Evaluation of the National Mutual Acceptance: the future of ethical review of clinical trials

B. Davies, A. Armstrong, M. Fitzpatrick

College of Law and Justice

Victoria University

The NMA offers many opportunities but for the NMA to achieve its aims, it is critical that the nature and scope of research governance is understood by all key stakeholders.

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From the Dean of the Victoria University College of Law and Justice

It gives me great pleasure to introduce this Report which is one in a series of Occasional Papers issued by the College of Law and Justice. The Report presents the results of research conducted by Dr. Bernice Davies and supervised by Professor Emeritus Anona Armstrong and Dr. Maree Fitzpatrick. The full thesis *Regulating the Regulators: Evaluation of the Corporate Governance of Clinical Research Undertaken Through National Mutual Acceptance* can be accessed through Victoria University's Research Repository.

Trialling innovative medications, medical devices and therapies offer significant benefits to the health and wellbeing of Australians as well as making a major contribution to PHO revenue. Over $1B is invested in clinical trials in Australia. In the past, the process has been criticised for its inefficiency and resulted in loss of business to overseas competitors. National Mutual Acceptance is a new system of single ethical review by which hospitals collaborate to review and approve the conduct of the trials.

The College's research is focussed on raising our ERA output by encouraging publications, growing our postgraduate programs, and achieving an impact from our research. This project has the potential to have a major impact on both the regulation of the industry and the processes underpinning the reviews.

This publication is a vital step in the promotion of the College of Law and Justice and its distinctive research and contemporary multidisciplinary research program. We thank the Department of Health, the hospitals and the applicants for their support in contributing to this research.

Please pass on this report to those who may be interested in working with us or getting in touch to learn more about the College.

Professor Michael Stuckey

Acknowledgements

This research would not have been possible without those who participated in the survey, and to those who generously gave their time for interviews.

We also thank Victoria University for allowing this course of study to be undertaken. This research was supported by the Victorian University Vice Chancellor's Graduate Research Award 2016 (incorporating) Australian Postgraduate Award.

Authors

Dr. Bernice Davies, BAppSci (Hons) PhD, works in the public health sector and her major research interests are research governance and ethics. Challenging the "invisibility" of research administration, her cross-organisational studies have highlighted the critical need to examine why certain behaviours occur. This research was supported by the Victorian University Vice Chancellor's Graduate Research Award 2016, incorporating the Australian Postgraduate Award.

Professor Emeritus Anona Armstrong AM PhD FAPS FAICD FIPAA (Vic) FAES is former Director of the Corporate Governance Research Centre and Professor of Governance in the College of Business, Victoria University. She is Chair of the Corporate Board at Southern Cross Education Institute-Higher Education. Her major research interests are evaluation, governance and ethics. She has supervised over 70 postgraduate theses and published many books and papers on these topics.

Dr. Maree Fitzpatrick PhD, Ma.Ed, B.Ed.,Post Grad Cert Leadership .As an Honorary Fellow with the College of Law and Justice at Victoria University, Dr Fitzpatrick is a supervisor and mentor for Post Graduate candidates. Maree also lectures in the Masters International Corporate Governance unit at La Trobe University. She is passionate about equitable governance.

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List of key terms and acronyms

CPI	Coordinating Principal Investigator
CRO	Contract Research Organisation
HREA	Human Research Ethics Application (replaced the National Ethics Application Form (NEAF) in 2017)
HREC	Human Research Ethics Committee
MOU	Memorandum of Understanding for mutual acceptance of scientific and ethical review of multi-site human research projects undertaken in Public Health Organisations
National Statement	National Statement on Ethical Conduct in Human Research (NHMRC)
NHMRC	National Health and Medical Research Council
NMA	National Mutual Acceptance
PHO	Public Health Organisation
PI	Principal Investigator
RGO	Research Governance Officer
SOPs	Standard Operating Procedures
Sponsor	The trial sponsor is an Australian entity and responsible for the initiation, management, financing (or arranging the financing) of the trial and carries the medico-legal responsibility associated with its conduct.
SSA	Site Specific Assessment (includes research governance review/institutional authorisation)
VSM	Victorian Specific Module (completed for ethics applications involving Victorian sites to address Victorian legislation)

Executive summary

This report presents a summary of research conducted by Dr. Bernice Davies for her PhD thesis that investigated how the National Mutual Acceptance (NMA) model of single ethical review has currently impacted, and how it is likely to impact in future, on the research governance practices of public healthcare agencies participating in multi-site clinical trials (Davies, 2018). Clinical trials are research studies aimed at evaluating a medical, surgical, or behavioural intervention. Under the NMA, a proposal to conduct a human research project at public healthcare sites in more than one participating jurisdiction may submitted to a single reviewing human research ethics committee (HREC) that has been certified by the National Health and Medical Research Council (NHMRC). Organisations from participating jurisdictions then accept the single scientific and ethical review in place of conducting their own review. Each organisation undertakes an individual site specific or governance review to determine the capacity of the organisation to undertake the research. Together the ethical approval and site specific authorisation provide the permission required for the study to be conducted.

The study was based on the theory of institutional isomorphism which refers to how the social processes involved in mimetic, coercive, and normative isomorphism influence organisational behaviour, such as acceptance of the NMA.

The aims of the study were:

- To evaluate the research governance practices of Victorian public healthcare agencies involved in multi-site clinical trials and to determine the extent of compliance with the purpose and objectives of the NMA.
- To determine the impact and success of the NMA on the research governance practices of Victorian public healthcare agencies involved in multi-site clinical trials.
- To determine whether differences between the ways the NMA was perceived existed between those personnel applying for research approval (Applicants) and those ensuing that the research was consistent with current regulatory requirements (Regulators).

Methodology

The methodology was a mixed method design consisting of a survey of 149 participants and interviews with 21 respondents. Survey participants represented all levels of stakeholders in the outcomes of the trials divided into research Applicants and Regulators. Interviewee participants ranged from executives and senior management, to senior members of research teams and research administration (Table 1).

Table 1: Numbers and characteristics of study participants

	Phase 1 Survey		Phase 2 interviews	
	%	**Freq**	**%**	**Freq**
Age				
≤50	77%	115	57%	12
≥51	23%	34	43%	9
Education				
Post Grad	32%	48	33%	7
Bachelor	58%	87	67%	14
Pre Tertiary	9%	14	0	0
Gender				
Male	25%	37	48%	10
Female	75%	112	52%	11
Role				
Applicant	61%	91	19%	4
Applicant/Regulator	-	-	10%	2
Regulator	39%	58	71%	15
Level				
Senior Management	-	-	38%	8
Middle management	-	-	33%	7
Management	36%	54	N/A	N/A
Non-Management	64%	95	29%	6
Years in role				
≤5	44%	65	19%	4
≥6	56%	84	81%	17

Key findings

The results of the study revealed the following.

Importance of research: (p 31)

- 80% thought clinical trials should be a core activity of their institution.
- 20 % did not think research breaches of standards should be reported to the Board/Senior Management.
- Neither NMA nor research governance is understood at board level.
- Final authorisation or contract sign-offs were often delayed.
- 90% agreed that NMA was important to clinical trials regulation.

Summary

There was no user representation in the system.

There is little accountability for compliance with NMA.

NMA did decrease the number of duplicated ethical reviews.

Coercive isomorphism (p 32)

Coercive isomorphism is confirmed by perception of the NMA legitimacy

- All Public Health Organisations (PHO) had written policies and procedures.
- 90% agreed that NMA was important to PHO regulation of research.
- A high level of compliance to the dedicated IT system, but institutions had additional procedures which were complied with rather than with the NMA.
- Persistent variations in procedures existed across states.
- The role of the lead site was subject to a heavy administrative workload.
- There was no single system.

Summary

Organisational leadership, (in particular the support of the CEO) was a crucial factor in NMA success.

Knowledge and commitment from senior personnel was limited.

Mimetic isomorphism (p 33)

Mimetic isomorphism develops when organisations deliberately model themselves on other organisations in order to gain legitimacy.

- PHO have different organisational cultures which inhibits adopting other PHO processes.
- Lack of senior personnel engagement in research governance limited the will to explore other PHO research governance.
- There was no single system to encourage best practice development.
- Department of Health and Human Services reports of compliance with NMA times were regarded as "fiction".

Summary

If networking and imitation occurred, it was at a unit or personal level and opportunist rather than strategic.

Mimetic was not always seen as positive.

Normative isomorphism (p 34)

Normative isomorphism is associated with both professional and organisational legitimacy:

- There were no common position descriptions for research administrators.
- No specific governance course or education levels were required for regulators.

Summary

Research governance practices were seen as specific to the local needs of their organisation, rather than considering the NMA goal of a coordinated system.

Recommendations

Leadership

Leadership is required in both the initial introduction and the ongoing maintenance of the NMA. In particular, involvement of the Board of Directors would provide significant impact on performance of the NMA.

- Increase the understanding of the NMA of senior managers through education and training.
- Increase motivation for the involvement of senior personnel by introducing introduce research into key performance measures.

Stakeholder engagement framework

There were similarities and differences between stakeholders' perceptions of the NMA. A stakeholder engagement framework provides a strategic approach to determine the issues on which engagement is sought from stakeholders, how engagement is managed and to identify the best mechanisms for addressing any issues raised (Sinclair, 2010).

- How to promote research governance to the CEOs, senior management and Boards.
- Development of a dedicated research governance network, and an associated reporting network.
- The broadening of HREC membership to include members from agencies other than that where the HREC is housed.
- Involvement and participation of non-public sector research peers.

Future Development

Currently the NMA applies only to the public healthcare sectors of each jurisdiction, but multi-site research may include private, business or academic sectors.

- Create ethics and governance review structures that involve public and non-public research sectors, such as:
    - A centralised system involving a combined public and non-public HRECs.
    - Retention of individual HRECs the introduction of a quota system for HREC reviews of multi-site research.

Key Words

National Mutual Acceptance, NMA, research governance, streamlined ethical review, single ethical review, institutional isomorphism

Introduction

The purpose of this monograph is to present the findings from research conducted by Dr. Bernice Davies for her PhD thesis that investigated how the National Mutual Acceptance (NMA) model of single ethical review has currently impacted, and how it is likely to impact in future, on the research governance practices of public healthcare agencies participating in multi-site clinical trials (Davies, 2018).

In Australia, it is estimated that around 1000 new clinical trials are commenced annually by pharmaceutical, biotechnology and medical device companies representing a $1 billion investment (Australian Government & the Australian Trade and Investment Commission, 2017). More than 18,000 Australians annually participate in clinical trials sponsored by the medicines industry (Medicines Australia, 2011). Many trials involve international sponsors. They are usually conducted across several PHO or other medical institutions at the same time.

Traditionally, applications for approval to proceed at each site had to be obtained from each institution's Human Research Ethics Committee (HREC). Concerns regarding variation in research governance practices impeding multi-site research have been increasingly represented in literature (Braverman & Sidhu, 2011; Gorman, 2011; Health Outcomes International, 2015; Manville, Hackett, Gunashekar, & Morgan Jones, 2013; Prosser, Davey, & Gibson, 2015; Webster & Temple-Smith, 2013; White et al., 2016) and have generated extensive discussion and debate about research review processes in the Australian health system. Much of the research regulatory reform has been driven by commercial interests in timeliness and, in the public sector, by government need for capture of research performance (Clinical Trials Action Group, 2011).

In the past, the process has been criticised for its inefficiency, and that the length of time required to gain approval has held up trial commencement. This raises concerns that, in order to expedite data collection, clinical trials were being undertaken at international sites rather than in Australia.

The Australian Government, in partnership with industry and other stakeholders has responded by implementing a series of reforms to make clinical trials in Australia more competitive and to encourage further and ongoing investment (National Health and Medical Research Council, 2014b). A critical component of regulatory reform has been

the introduction of single or streamlined ethical review intended to reduce duplication in the conduct of scientific and ethical review of research projects performed at more than one site. Australian state and territory Departments of Health signed a Memorandum of Understanding (MOU) for mutual acceptance of ethical and scientific review of the multi-centre human research projects undertaken in Public Health Organisations (PHO). Currently, the Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria and Western Australia participate in the National Mutual Acceptance (NMA).

Clinical Trials

Clinical trials are human research studies aimed at evaluating a medical, surgical, or behavioural intervention. They may be sponsored by a variety of personnel: investors, academia, researchers, medical institutions, industry and other stakeholders, or PHOs.

Commercial clinical trials contribute to the development of a medicinal product or device but may also include post-marketing surveillance studies. These trials occupy a unique position in healthcare, posing both advantages and disadvantages to participating sites. They can offer substantial clinical benefits through trialling innovative medications, medical devices and therapies that are cost-neutral to the trial participant (Clinical Trials Action Group, 2011) as well as providing commercial investment to their hosts. For example, in Australia, a significant portion of the AU $1 billion invested annually in pharmaceutical research and development is directed at commercial clinical trials (Medicines Australia, 2011). However, clinical trials, also carry a range of clinical and non-clinical risks to those involved, so that, in Victoria for example, public sector agencies are required to maintain a risk management framework that aligns with expectations of the state's insurer (Victorian Managed Insurance Authority, 2015). The responsibility for determining capacity to undertake a clinical trial rests with the organisation.

A clinical trial is a form of human research designed to establish the effects of a medical intervention, such as a treatment or diagnostic procedure (The National Health and Medical Research Council, the Australian Research Council and the AustralianVice-Chancellors' Committee, & Commonwealth of Australia, 2007). To reduce the possibility of bias, clinical trials collect data through a randomised control model. This model is generally seen as the "gold standard" in medical research (Weinberger et al., 2001). Commercial clinical trials, which can involve the testing of innovative drugs or medical

devices, rely upon this model to collect the stringent safety and efficacy evidence required for the registration. It is critical that all participating sites conform to the study protocol, expected study behaviours and to the timeliness of key study milestones.

Commercial, multi-site clinical trials operate as a highly regulated and competitive global industry. Countries intending to host international investment need to accurately measure their research operations to understand and promote their capabilities to research sponsors (Manville et al., 2013; National Health and Medical Research Council, 2014b) . However, in Australia, there has been limited national data available on clinical trial performance, including participant recruitment and retention rates. Thus, the new regulatory regime of single ethical review was introduced to harmonize bureaucratic processes and to capture performance data across all stakeholders. Collaboration in NMA across several sites ensures that sufficient participants are available for a trial, saves costs and avoids delays to all who participate, including the PHOs where the trials may be held.

National Mutual Acceptance

National Mutual Acceptance is a national system for mutual acceptance of ethical and scientific review for multi-site clinical trials conducted in PHOs. Mutual acceptance is where a proposal for a multi-centre project conducted in PHO's across the participating states is ethically and scientifically reviewed once only by a Human Research Ethics Committee (HREC) that has been certified by the NHMRC[1].

The scope of NMA includes any form of human research as defined in the National Statement on Ethical Conduct in Human Research or National Statement (NHMRC, 2007) for which an application must be made to a HREC for the purpose of being conducted in the public health sector.

Figure 1 outlines the requirements that allow the NMA to operate. Participating jurisdictions are required to sign an inter-jurisdictional Memorandum of Understanding (MOU) to enable publicly funded health organisations within their jurisdictions to accept the scientific and ethical review of an NHMRC certified reviewing HREC. Victorian organisations participating in multi-site research have a formal agreement with the

[1] Further information on the National Certification Scheme can be found at https://www.nhmrc.gov.au/health-ethics/national-approach-single-ethical-review/institutions-certified-ethics-review-processes.

Department of Health & Human Services (DHHS) regarding their participation in the streamlined system. These agreements ensure that:

- PHOs accept the ethics approval through the NMA and will not undertake any further review by their organisation's HREC, acknowledging there are some exceptions in jurisdictions.
- A 60 calendar day benchmark is applied for scientific and ethical decision making.
- There is consistency of HREC review according to the National Statement (NHMRC, 2007).
- That PHO undertake a process of site specific assessment (SSA).
- Research projects do not commence at a site without HREC approval and site authorisation. (Victorian Department of Health and Human Services, 2013).

Standard Operating Procedures (SOPS) provide general guidance for investigators, trial coordinators, sponsors, Contract Research Organisations (CRO) and other parties undertaking human research projects within public health organisations. Scientific and ethical review should be in accordance with the National Statement on Ethical Conduct in Human Research (NHMRC, 2007). The PHO is responsible for undertaking a review of its capacity for conducting a trial.

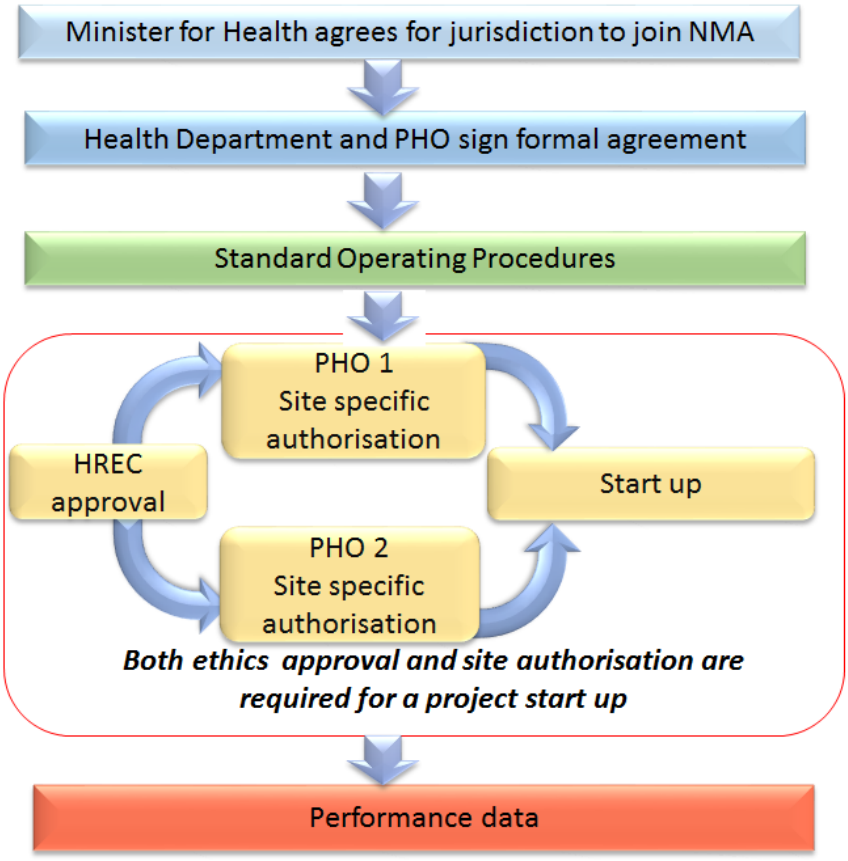

Figure 1 Overview of the NMA system

Under the NMA, applications for scientific and ethical review of studies must be submitted on a Human Research Ethics Form (HREA) via a dedicated website to the HREC of the Coordinated Principal Investigator's (CPI) choosing. If at least one trial site is located in Victoria, a Victorian Specific Module (VSM) must also be completed to explain how the project interacts with Victorian legislation.

At the same time as the ethical review is being conducted, each participating organisation performs a site specific assessment (SSA) to ensure that it is capable of undertaking the project. Research governance refers to the structures that ensure legal compliance, risk and financial management and accountability associated with a participating site. Research governance obligations are assessed in the process of site specific assessment. The NMA model requires that both the ethics review and site specific authorisation be completed before the project may commence (start-up) (Figure 2).

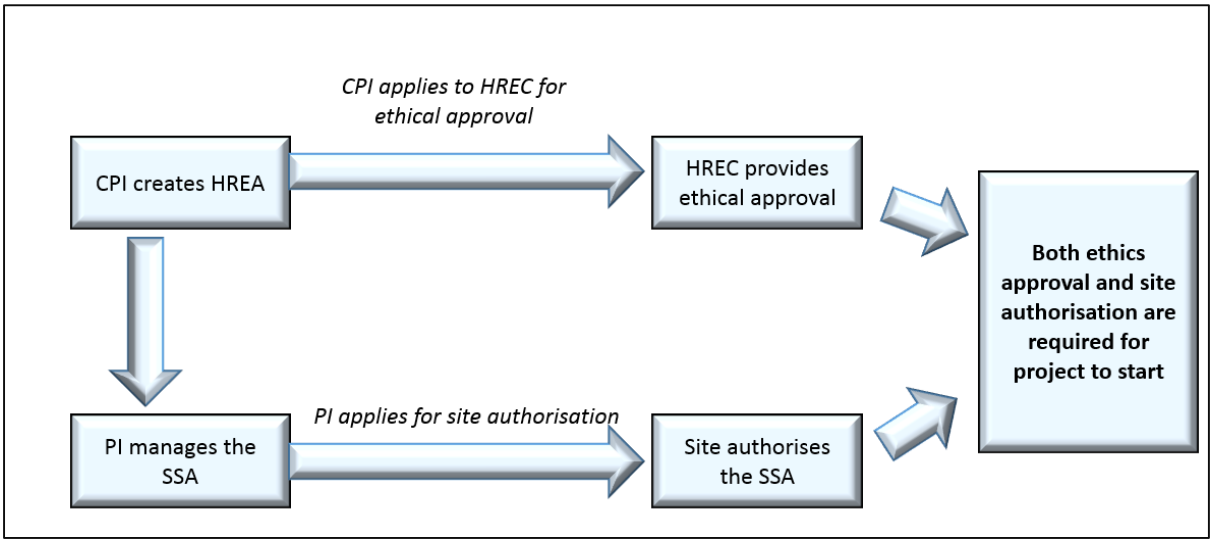

Figure 2: Overview of the ethical and site specific review

RESEARCH GOVERNANCE

In general, corporate governance is concerned with the structures and processes for decision-making, accountability, control and behaviour to add value to the organisation (Armstrong, Jia, & Totikidis, 2005). Research governance is about the practices employed by organisations to demonstrate accountability for research integrity. Historically, the onus for determining the ethical and operational capacity of research studies fell to the organisation undertaking the research. For over fifty years, organisational Human Research Ethics Committees (HRECs) have become familiar institutions, reflecting the culture and practices of their individual healthcare services and entrenched in the organisation's legal, indemnification and monitoring practices (Breen, 2005).

In Victoria, this responsibility is further compounded because Victoria's public health agencies are incorporated public statutory authorities, and thus independent legal entities (Victorian Department of Health, 2013b) embodied with a sense of self-determination. Organisations are responsible for any research performed under their auspices (Victorian Managed Insurance Authority, 2015) and for the responsible conduct of researchers (National Health and Medical Research Council & the Australian Research Council and Universities Australia, 2007).

The ramifications of the single ethical review on the traditional expectations of research integrity, and the extent to which the NMA model has fostered a culture of common research governance behaviours, are unknown.

Theoretical Foundation of the Study

As the study looked to examine the deeper and more resilient aspects of research governance, Institutional Isomorphism was selected as a theoretical basis. The theoretical constructs are described below.

Organisational legitimacy is a critical, but somewhat abstract concept, that involves alignment of an entity to a social system of norms, values, beliefs, and definitions (DiMaggio & Powell, 1983). Accordingly, it is not enough for organisations to operate efficiently but they must be seen to do so to appear legitimate to their stakeholders (Deephouse, 1996; Suchman, 1995). Therefore organisations facing the same environmental constraints tend to develop similar behaviours and structures.

Isomorphic pressures influence organisational behaviour through adaptation to a socially constructed environment (Boxenbaum & Jonsson, 2008). There are three interconnected influences: coercive, mimetic and normative.

Coercive isomorphism involves pressures from other entities on which they are dependent, such as, governmental mandates or legislative requirements (DiMaggio & Powell, 1983). As public healthcare relies heavily on government funding (Australian Institute of Health and Welfare, 2014), it would be expected that the government would exert coercive pressure, and that the success of this would be evident in the achievement of the government's objectives.

Mimetic isomorphism develops when organisations deliberately model themselves on other organisations in order to gain legitimacy (DiMaggio & Powell, 1983). Literature suggests that the pressure to copy or emulate the activities, systems, or structures of other organisations, is particularly strong in times when goals are ambiguous or when organisational technologies are poorly understood (DiMaggio & Powell, 1983). Mimicking a more successful peer becomes a "safe" way to proceed and conserves the costs of searching for actions to reduce the uncertainty being faced by the organisation (Meyer & Rowan, 1977).

Normative isomorphism is associated with both professional and organisational legitimacy. Professionalisation refers to the pressures brought about by a profession establishing a cognitive base (DiMaggio & Powell, 1983). Pressures can be exerted through formal education or professional networks. The end result is that personnel from similar backgrounds will approach problems in much the same way.

Aims of the Research

The aims of the study were:

- To evaluate the research governance practices of Victorian public healthcare agencies involved in multi-site clinical trials and to determine the extent of compliance with the purpose and objectives of the NMA.
- To determine the impact and success of the NMA on the research governance practices of Victorian public healthcare agencies involved in multi-site clinical trials.
- To determine whether differences existed between those personnel applying for research approval (Applicants) and those ensuing that the research was consistent with current regulatory requirements (Regulators) impacted on the way the NMA was perceived.

Research questions

If the NMA is viewed as legitimate, health care agencies should show recognition of research activity. In relation to whether the NMA was perceived as a legitimate activity the research questions examined:

How well did the various stakeholders understand the NMA process?

How well did they comply with the process?

How well did they collaborate with other agencies?

How was the authority of the NMA perceived by the various stakeholders?

If the NMA is a coercive influence, health care agencies should demonstrate compliance with the standard operative procedures. In relation to whether the NMA acted as a coercive influence, the research questions were:

Did the NMA meet the governments' research priorities?

Was the NMA efficient and effective? For example: did the reviews meet the timeliness target of completion within 60 days?

How effective was the NMA in attracting new requests for clinical trials?

Was the NMA perceived as more efficient and timely than single agency review?

Were the leadership arrangements satisfactory?

How satisfied were stakeholders with the NMA?

If the NMA is a mimetic influence, health care agencies should collaborate with other agencies and learn about their practices. In relation to whether the NMA acted as a mimetic influence, the research questions were:

Were similar standards adhered to by all agencies?

Was performance data collected? How was it used?

If the NMA is a normative influence, health care agencies should participate in professional standards. In relation to whether the NMA acted as a normative influence, the research questions were:

Are there standardised qualifications to work in the research sector?

Were RGO's allocated the same tasks and responsibilities in different organisations?

Was there a professional network for research governance administrators?

Finally the stakeholders were asked how the performance of NMA could be enhanced in future.

Methodology

The methodology was a mixed method design consisting of a survey of 149 participants representing all levels of stakeholders (Table 1) and interviews with 21 research "leaders" (Table 2).

Table 1: Survey respondent profiles

Variables	Response proportion by category		Total Responses	
	%	Freq	%	Freq
Age			100%	149
≤50	77%	115		
≥51	23%	34		
Education			100	149
Post Grad	32%	48		
Bachelor	58	87		
Pre Tertiary	9%	14		
Gender			100%	149
Male	25%	37		
Female	75%	112		
Role			100	149
Applicant	61%	91		
Regulator	39%	58		
Level			100%	149
Management	36%	54		
Non-Management	64%	95		
Years in role			100	149
≤5	44%	65		
≥6	56%	84		

Table 2: Interview respondent profiles

Variables	Response proportion by category		Total Responses	
	%	Freq	%	Freq
Age			100%	21
≤50	57%	12		
≥51	43%	9		
Education			100%	21
Post Grad	33%	7		
Bachelor	67%	14		
Pre Tertiary				
Gender			100%	21
Male	48%	10		
Female	52%	11		
Role			100%	21
Applicant	19%	4		
Applicant/Regulator	10%	2		
Regulator	71%	15		
Level			100%	21
Senior management	38%	8		
Middle management	33%	7		
Non-management	29%	6		
Years in role			100%	21
≤5	19%	4		
≥6	81%	17		

Survey responses were separated into Applicants and Regulators. Applicants were defined as those involved with submitting a multi-site clinical trial or research study, such as researchers, trial coordinators, research sponsors and contract research organisations (CROs) who acted as the local sponsor where an international sponsor is not an Australian legal entity. The Regulator sample included public healthcare agency personnel involved with ensuring that a clinical trial conformed to all the requirements of the healthcare agency, including all the relevant legal and regulatory conditions. This included research office staff, managers and directors, organisational executives and HREC members, employed at a range of agency levels. (Figure 3)

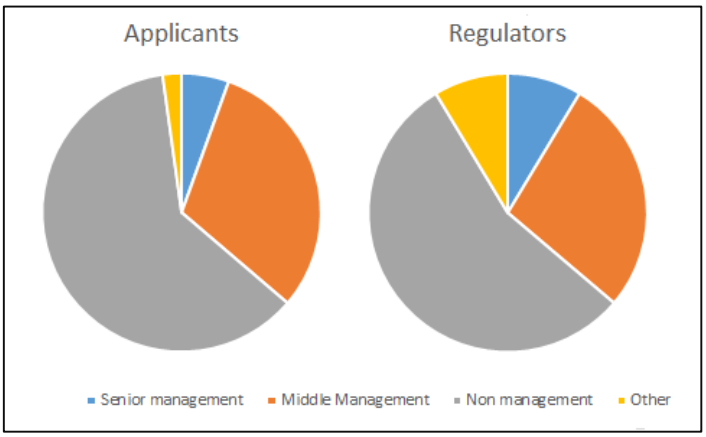

Figure 3 Characteristics of survey participants

"Leaders" were personnel actively involved in developing awareness of multi-site research and streamlined review. Research leadership was not confined to organisational roles. Other research leaders led from their professional capacity, such as an experienced researcher or trial coordinator. (Figure 4)

Figure 4 Characteristics of interview participants

Ethics review

Ethical approval to conduct this study was provided by the Human Research Ethics Committee, Victoria University on 17 February 2015. Accordingly, interview transcripts were de-identified and pseudonyms used for any identifiers such as people or organisations. During the study, data was securely stored in a locked filing cabinet and a password protected computer which was accessible only to the author. At the completion of the project, the data will be retained for five years before being destroyed.

Participant's quotations appear in italics. All are anonymous and confidential as part of the ethical requirements of the University.

Results

Importance of research and the NMA

Nearly all respondents (over 80%) indicated strong agreement that research should be a core PHO activity. There was strong agreement (over 80%) from all respondents that PHO undertaking research have written site policies and procedures and that research performance measures and ethical breaches should be reported to the Board or senior management. However, only 14% of Applicants and 19% of Regulators agreed that research was regarded as important in PHOs. They highlighted lack of engagement of senior personnel.

> *Nor am I sure that our CEO really knows about us, except as a photo opportunity in research week.*

> *I don't believe that we are anything but a curiosity to most of the executive. We have research week, that the CEO attends, but even still I don't think that he sees researchers. I think he sees it as a university thing.*

The major focus of healthcare agencies is clinical care and the *high level of specialisation* required for involvement in research prohibits senior management and the Board from understanding the complexities of research administration and governance.

> *At this stage, I don't think it's a good idea to involve the Board or senior management in the operational matters of the office because they really don't know much about what research involves and they'd just hold everything up. I think high level reports, overall numbers etc. would be appropriate.*

Lack of appreciation of NMA or research governance at board level was manifested in operational delays, such as delays in final authorisation or contract sign-offs.

> *It [research contract] can sit there for two weeks because its "only research". They can make it quite difficult for us. The CEO is not saying to these heads "get these forms done quickly because it's really important."*

Was the NMA a coercive influence?

Nearly all respondents (90%) agreed that that NMA should be important to the way PHO's regulated their research. There was also strong support for fast authorisation and compliance with NMA operating procedures; that senior PHO management should ensure compliance with NMA targets and that PHOs should use of the same forms and processes. Applicants indicated greater support than Regulators. However, over half of all respondents (56%) indicated that the NMA did not influence PHO practices.

Typically, the authority of the government to introduce the NMA into the public health sector was acknowledged:

> *The good thing about the National Mutual Acceptance [NMA] is that you've got the approval from the government to do it. That authority to do this has been great.*

[An organisation undertaking research] *should be aware of its research obligations just as much as the clinical roles. It should be part of the hospital accreditation process.*

Participants, however, observed that there was no single system of research review.

> *Different institutions have … different issues, different expectations, different funding models, different boards, different staff - all that sort of thing.*
>
> *That's my frustration of having different HRECs reviewing … every HREC is different.*

Some respondents expressed concern on how the NMA impacted on their practices. They observed that *it was assumed that the big guys in town are the best, but this is not necessarily so. In fact it's not been our experience*. It was perceived that each HREC, all of which were based within an organisation, developed practices according to their parent administration rather than the standard operating procedures.

There were also concerns the role of the lead site was subject to a heavy administrative workload involved in applying for ethical consideration and approvals, intensified with variations in the *logistics and the differences in the HREC requirements for submission.*

Regulators acknowledged that local needs were prioritised over the NMA requirements and that different practices were occurring.

> *Sometimes you think there's not the staff or resources to do it in the way we are supposed to. It's much better to do certain things the way that suits you. You can't stick to a guideline if it doesn't work.*

Regular reports were provided by the Department of Health and Human Services to the Chief Executive Officers of participating healthcare organisations listing the ethics and governance approval times. Despite these reports being drawn from the data within the dedicated IT system, research manager participants stated that the metrics being reported were not correct.

> *Nobody believes those reports when they come out from the DHHS, they just look at them and go "fiction" and put it in the bin.*

> *I haven't got the time to worry about that. My CEO understands that, as do most CEO's, that the reports they get from the health department they just chuck them straight in the shredder.*

Was the NMA a mimetic influence?

Mimetic influences develop as organisations intentionally seek to understand the operations of a more successful peer. More Regulators (85%) than Applicants (60%) supported research offices having opportunity to network, benchmark and compare to others research offices. There was also greater uncertainty in Applicant responses. These results indicate that the Applicants' perspectives are dominated by the outcome of the research review process but the Regulators are more concerned with the practices of research governance.

In practice, however, opportunities to mimic were limited. Lack of senior management engagement with the NMA meant that any networking or imitating was done at by those *active at the coal face and who is driving it and working in that space in order to expedite processes and to understand what makes it better*. Smaller groups were able to detect more immediate goals, such as development of a research contract for a trial that many of the members were participating in and they were also able to see the immediate impact of any change efforts.

Mimetic pressures were not always viewed in a positive light.

I don't want people to be doing random things outside the agreed system. The agreed system is the basis of what we are doing.

So during those conversations your colleagues would say "oh by the way, in NSW this happens or QLD, we don't worry about that but we do this instead". A lot of this is learn as you go, which isn't a bad thing but it's not necessarily promoting a good, consistent, robust system.

Was the NMA a normative influence?

Normative pressures develop as a consequence of social influence, such as professional standards, education and hiring staff from a peer organisation. These activities pressure an organisation to behave in accordance with their peers. All Regulators and over 90% of Applicants agreed that professional standards in research governance are important. Regulators were also more supportive for research governance staff having common position descriptions and similar responsibilities, a career path or agreed professional standards. More Applicants disagreed that research governance units do have professional standards.

Limitations in the development of normative influences were related to the continued focus on local needs. There was no specific certification required to work in research administration.

Those are the inconsistencies. We don't have a common understanding of the process, we don't have a common standard of what's acceptable.

The first thing I did when I started was to ask for a manual of what I am supposed to do. I asked my manager. He said that there isn't a manual for the RGO role.

When participants reflected on the credentials or education required to work in research governance they had a variety of interpretations.

I don't think that formal education is what makes the difference. It's the interest in the field that helps them understand why we are doing what we are doing. So some sort of qualification that indicates interest is a good thing but not absolutely vital.

The best way to learn is to be put in that environment and work with people who do a good job. That's the best training. Now that could be part of a course, a structured internship program.

The future of the NMA

When interview participants were asked to describe their expectations of the NMA in the future, they used terms such as *coordinated, standardised* and *seamless* to indicate a system of single ethical review through which multi-site research projects moved through various review points in a fast and synchronised manner. The most pressing requirement was that the NMA *worked the way it is meant to work*.

Standardisation was perceived as the backbone of single ethical review. The basic tenet is that, although researchers might apply to different HRECs, and different healthcare agencies, the same application processes should apply. Most thought that the authority of the NMA to enforce standard practices should be enhanced.

There is a need for a central research body with the authority to impose upon the individual states and territories … The NHMRC is central to research review but it does not have dominion over the states.

A suggested alternative to a formal authority was the creation of a set of standards or principles that would be accepted by many.

That's doesn't mean a body like the NHMRC but maybe it's more like GCP [Good Clinical Practice]. Not law. Not strictly speaking enforceable. But if you don't have evidence that you comply, no one will do business with you. If we could get the current powers to agree to one set of standards, then I think we could work with that. Yes, I think we could work with that.

Others reflected on the need to the NMA to harmonise with their own practices

Two things – firstly that it is a streamlined system; that the system of research review is faster than before, with no loss of efficiency, but secondly that it is invisible.

Discussion

Legitimacy

The idea of legitimacy is key to compelling people to uphold certain behaviours that support this institution rather than performance (DiMaggio & Powell, 1983). Thus, if the NMA is to be viewed as legitimate, health care agencies should first show recognition that research involves others.

How well did the various stakeholders understand the NMA process?

Public health strategy centres largely on financial stewardship, clinical care performance and ensuring compliance with statutory requirements (Victorian Department of Health, 2008). Both the Board of Management and the CEO have obligations to the Minister for Health and the Department of Health and Human Services (DHHS) (Fitzpatrick, 2008) but, currently, agencies are not accountable to the Minister for the performance of research they perform, despite signing an agreement with the DHHS to support the NMA.

The majority of study participants felt that research should be a core activity of PHOs but that there was variable interest from senior management. Consequently, senior management did not recognise that the NMA required their organisation to cooperate with others and were unable to act as champions or role models of the national model. There was more appreciation of the NMA from less senior stakeholders, but, while their expectation was that the NMA should provide a more efficient system overall, their focus was on their immediate tasks.

How well did they comply with the process?

This study provides evidence of support in principle for the continued use and development of a national review system but the study participants have also provided an emic perspective on the strategic and operational elements of the national model that showed the guidelines were not always followed. This meant that, while there was high level of compliance with formal application processes through the dedicated IT system, most agencies had additional requirements such as submitting applications as ‘hard copy’ or on an alternative electronic system. Thus, there was no single agreed system.

How well did they collaborate with other agencies?

Despite the intent to create a national system, the study findings presented a number of barriers to collaboration between agencies. Clinical trials in Australia are regulated at a number of levels under Commonwealth, state and territory legislation. Several participants described incidents where interstate ethics committees had not considered Victorian legislation, as described in a specific document Victorian Specific Module (VSM), in their deliberations. Potentially, this is problematic because a trial that is legally acceptable research practice in one state, may not be acceptable in another. State and territory differences have been outlined in NHMRC information (2014a).

Both research Applicants and Regulators described their frustration in dealing with a lack of consistency and transparency in areas such as approval scope, processes and timeframes of different Victorian agencies. This is consistent with current literature (Health Outcomes International, 2015).

How was the authority of the NMA perceived by the various stakeholders?

A critical aspect of the NMA is the expectation that all steps of research review, irrespective of the reviewing entity, will be undertaken in a similar manner. Disparity in priorities, performance goals and review practices of different agencies weaken the authority of the national approach. In particular, one organisational strategy described in literature involves decoupling or the creation and maintenance of gaps between formal policies and actual organisational practices (Boxenbaum & Jonsson, 2008). This enables an organisation to retain legitimacy with their external stakeholders while simultaneously maintaining internal flexibility to address practical considerations (Meyer & Rowan, 1977). Evidence of decoupling from the NMA ranged from differences in application forms and processes to performance goals.

While decoupling is a recognised strategy to allow agencies to appear to adhere to inappropriate guidelines in order to preserve organisational efficiency (Boxenbaum & Jonsson, 2008; Meyer & Rowan, 1977), there is potential for a “legitimacy facade” (MacLean & Behnam, 2010) to be developed. In a system model, such as the NMA, the use of non-standardised practices may negatively impact accepting organisations. In turn,

there were indications of a lack of trust in the national system as Applicants restricted their applications to a single ethics committee that they were familiar with.

The NMA as a Coercive influence

As the NMA was a government mandate, it would be expected that it would meet government objectives.

Did the NMA meet the governments' research priorities?

The NMA is a component of the Australian government's strategy to position Australia within the global economy (National Health and Medical Research Council, 2014b). It finds its genesis within the waves of regulatory reform that have arisen in Australia since the 1980s. These reforms brought an enhanced management of intergovernmental relations in Australia, an emphasis on productivity and efficiency through the Council of Australian Governments (COAG) and markedly changed funding and policy responsibilities between the levels of government (Carroll & Head, 2010). A significant driver of these reforms was the standardisation of arrangements between states such as the basis of the NMA. One indication of meeting the government's priorities is development of National Aggregate Statistics (NAS) (Clinical Trials Jurisdictional Working Group, 2017).

Was the NMA efficient and effective? For example: did the reviews meet the timeliness target of completion within 60 days?

A significant driver of the NMA was the standardisation of research review arrangements between jurisdictions to address the benchmark of 60 days, which is consistent with international target metrics (The European Parliament and the Council of The European Union, 2001). Measuring the likely study start-up time is a critical metric for commercial trial sponsors in determining global placement of clinical trials.

Study participants agreed that the NMA did decrease the number of duplicated ethical reviews, but noted that not all reviews were completed within 60 days, which is consistent with current literature. For example, the 2015-6 National Aggregate Statistics (NAS) found that 89 per cent of clinical trials met the 60 day benchmark with the

'administrative clock[2]' operating. Without the clock, 46 per cent of clinical trials were approved within the 60 day period. (Clinical Trials Jurisdictional Working Group, 2017).

In addition to variable timelines, the study found that lack of consistency and transparency in application processes placed formidable burdens on both Applicants and Regulators. While this finding is consistent with current literature (Health Outcomes International, 2015), it raises questions about why participating entities in the NMA continue to respond in different ways. Possible reasons included:

- Most of the HREC members are volunteers and fit in HREC responsibilities around their other duties.
- The dedicated IT system did not meet user demands so that alternative systems were created.
- Research was not prioritised, so that final authorisation or contract sign-off were delayed.

How effective was the NMA in attracting new requests for clinical trials?

Whether or not the NMA did encourage increased research investment was not yet clear to the research participants. In general, it was felt that research investors were attracted by a good business development plan and the track record of individual sites. This is not to say that the NMA might not provide a strong mechanism in the future.

Was the NMA perceived as more efficient and timely than single agency review?

The study participants expressed expectations that the NMA would provide a faster, streamlined system; with no loss of efficiency and easier to manage than multiple reviews undertaken at each participating organisation. However, their expectations of the NMA were only partly met and there were a number of concerns regarding:

- The system of single ethical differed for each review entity and between jurisdictions.

[2] The administrative clock is a specialised process used for measuring the specific intervals of when responsibility for processing a research application rests with the research office and when it rests with the applicant.

- Lack of consistency in the requirements for HREC application and governance authorisation.
- Lack of awareness and support from senior management.
- The role of the lead site was described as problematic due to the heavy administrative workload involved in applying for ethical consideration of the project and any post approval items on behalf of all participating sites.
- The fate of a multi-site project where no site was prepared to take on the lead role was not clear.

Were the leadership arrangements satisfactory?

Although the need to address duplicative reviews in multi-site research was well recognised, the task of engaging different agencies to behave similarly in a system presented very complex policy problems that were not recognised. The NMA was seen as a government initiative that research Applicants and Regulators were obliged to comply with and there was limited leadership or championing of the NMA from senior management within the health agencies.

How satisfied were stakeholders with the NMA?

Lack of stakeholder "voice" was raised in both study phases and suggested a need to understand and weigh up the interests of key stakeholders when making taking strategic decisions regarding the NMA. When participants reflected on the future of the NMA, they identified a significant need for professional input from those working within the sector. This involved a strong and consistent knowledge base, opportunities to network and opportunities to voice suggestions and complaints regarding the NMA.

The NMA as a Mimetic influence

If the NMA is perceived as having value to the organisation, then it could exert mimetic pressures on organisations to encourage them to imitate a more successful peer in order to increase their stakeholder appeal. However, while there was support for opportunities to network and share ideas, there was also strong belief that research administration practices needed to centre on local needs and thus mimicking the practices of others would not be appropriate.

Were similar standards and processes adhered to by all agencies?

While there was a comprehensive knowledge of expected research application and management practices, there was also prevalence of additional systems that were specific to individual agencies. For example, most research offices required multi-site Applicants to provide the research application through email or USB. Some research offices used a pre-submission review and others required a hard copy application. Some offices used the dedicated IT system for all research, some only used it for multi-site studies. Thus there was a no consistent process used in all agencies.

Was performance data collected? How was it used?

While the dedicated IT system offered reporting functions, it was seen to have limited value. For example, performance metrics such as time to site endorsement and overall number of studies were inaccurate. In particular, Government reports of site authorisation times that were based on the time from ethics approval were seen as problematic for sites that were added later to the study. These sites were added as an amendment to the initial submission but their time to authorisation was still taken from the initial ethics approval. Many sites did not record non-NMA studies in the dedicated IT so it appeared that their research workload was less than in actuality.

With a few exceptions, there was a general distrust of the accuracy of data drawn from the dedicated IT system. Some research offices had retained their own reporting facility, using their own, independent data capture. For those who were using the dedicated IT system, reporting was limited to their own performance and there was no inter-agency benchmarking.

The NMA as a Normative influence

If the NMA wields Normative influence in research governance, it would be expected that there would be an emphasis on common behaviours and roles evident through professional bodies, standard job descriptions and specific standards of education.

Are there standardised qualifications to work in the research sector?

Although the majority of respondents in this study possessed tertiary qualifications, the entry levels requirements to work in the sector varied. Research Applicants were generally required to possess tertiary education and clinical experience in their area of

study. For example, while not specifically requiring that clinical trial investigators possess a medical degree, Good Clinical Practice (GCP) refers to the necessity of appropriate qualifications to assume responsibility for the proper conduct of the trial (International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use (ICH), 2016; Therapeutic Goods Administration, 2006). The qualifications for research Regulators were less specific. There was no specific research governance course required and education levels of the Regulator respondents ranged from secondary levels to post–doctorate.

The study found that whether or not there should be a standard entry level or qualification required was a contentious issue. Female Regulators tended to support the concept of standardisation in research governance whereas male Regulators and research Applicants showed less support. Interviews with senior Regulators highlighted the need for an understanding of local needs, rather than cross-organisational decision-making. There were suggestions that mentoring of new recruits would be more effective than a specific course in research governance.

Literature exploring HREC administrator roles suggests that these are invisible roles, perceived to have limited autonomous decision-making as their power is drawn from association with the HREC (Dunscombe, 2008; Kasule, Wassenaar, IJsselmuiden, & Mokgatla, 2016). However, research governance personnel ensure that site specific requirements, including compliance any legislative and regulatory requirements, suggesting that the genesis of their authority is drawn from both the PHO and the broader environment.

Were RGO's allocated the same tasks and responsibilities in different organisations?

Each agency is responsible for developing their own position descriptions for their research administration personnel. The scope of the position related to the organisational capacity. For example, personnel in the role of Research Governance Officer (RGO) in larger units tended to have dedicated tasks but in smaller units one person could undertake several roles and a broader responsibility.

Was there a professional network for research governance administrators?

While study findings indicated support for opportunities to network, there was no single network dedicated to dialogues on research governance. There were many opportunities where research governance was discussed such as the Victorian Research Governance Network (which has since fallen into disuse) or forums organised by the DHHS.

The future impact of the NMA

Taken together, findings from the survey and interviews illustrate the relative strengths and limitations of the NMA in initiating organisational change. The greatest impact from the NMA was through coercive pressure. Those Victorian organisations that are signatories to the DHHS MOU to participate in the NMA were required to accept a single ethical review and use the dedicated IT system. However, there were signs that the agencies were decoupling from the goals of the national system and retaining their own local focuses. This, in turn, weakened the potential for the NMA to evoke mimetic and normative influences.

In relation to the study aims, the study found limitations in compliance with the purpose and objectives of the NMA. Organisational focus remained at local level rather than the system. The retention of local practices restricted the development of a research governance system applicable to all agencies involved in multi-site clinical trials.

Personnel were not unified in the way they valued the system. Applicants were more concerned with output, such as the speed of approval, whereas Regulators were more concerned with processes. However, the study also found that, in both groups, the more experienced personnel were more likely to resist the national system.

Expectation of the future of the NMA was tied to increasing authority to compel compliance with NMA operating standards as well as a seamless connection with organisational culture and practices.

Recommendations

These study findings suggest that further examination of the NMA is needed. In particular the mixed views on research review arrangements and the confusion about their purpose found in the study needs addressing. Priority should be given to mechanisms that assist in establishing the NMA goals within research governance practices.

Leadership

Leadership, in particular, that of the Board of Directors, is required in both the initial introduction and the ongoing maintenance of the NMA. Leadership goals must include identifying the external drivers impacting on adoption on the NMA, chiefly those related to improved accountability, efficiency and compliance with regulatory requirements. Some of the items that might be considered under this auspice include:

- Develop a clear vision for the NMA and communication of that vision to all personnel.
- Increase senior personnel understanding of the NMA.
- Increase personnel motivation to support NMA, such as through key performance measures.

Stakeholder engagement framework

There were similarities and differences between stakeholders' perceptions of the NMA. While the majority of respondents identified discrepancy between their expectations and their experiences of the NMA, there were inconsistencies in how those issues should be addressed. This supports the study finding of the need for a stakeholder voice but suggests a need for a framework for fostering a stakeholder input (Victorian Government, 2018). A stakeholder engagement framework provides a strategic approach to determine the issues on which engagement is sought from stakeholders, how engagement is managed and to identify the best mechanisms for addressing any issues raised (Sinclair, 2010).

Some of the items that might be considered under this auspice include:

- How to promote research governance to the CEOs, senior management and Boards.

- Development of a dedicated research governance network, and an associated reporting network.
- How to ensure that ethical and scientific considerations of research reviews are consistent with the participating organisations, for example, broadening of HREC membership to include members from agencies other than that where the HREC is housed.
- How the involvement and participation of non-public sector research peers is managed.

Future Development

Currently the NMA applies only to the public healthcare sectors of each jurisdiction, but multi-site research involves other sectors. It is strongly recommended that, in any discussions pertaining to development of the NMA, priority be given to the creation of opportunities to broaden the NMA scope into private and not-for-public healthcare sectors as well as academic sectors.

- Create ethics and governance review structures that involve public and non-public research sectors. There are different options that may be considered such as:
    - Centralised system involving a combined public and non-public HRECs.
    - Retention of multiple individual HRECs but introduce a quota system for HREC reviews of multi-site research.

Conclusion

This research has shown that nationalisation of ethical review of research is a complex and multi-dimensional issue, which crosses historical practices and organisational cultures. In determining the appropriate balance between a nationalised system and local decision-making, various factors are in tension. A single system can help ensure uniform and consistent standards, minimise inequalities, avoid the duplication of services and facilitate economy of scale, coordination and harmonisation of services which then allows for collection of overall performance data. Local decision-making, on the other hand, can help enhance local autonomy and empowerment and thus encourage development and control of organisational research endeavours.

Institutional theory suggests that changes to organisational behaviours is likely to involve a combination of pressures, a centralised control over the major objectives joined by professional and social pressures over the ways in which those objectives are achieved. Theory also suggests that the solution to questions of organisational change rests with the value that the organisation places on the issue.

A national system of single ethical review may be an effective way of minimising the time to research start up and positioning Australia as effective competitor for international investment. However, it is essential that these processes and practices are transparent throughout the participating organisations. For the NMA to achieve its aims, it is critical that the nature and scope of research governance is understood by all key stakeholders.

Addendum

Since this study was undertaken, there have been a number of changes in the research governance landscape that point to the need for further exploration of a national review system. In particular, there are currently three separate information technology systems used for the processing of research application in the public health sectors. These are firstly Western Australia, secondly New South Wales, South Australia and Australian Capital Territory and thirdly Victoria and Queensland. Although there are 'cross over mechanisms' that allow ethics review to be accepted from other jurisdictions, these different system involve different user experiences and point to a lack of harmonisation in the processing of applications and consequent data collection.

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