than anticipated"
Site setup delay	27	"Pandemic meant we couldn't get into the hospitals [specific hospital dept indicated] to commence recruitment." "For a simple clinical trial, we have had challenges with some site set-up when clinics are in a 'private' rather than public indemnity arrangement" "The perceived and actual additional workload is beyond the capacity of some sites due to pandemic related resource constraints"
Staff had COVID-related clinical obligations	11	"Site recruitment has been limited by reduced availability of research coordinator staff across the board and redeployment of site investigators to other roles such as COVID. " "Staff lost due to COVID-19" "Many preferred, reliable trial sites were reluctant to take on the study due to overstretched staff due to the pandemic"
Difficulties finding/ recruiting staff	9	"Employing suitable research staff was problematic. The salary scales utilized by MRFF are not sufficient to be competitive in the current climate and thus it is extremely difficult to attract appropriate staff." "Slow to progress through start-up (outside of COVID delays) - substantial shortage of trial coordinators nationwide"
Budget is limited	6	"We could not meet sites expectations for PP reimbursement (about 10-20% of their reimbursement for industry-funded trials). Most sites will be operating at considerable loss/ in-kind by participating." "Investigator initiated trials typically do not present the same magnitude of financial reimbursement for sites as industry sponsored studies."
COVID disruption/ delay (nature unspecified)	5	"These impacts are COVID-related." "Covid disruption +++"
Ethics delays	5	"delays from ethics had a flow on effect to recruitment"

		"General delay due to local site ethics"
Unclear answer	5	
Governance processes delay	4	"Once opened, all sites recruited quickly and effectively, validating the trainee led model and trial protocol. Many sites had long lead times due to inappropriate governance processes, and had the trial depended on those sites, it would have failed to recruit on time in budget"
Protocol/ design required changing	3	"needed to vary protocol as recruitment was delayed and so design of study had to vary"
Multi-institutional agreement delay	3	"executing a multi institutional agreement rapidly to allow for trial commencement was very challenging especially given we had [N>10] partners"
Delays to study start/completion	3	"trial took a year longer than planned, in addition to pandemic related delays. the planned sample size was not quite achieved when funds ran out but we came close"
Not applicable	2	
Delays (type unspecified)	1	"Delays"
Difficulty accessing workspace	1	"During the pandemic we were unable to access space to locate the new team"
Grand Total	**114**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

19 NHMRC respondents provided free-text responses which cited, in aggregate, 27 issues. Most commonly, these mentioned patient recruitment delay (n=7) and site setup delay (n=6).

Table 95 Site recruitment or site setup - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 19)	Sample quote(s)
Patient recruitment delay	7	"Delayed timeframes due to lower than anticipated recruitment due to the pandemic" "Recruitment rate halved."
Site setup delay	6	"Changeover of staff meant that there was no local clinician to advocate for the site being used for research. This delayed us bringing all our planned sites on board." "We had to abandon some planned sites due to staff changeover"
difficulties finding/ recruiting staff	5	"delays in recruiting staff who can work in the hospital setting" "site staff were exhausted post pandemic" "We had a site unable to join and recruit for the trial due to pandemic-related hiring freezes"
Delay to study start/ completion	3	"We had to change the Institution where the study was to be housed in Melbourne which resulted in delays." "the omicron outbreak in 2022 overwhelmed [clinical setting where the study was to take place], so we deferred commencing recruitment till Spring time"
Staff had COVID-related clinical obligations	2	"site PI's are all practicing clinicians with limited time availability, especially over COVID"
Delays (type unspecified)	1	"Delays"
Unclear answer	1	
Ethics delays	1	"Site set-up in New Zealand has been more straightforward with a single national ethics process leading to only local site specific and clinical research agreements needing to be arranged. In Australia, it has been a very different process. Each hospital has its own requirements in regards to local ethics approval, even with NMA in place."
Governance processes delay	1	"Rotating research staff especially RCs meant delays in local submissions to governance and site education."
Grand Total	**27**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Recruitment of trial participants

MRFF respondents to the survey commonly experienced challenges around recruitment of trial participants – 46% of the respondents reported this, and this was the most common answer.

For the majority of NHMRC respondents, this challenge was not yet applicable (51%), although a sizeable proportion (30%) reported encountering difficulties in implementing or conducting their trial due to issues around recruitment of participants.

Table 96 Recruitment of trial participants

	MRFF (n=213)		NHMRC (n=74)	
Yes	98	46%	22	30%
No	64	30%	14	19%
Not yet applicable	51	24%	38	51%
Total	**213**	**100%**	**74**	**100%**

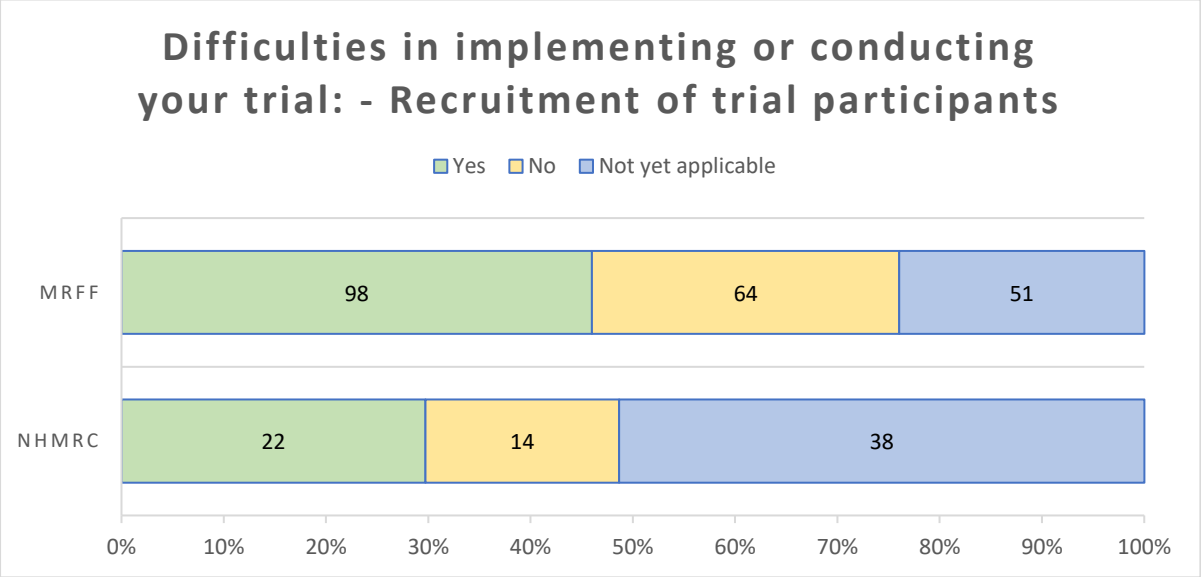


Figure 57 Recruitment of trial participants

97 MRFF respondents provided free-text responses which cited, in aggregate, 112 issues. Most commonly, these mentioned patient recruitment delays (n=35) and difficulties in accomplishing the recruitment target (n=28).

Table 97 Recruitment of trial participants - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 97)	Sample quote(s)
Patient recruitment delay	35	"COVID delays in recruitment" "Due to the number of delays mentioned we were required to extend recruitment by 10 months." "Due to the pandemic, and the associated lockdowns, we did not recruit at the rate that was predicted [prior to grant submission] and as a result our recruitment has taken longer and been slower."
Recruitment target difficult to accomplish	28	"not meeting goals for recruitment" "Recruitment saturation prior to full sample size recruitment [N indicated]. Need for additional recruitment sites." "We have had to engage professional recruitment agency and find additional $50,000 to do so. We have never had trouble recruiting before but suspect a covid impact."
Delay to study start/completion	19	"delays in trial progress" "lengthened timelines, delayed primary outcome timing, delayed publication of results" "we will not finish on time as this has been challenging."
Delays (type unspecified)	8	"Delays"
Unclear answer	6	
Staffing availability challenges	4	"Clinical services still so impacted by Covid this year. Numerous staff shortages, staff working across different teams to cover shortages, staff burn-out, meant recruitment of patients another task to add to their workload."
Not applicable	4	
Protocol/design required changing	3	"With approval from ethics, we reduced target recruitment to accommodate [COVID-related recruitment delays] and implemented virtual consent procedures."
Consent challenges	2	"As per ethics requirement, clinicians needed to tell patients about study and provide PIS for patient to consider, they then needed to wait until second visit to get consent (so patient had time to consider). Covid changed pattern of practice of [allied health area] and 2nd visit did not happen as frequently as previously, thus consent was challenging for clinicians to get."
Costs	2	"lengthening study, pressure on budget"
Governance process delay	1	"Potential participants were not able to be recruited into the trial because of governance delays."
Grand Total	**112**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

22 NHMRC respondents provided free-text responses which cited, in aggregate, 29 issues. Most commonly, these mentioned patient recruitment delay (n=12) and difficulties reaching recruitment target (n=7).

Table 98 Recruitment of trial participants - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 5)	Sample quote(s)
Patient recruitment delay	12	"It is hard to say as the study is ongoing but we have probably recruited around 30-40% fewer of our in scope sample than we had anticipated." "Recruitment took a little longer than planned, and we will fall slightly short of the target sample size."
Recruitment target difficult to accomplish	7	"monthly recruitment below anticipated numbers due to impacts with site set-up and COVID" "reduced referrals from clinicians and the last-minute switch to telehealth from face-to-face interviews. Even when face-to-face interview had resumed, a lot of people were still uncomfortable with human contact and we presume this greatly reduced the recruitment."
Delay to study start/completion	3	"Delayed recruitment due to Covid has extended out trial timelines" "study was paused"
Costs	3	"Need to extend recruitment period, extra costs" "With ongoing delays, it is currently projected that the trial will need a further later shift in expected recruitment end date. With the primary outcome being 2 year follow-up, this will add to delayed reporting and also the need to apply for additional funding support once existing grants finish."
Staffing availability challenges	2	"We have potential trial participants we can't see because we can't get staff - and therefore we are losing participants"
Unclear answer	2	
Grand Total	**29**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Recruitment of trained trial or research personnel

Majority of MRFF respondents (66%) and nearly half of NHMRC respondents (47%) to the survey, reported no difficulties with the recruitment of trained trial or research personnel.

Table 99 Recruitment of trained trial or research personnel

	MRFF (n=213)		NHMRC (n=74)	
Yes	62	29%	15	20%
No	141	66%	35	47%
Not yet applicable	10	5%	24	32%
Total	**213**	**100%**	**74**	**100%**

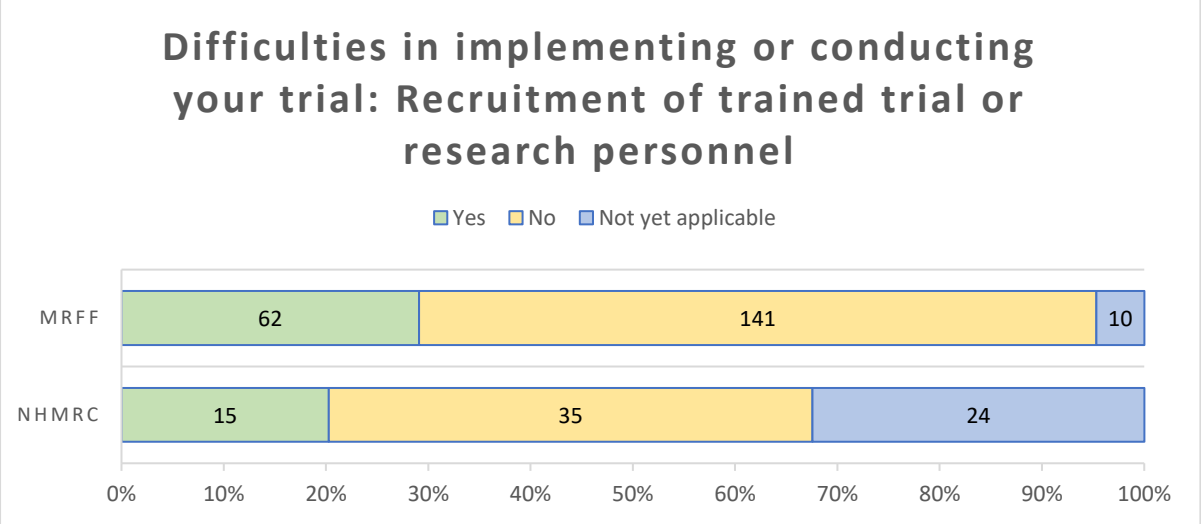


Figure 58 Recruitment of trained trial or research personnel

61 MRFF respondents provided free-text responses which cited, in aggregate, 85 issues. Most commonly, these mentioned difficulty in finding staff (n=33) and delays to study start / completion (n=16).

Table 100 Recruitment of trained trial or research personnel - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 61)	Sample quote(s)
Difficulty finding staff	33	"Challenges recruiting research manager, study coordinator, research assistants for trial across sites, in the context of broader workforce challenges post-pandemic." "It has been difficult to recruit research assistants. There is a general shortage of relevant academic staff across the sector" "Almost impossible to hire clinical trial co-ordinators at present - difficult to attract and retain good staff and to compete with pharma"
Delays to study start/ completion	16	"Delay in starting study at some sites" "All sites had issues with research personnel shortages which delayed both start up and rate of recruitment to a greater or lesser extent."
Recruited staff less experienced/ needs more training	15	"Recruitment of staff has become more tough recently to COVID pandemic. Fewer candidates appropriate candidates are applying for jobs in this current climate and often require more extensive training." "Trained Clinical Trial Coordinators are extremely difficult to find. We had to hire someone inexperienced and train up. We need more capacity building in this area."
Staff has competing commitments	6	"Difficulty recruiting and resourcing the trial as intended, as all teams were very stretched (i.e. workload) due to ongoing impacts of the pandemic on other research projects and other commitments (e.g. teaching)" "The impact of reduced frontline nursing staff has led to low parent engagement and many of the eligible subjects are missed."
Not applicable	3	
COVID disruption (type unspecified)	3	"COVID-19 delays"
Unclear answer	3	
Delays (type unspecified)	2	"Delays."
Budget limitations	2	"Limited staff with experience available at payrate available within grant."
Need for other employment	2	"Because of significant delays, junior members of the research team had to look for other positions to stay afloat"
Grand Total	**85**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

15 NHMRC respondents provided free-text responses which cited, in aggregate, 22 issues. Most commonly, these mentioned difficulties finding staff (n=11).

Table 101 Recruitment of trained trial or research personnel - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 15)	Sample quote(s)
Difficulty finding staff	11	"Small pool of available skilled staff in remote locations." "With COVID, finding the skilled workers for this has been hard" "Project manager and site research staff both had difficulties in finding large numbers of skilled applicants
More secure employment in industry/ clinical practice	2	"we're not retaining BPsych(Hons) research assistants in academia as much as we would like to, as they see a career in research to be too difficult due to funding uncertainty, short contracts, etc."
Delays to study start/completion	2	we could recruit more participants and finish more quickly if we could find staff
Higher wages in industry/ clinical practice	2	Now, the current job market is meaning that many research personnel are accepting higher paid jobs with industry/pharma rather than working in research institutes Very difficult to recruit talented researchers/bioinformaticians due not being able to offer competitive wages compared to industry
Recruited staff less experienced	1	"Recruitment of staff has become more tough recently to COVID pandemic. Fewer candidates appropriate candidates are applying for jobs in this current climate and often require more extensive training."
Budget is limited	1	"our budget is limited so we can only afford them [type of allied health care professional] for the period when they are conducting assessment and therapy, and the unstable nature of the work means we train them up and they leave for better work opportunities"
Unclear answer	1	
Impact on staff from working remotely	1	"Employing staff was difficult for all the obvious reasons - we had staff who did not meet each other face to face for long periods. Staff had mental health problems and were juggling priorities and knowing how to support them and manage these new issues in the early stages before good systems were set up was difficult."
Delays (type unspecified)	1	"Delays"
Grand Total	**22**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Access to biostatistical support

Few survey respondents – 3% of MRFF respondents and 1% of NHMRC respondents – reported difficulties in implementing or conducting their trials due to difficulties accessing biostatistical support.

Table 102 Access to biostatistical support

	MRFF (n=213)		NHMRC (n=74)	
Yes	6	3%	1	1%
No	188	88%	55	74%
Not yet applicable	19	9%	18	25%
Total	**213**	**100%**	**74**	**100%**

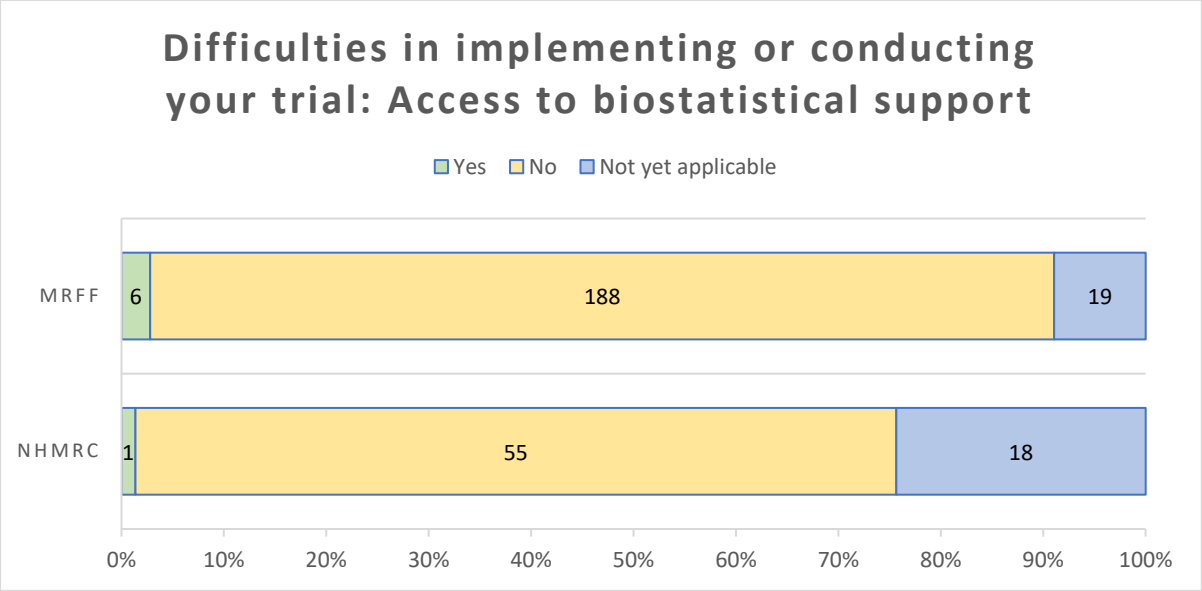


Figure 59 Access to biostatistical support

6 MRFF respondents provided free-text responses which cited, in aggregate, 6 issues. Most commonly, these mentioned the shortage of biostatisticians (n=2).

Table 103 Access to biostatistical support - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 6)	Sample quote(s)
Shortage of biostatisticians	2	"Limited access to biostatistical support through the [Institution]. Got biostatistician on board from local health district but he left his role."
Not applicable	2	
Delayed the study	1	"Delayed study elements."
Grant insufficient to cover salary	1	"There will be a significant salary gap for biostats support which the grant will not cover. Will need to obtain funding through other means to cover this in order to complete a robust trial."
Grand Total	**6**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

1 NHMRC respondent provided a free-text response, citing difficulties in recruiting a biostatistician.

Table 104 Access to biostatistical support - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 1)	Sample quote(s)
Difficulties in recruiting a biostatistician	1	Respondent provided information that the study hired a biostatistician who did not commence on start date as planned, and the recruitment had to be repeated. [The information provided here is paraphrased rather than quoted due to reidentifiable information provided in the response quote]
Grand Total	**1**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Did you experience data analysis issues at the post-data collection stage?

For the majority of both MRFF survey respondents (83%) and NHMRC respondents (91%), difficulties pertaining to data analysis at the post-data collection stage were not yet applicable.

Table 105 Did you experience data analysis issues at the post-data collection stage?

	MRFF (n=209)		NHMRC (n=71)	
Yes			2	3%
No	36	17%	4	6%
Not yet applicable	173	83%	65	91%
Total	**209**	**100%**	**71**	**100%**

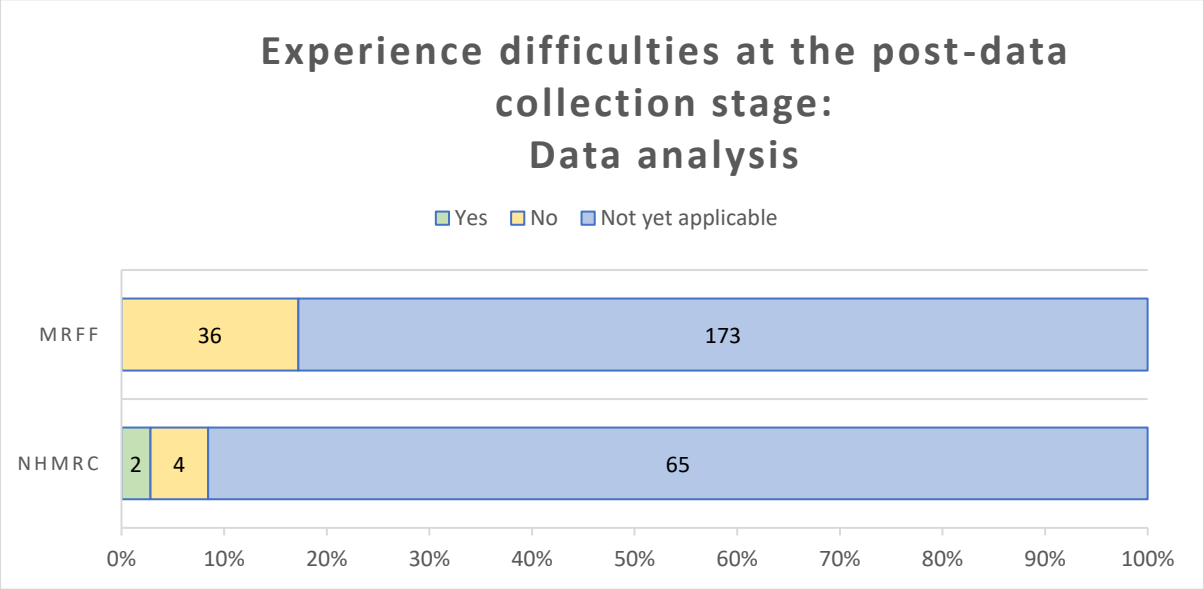


Figure 60 Did you experience data analysis issues at the post-data collection stage?

Stakeholder comments around recruitment challenges

The above findings were presented to the stakeholders

The stakeholders' responses to this data focused on the following areas: recruitment issues, site issues, personnel issues, materials, ethics, and other relevant observations. The issues, comments or questions under each area, included:

Site issues (including governance and contracts)

- Barriers to conducting trials happen at site-specific agreements, and contractual agreements. Funders do have a role to try to speed this along
- Starting a big trial usually happens at a couple of sites, to iron out the issues – one does not start at dozens of sites at once. There is a lot of preparatory work prior to trial starting
- One cannot recruit participants before recruiting sites

- It may not be possible to simplify site specific approvals – this has to be done individually at each site
- Contracts vary across institutions, but there may be a standard contract
- It would be reasonable for the funder to ask to name at least some of the trial sites, even if a letter from them is not yet available – this could assist with visibility and recruitment of trained personnel
- There used to be more delays with SSA – now they are approximately 1 month
- There have been a few attempts to identify standard charges for each budget items, which could allow governance to make a determination that the trial budget is on par with what is expected – this is usually the main delay with the sign-off
- The main problem in [disease area] is site recruitment – clinicians do not want to be involved

Recruitment issues (patients/participants)

- The PIs don't usually understand the difficulties encountered by trial managers regarding implementing or conducting the trial, or recruitment of participants (suggesting that the level of difficulties reported may have been higher, had trial managers been surveyed)
- Patients do approach clinicians about participating in trials having learned about them from clinicaltrials.gov – the ANZCTR is not as easy to search
- COVID has led to considerable delays in recruitment – but the extensions on funded trials may not have been long enough in some cases
- Grant applications could be more explicit about the size calculation and evidence to back that calculation up
- Recruitment issues can be mitigated by pilot-testing the inclusion criteria – e.g. via small pilot trials or cohort studies, and these can also be used for power calculations

Personnel recruitment issues

- There are not enough research nurses
- A master's programme teaching trial coordination could be an enabler
- Clinical research organisations often pay better, so after an individual is trained, they may leave for one of those organisations
- Governance and personnel have been significant problem. It can take months to recruit a staff member – that is a big barrier
- I'm surprised many are saying they are not having issues with site recruitment or setup, and research personnel – we have felt strong concerns about those areas

Other

Uptake and fidelity of the intervention

For the MRFF survey respondents, challenges associated with the uptake and fidelity of the intervention were rarely experienced – 62% 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 106 Uptake and fidelity of the intervention

	MRFF (n=213)		NHMRC (n=74)	
Yes	14	7%	4	5%
No	132	62%	26	35%
Not yet applicable	67	31%	44	60%
Total	**213**	**100%**	**74**	**100%**

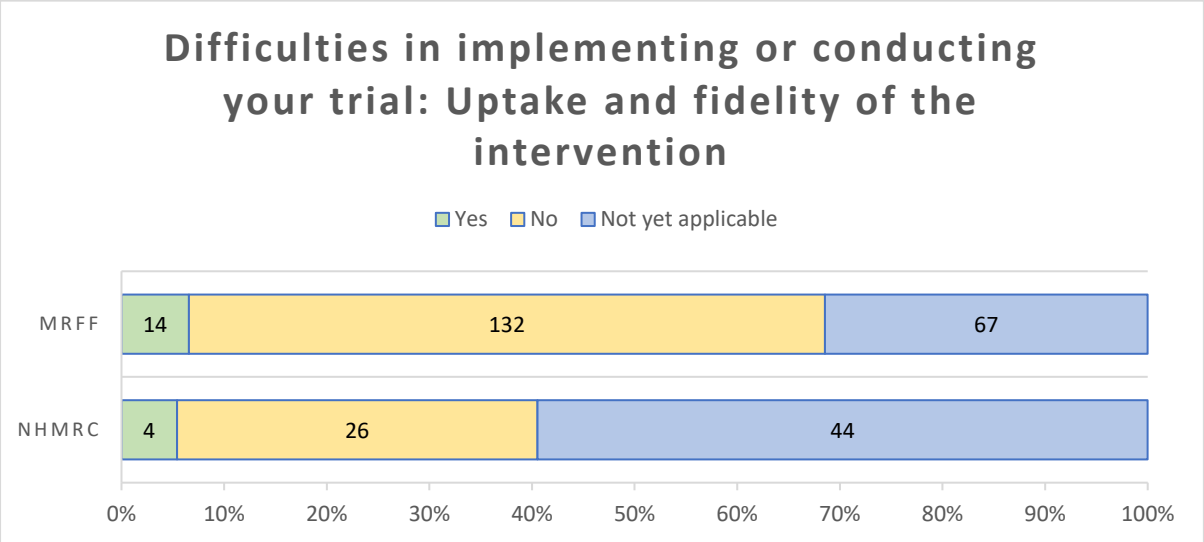


Figure 61 Uptake and fidelity of the intervention

12 MRFF respondents provided free-text responses which cited, in aggregate, 16 issues. Most commonly, these mentioned COVID-related challenges (n=4).

Table 107 Uptake and fidelity of the intervention - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 12)	Sample quote(s)
COVID-related challenges	4	"COVID related changes in care models that has been very disruptive to the planned experiments" "impacted due to the pandemic and need to attend on site"
Protocol deviations	2	"Reduced protocol compliance" "Some sites did not follow protocol at all times"
Need for sample size increase	1	"need to increase sample size"
Yet to be evaluated	1	"we will evaluate this"
Lower uptake than expected	1	"Lower than anticipated uptake"
Decreased capacity to engage with the community	1	"The reduced capacity to engage with the community and use community-based approaches to drive the messages impacted the intervention. Simple issues such as the willingness of individuals to attend face-to-face sessions, or the incapacity to hold face-to-face sessions, limited the number of people able to engage in the codesign activity. Moving this to online activity partially alleviated this but did not completely alleviate it as it meant that the codesign was limited to those able to and willing to engage online."
Poor adherence to the intervention	1	"poor adherence/completion of [the intervention]"
Decreased staff engagement	1	"Reduced enthusiasm for staff participation"
Staffing challenges	1	"Challenges with intervention continuity with changes in staffing"
Delays to receiving results	1	"assay delays meant delays in receiving results of [specified test] (meant to be within 2 weeks of randomisation)"
Costs of intervention	1	"Daily [procedure] was proven useful. At present the costs make it difficult for every patient"
Increased risk of harms	1	"Greater risk of AE's [adverse events]"
Grand Total	**16**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

4 NHMRC respondents provided free-text responses which cited, in aggregate, 4 issues (see Table below).

Table 108 Uptake and fidelity of the intervention - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 4)	Sample quote(s)
Attrition	1	"attrition has resulted in a less representative sample, i.e., retention of those from more advantaged socioeconomic areas, young people with low language skills less likely to be retained."
Care beyond the intervention is required by study participants	1	"Due to the life complexities experienced by some participants with [specified condition], counsellors providing the intervention under study are sometimes finding they are having to 'hold' or refer the participant for more intensive care, rather than deliver the intervention as intended."
Challenges assessing intervention impact	1	"Diluting assessment of intervention impact"
Unclear answer	1	
Grand Total	**4**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Disruptions due to the pandemic

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 pandemic-related disruptions.

Table 109 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%**

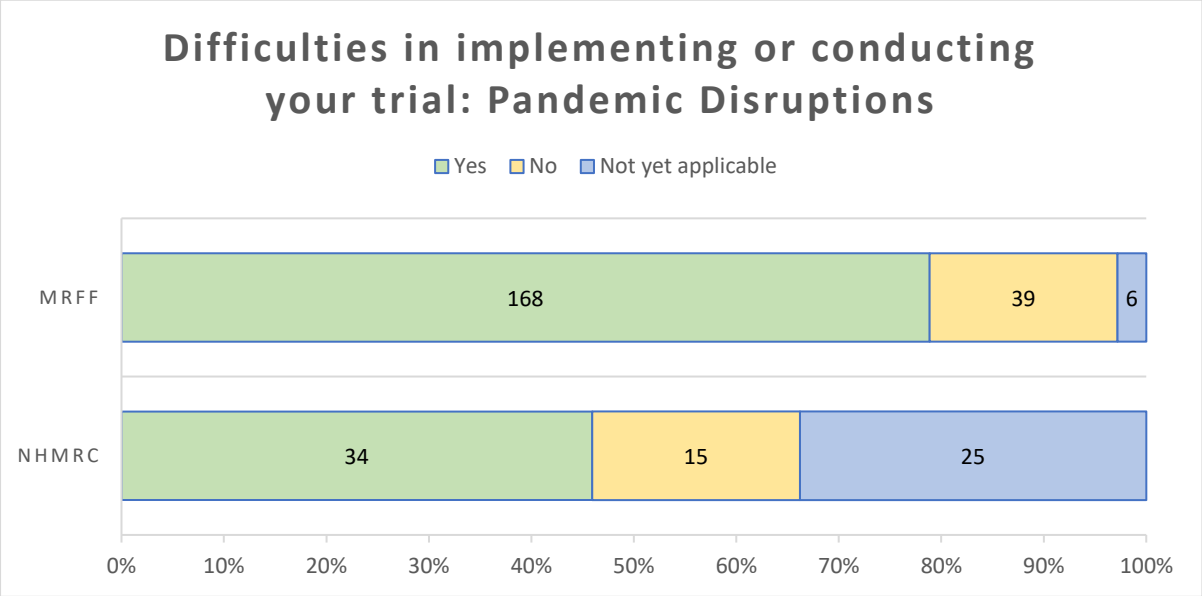


Figure 62 Disruptions due to the pandemic

166 MRFF respondents provided free-text responses which cited, in aggregate, 274 issues. Most commonly, these mentioned patient recruitment delays (n=87), delays to study start or completion (n=33) and staff availability (n=28).

Table 110 Disruptions due to the pandemic - free-text responses MRFF

Responses (MRFF)	N respondents raising each issue (N respondents total = 166)	Sample quote(s)
Patient recruitment delays	87	"Could not recruit participants due to hospitals ceasing all research activity" "Delayed start of recruitment / intervention delivery at sites due to COVID-19 restrictions on health care services" "Difficulty recruiting and retaining participants."
Delay to study start/ completion	33	"Delays in start date as our patients come from all over Australia" "In the first half of 2020 the trial was put on hold due to the pandemic. Throughout 2021 progress at some sites, particularly those in NSW and Victoria, was slow due to prolonged lockdowns." "Our intervention is meant to be delivered face to face. We delayed as long as we could during the pandemic to begin recruitment and intervention delivery."
Staff availability	28	"Availability of trial staff at participating hospitals, mostly due to COVID" "general practice staff including practice nurses leaving the profession as pandemic related work pressures became excessive. " "Difficulty in engaging with GPs, clinics and stakeholders, and difficulty in employing project management staff."
Site start delay	25	"Delayed site start ups and loss of potential sites due to clinical overload" "Many sites had temporary holds to recruitment during the worst of the pandemic, especially in Melbourne and Sydney." "Site start up and initiation of recruitment was slow due to reduced capacity at sites"
Protocol/ design required changing	22	"moving to virtual decentralised design due to inability to undertaken in-person assessments in hospital clinics" "We did get ethics approval to amend our protocol to include teletrials options, but this came with additional budget expenditure due to the safety monitoring of the trial."
Study materials availability	21	"Supply chain interruption thus unable to source trial drug" "delays in accessing consumables" "Withdrawal of pharmaceutical company support during this period"
Staff had COVID-related	14	"Clinical staff involved as site PIs and Research co-ordinators were less available as they were seconded to only working

Clinical obligations		clinically to make up for staff shortages in ED due to staff ill with COVID 19." "Research support staff [in hospitals] were seconded to clinical roles" "Primary Health Networks and GPs unable to engage in meetings to set up the pilot components of the trial due to time commitments related to running vaccination hubs."
Governance delay	13	"site infrastructure was decimated. No capacity for site governance approval" "We are still experiencing major delays. We were effectively excluded from research in the health system for 2 years. Initially, due to health services (quite rightly) focussing their efforts on the COVID response. However, even after opening up to researchers, there is 1) a backlog of ethics and governance approvals, 2) a massive loss in research momentum, 3) loss in rapport with staff, 4) staff burnout leading to a lack of interest in the 'additional' burden that research imposes. 5) less interest by the public in research. We anticipate that these impacts will continue for a very long time to come." [NB: this comment was coded to multiple themes including governance, but is reproduced here in its entirety for context]
costs	9	"had to stop of course. then the medications expired and we had to order new medications to resume and complete the trial. probably cost about $100k in additional staff time and medication costs" "Central trial costs continue (staffing especially) even when we are not recruiting participants"
Ethics delays	8	"delays in ethics approvals" "Ethics review was slow due to prioritisation of Covid related projects."
Delays (type unspecified)	4	"Delays"
Unclear answer	4	
Contracts execution delay	3	"Delays in contract agreements"
Multi-institutional agreement delay	3	"Mainly delays in getting MIA [multi-institutional agreement] and CTRA [clinical trial research agreement] execution"
Grand Total	**274**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

34 NHMRC respondents provided free-text responses which cited, in aggregate, 64 issues. Most commonly, the responses cited issues around delays to study start or completion (n=16) or patient recruitment (n=15).

Table 111 Disruptions due to the pandemic - free-text responses NHMRC

Responses (NHMRC)	N respondents raising each issue (N respondents total = 34)	Sample quote(s)
Delay to study start/ completion	16	"Total delay of about 18 months and an extra cost of $1.2-1.5 millions" "Essentially at present, this has put trial completion back by 1 year."
Patient recruitment delays	15	"inability to recruit for large periods of time" "Periods of reduced or no access to participants medical centres, hospitals or at home in communities for recruitment and follow up."
Staff availability	8	"Disruptions to working arrangements and staff being on sick leave." "the national shortage in staff then continues to impact a number of sites in the availability of research staff"
Protocol/ design required changing	5	"we had to move all data collection to phone based, and it also seems that we have missed some secondary outcomes" "The pandemic required new protocols for collecting biospecimens, adding higher costs"
Staff had COVID-related obligations	5	"Reduction in capacity of investigators and site investigators due to clinical duties" "Research staff being returned to clinical duties"
Site start delay	3	"Sites would not proceed with start up activities for a [non-COVID] condition during the pandemic."
Costs	3	"Financial impact: significant increase in cost of study material and medications, logistics and distribution costs." "There were also budget impacts as a result of everything taking longer and being more complicated"
Ethics delays	2	"Delayed ethics submissions, not accepting non-covid applications."
Contracts execution delay	2	University capacity to process relevant contracts significantly delayed commencement of project
Governance delay	3	"Many sites would not even start ethics approval or governance processes due to staff shortages."
Delays (type unspecified)	1	"Delays."
Delay to grant submission	1	"Delay to completion of pilot trial which delayed submission of grant"
Grand Total	**64**	

Where a quote mentioned a potentially identifiable detail, this was modified to protect the privacy of respondents. Modified text is identified in [square brackets]. N respondents and N Grand Total differs for some questions, as some respondents raised more than one issue in their response.

Barriers and facilitators

What do you see as the main barriers and facilitators to efficient conduct and successful outcomes for funded trials in Australia?

No data was presented as part of this question, during the Stakeholder Consultation.

The stakeholders mentioned a broad range of barriers – with recruitment of patients being mentioned most frequently (n=8).

Table 112 Main barriers and facilitators to efficient conduct and successful outcomes for funded trials in Australia?

Barriers mentioned	Number of respondents
Recruitment of patients	8
Ethics	4
Contracts between universities and (hospital) sites	3
Governance approval	3
Recruit researchers	3
Site specific approvals	3
Geographic distribution	2
Infrastructure	2
Money/Funding	2
Start- up cost	2
Amount of money for a study to charge per patient enrolment	1
Funding of health services	1
Funding to correct trial	1
Partners pull out	1
Research is too expensive in Australia (older complaint)	1
Statistics, analysis	1
Trials that were funded and never recruited	1

Can you suggest any options for reducing those barriers or enhancing the facilitators?

No data was presented as part of this question.

The stakeholders' responses included: suggestions for reducing the barriers or enhancing the facilitators, or other relevant comments. The issues, comments or questions raised under each category, included:

Suggestions for reducing the barriers or enhancing the facilitators

- MRFF is involved with the MTPConnect programme, which helps to improve the issue of the research workforce in Australia, which may help with some of the issues mentioned by the survey respondents
- Very few universities have setup clinical trial centres that have core staff (especially senior staff) who know how to setup a trial and are able to retain those people between funding cycles – more organisations need to do that
- NIHR's patient and public involvement initiative has had a beneficial impact on recruitment – in Australia, there is a lack of consumer/community involvement in trials
- UK system has clinical trial units, which are generic coordinating centres that take responsibility for central coordination of the trial – project management, protocol design, data management, statistics, health economics, etc. These units are accredited. To receive funding from NIHR, MRC, Wellcome, etc, one needs to use an accredited clinical trial unit. This approach has transformed clinical trials in the UK into one of the most successful clinical trials ecosystems. In Australia, there are probably 6-7 high-quality trial coordinating centres. But many MRFF- and NHMRC-funded centres are running outside of that system. The lack of central, structured coordination is probably a major driver of failed trials in Australia
- Very few trials that are endorsed by a clinical trial network fail – this is because those trials have been through internal, network peer-review before being submitted to a funding agency. It's a strength of the networks that they consist of clinicians who would be undertaking those trials – so if those clinicians think that the proposed research is not important or not feasible or they don't wish to be a part of this, that trial does not get the endorsement.

For conducting clinical research in Australia, what human and resource constraints do you see in current or future research capacities?

No data was presented to stakeholders as part of this question.

The stakeholders' responses focused on: staffing issues, budget issues, and other relevant comments. Issues, comments or questions raised, were as follows:

Staffing issues

- There is a labour shortage, especially with more skilled staff e.g. health economists and biostatisticians
- A lot of modelling and expertise is required to do really progressive and more adaptive or platform trial designs. Developing a sort of a 'hub system' of experts could help.
- Employing core staff is very difficult. But I think the best they can do is support clinical trial networks. I do not think MRFF can do much beyond this.
- Lack of consistent training of clinical research staff (clinicians and non-clinicians)
- Staffing infrastructure rounds are very hard to find – there was the NHMRC clinical research infrastructure scheme which included people for a while, but may have discontinued. MRFF infrastructure funding focuses on physical infrastructure, not staff.
- There are large workforce problems in the clinical trials sector, at least at the site level. The issues include: budget for the clinical staff's research role, research coordinators on short-term contracts. When these research coordinators are offered a job elsewhere, they leave the project. The turnover is a problem because research coordinators who have been in their role for a longer term are much more productive than someone in their first year. This is very inefficient.

Budget issues

- Money continues to be a constraint. The amount of funding in some cases (e.g. NHMRC CTCS) is enough for 5% of applications. It takes a lot of time to put together an application, so it is a waste of time
- There is a widening gap between the reality of running a trial and what the grant funding bodies consider to be reasonable. The real differ from allowed costs.
- Grants rarely get the right amount of funding due. They come up short on staffing requirements. There are examples of panels cutting funding for staffing (e.g. trial manager) because it was perceived that a researcher should be doing some of those tasks.

Other relevant comments

- MRFF has invested into research infrastructure
- The shift by funding bodies towards impact of prior research as a track record measure is good, but unequal across areas – researchers focusing more on discovery research may have less here than implementation researchers
- Lack of central infrastructure resources is a challenge.
- We don't have a central producer of study materials. For placebo, there are only two companies in Australia and both are very small.

Could MRFF funding assist with reducing those constraints?

No data was presented to stakeholders as part of this question.

The stakeholders offered suggested approaches and examples for how MRFF funding could assist with reducing these constraints, as well as made other relevant comments. The following issues, comments or questions were raised:

Suggested approaches and examples

- We could look to other countries, to see what they are doing, e.g., New Zealand
- In the UK, NIHR provides startup funding to allow preliminary work to be done – e.g. 50k pounds. This helps to get the trial started up and going.
- UK's approach to staff training is to have centralised trial units. Large universities like Oxford and Cambridge don't need that help. But they help to solve the problems for researchers elsewhere, who do not know the governance processes, where to get the placebo manufactured, etc. I do not know how many of them exist in the UK but certainly several.
- The Department of Health in New Zealand implemented infrastructure that everyone can benefit from. The HAS funds the trials that can make use of that national infrastructure.

Other relevant comments

- There is a lot of work involved in trial setup – often one or two sites are initiated, before all the others start. There is a lot of work that needs to happen before patient recruitment occurs.
- It is difficult to recruit and retain qualified trials people, especially on University wages. They can earn a lot more money in the industry. What grants provide does not cover salaries, and a researcher often has to find additional money to cover the gap.
- Some communities are commonly excluded from trials because it is too difficult and expensive to involve them – this is a problem. We could tie funding to addressing these issues?