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ANALYSIS OF RECENTLY CONDUCTED CLINICAL TRIALS

FINAL REPORT

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HEALTH OUTCOMES INTERNATIONAL

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ABBREVIATIONS

| | |
|--------------------|---|
| AA | Approving Authority |
| ANZCTR | Australian New Zealand Clinical Trials Registry |
| CRO | Contract Research Organisation |
| CTAG | Clinical Trials Action Group |
| CTN | Clinical Trials Notification |
| CTX | Clinical Trials Exemption |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HOI | Health Outcomes International |
| HoMER | Harmonisation of Multi-centre Ethical Review |
| HREC | Human Research Ethics Committee |
| IHPA | Independent Hospital Pricing Authority |
| ICT | Information and Communications Technology |
| MOU | Memorandum of Understanding |
| National Statement | National Statement on Ethical Conduct in Human Research |
| NHMRC | National Health and Medical Research Council |
| NMA | National Mutual Acceptance |
| PI | Primary Investigator |
| R&D | Research and Development |
| RGO | Research Governance Officer |
| TGA | Therapeutic Goods Administration |
| UK | United Kingdom |
| USA | United States of America |

EXECUTIVE SUMMARY

The Australian Government Department of Health (the Department) appointed Health Outcomes International (HOI) to undertake a research project to conduct an in-depth analysis of recently conducted clinical trials in Australia to determine the critical success factors and/or reasons for failure of clinical trials in Australia. The focus of the research was on pharmaceutical and medical device clinical trials conducted within last five years that were commercially funded, and conducted in more than one jurisdiction.

The specific objectives of the project were to identify:

- 1) The key barriers or reasons for failure leading to a sponsor's decision to not place a commercial trial in Australia, and/or a trial conducted in Australia that fails to deliver either agreed participant numbers or high quality data
- 2) The key enablers leading to successful completion of a commercial clinical trial in Australia (e.g. a trial that either met or exceeded the sponsor's expectations).

The project was initiated in February 2015 and completed in June 2015.

E.1 METHODOLOGY

The primary data collection method for the project was a series of case studies conducted using semi-structured interviews with nominated representatives of pharmaceutical or medical device companies in Australia, with a focus on clinical trials conducted in Australia in the past five years. Case study discussion questions were informed by an initial literature scan pertaining to factors critical to the success or failure of pharmaceutical clinical trials in Australia, and by preliminary consultations with nominated peak organisations and jurisdictional representatives.

Case study participants were recruited via an invitation to participate distributed by representatives from Medicines Australia and AusBiotech to member organisations and/or other organisations with whom they were involved. The case studies chosen had to include examples of both pharmaceutical treatment and medical device trials, be conducted in the last five years (2010-2015), be commercially funded, involve a range of jurisdictions, trial phases, diseases/conditions, and both public and private healthcare settings, include at least one AusBiotech member organisation, and include examples of trials listed on the Australia New Zealand Clinical Trials Register (ANZCTR) as well as those not listed on this Register.

E.2 CASE STUDY PARTICIPANTS

A total of nine organisations participated in the project including seven pharmaceutical companies, one medical device company, and one contract research organisation (CRO) specialising in biopharmaceuticals, medical devices and diagnostics. All organisations are global, with two having global headquarters in Australia and seven having global headquarters overseas. Case studies covered trial phases 1-4, and conditions including

cancer, cardiovascular disease, diabetes, urological conditions and infectious diseases. Number of sites in Australia for case study trials ranged from one to over 20, and covered all states and territories except the Northern Territory. Trials were conducted in a mix of public and private institutions.

E.3 SUMMARY OF FINDINGS

Despite some variation in process for Phase 1 versus other phase trials, and differences in reported ease of investigator recruitment for novel versus more established therapies in some cases, key reasons for investment in Australia and enablers/barriers of successful trial conduct were similar across trial phases, diseases/conditions and organisations.

E.3.1 REASONS FOR INVESTMENT IN AUSTRALIA

The key reasons outlined in case studies, and supported by the preliminary consultations and literature scan, for investment by global pharmaceutical and medical device companies in conduct of clinical trials in Australia were:

- 1) Reputation of investigators to achieve recruitment targets
- 2) Available patient population based on feasibility assessment
- 3) Reputation of Australia and/or institutions for timely trial start up
- 4) Dedicated research teams including experienced investigators and study coordinators.

Cost was also reported to be a consideration for choice of country, but only after consideration of the above factors. However, Australia is seen as an expensive place in which to conduct trials, and although this is currently balanced by other factors such as data quality, timeliness of start up and capacity to recruit, it may become a deciding factor if we do not remain ahead of other countries in these other factors.

E.3.2 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct of clinical trials in Australia identified during the project were:

- 1) Clinical Trials Notification (CTN) scheme enabling quick regulatory timeframes
- 2) National Mutual Acceptance Scheme and reduced duplication in ethics approval documentation
- 3) Short ethics review timeframes for private sites
- 4) Experienced researchers and site study coordinators who can positively impact timely ethics and governance approvals, patient recruitment and provision of quality data
- 5) Standardised costing or corporate 'fair market stipulations' to assist with budget negotiations
- 6) Robust feasibility assessments and honest patient recruitment estimates
- 7) Established referral networks and national patient databases

Researcher understanding and compliance with good clinical practice (GCP) is an enabler of successful clinical trial conduct, but was reported to be a minimum requirement rather than a competitive advantage in most cases.

E.3.3 KEY BARRIERS OR REASONS FOR FAILURE OF CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key barriers or reasons for failure of clinical trial conduct in Australia were:

- 1) No national single ethics approval process is yet established, impacting time to trial start up and/or requirement for multiple ethics submissions and approvals
- 2) Reluctance of sites to become lead sites for ethics submissions due to additional work involved
- 3) Risk for companies associated with single ethics submission, as delays at that site can impact time to trial start up
- 4) Lack of consistency in Human Research Ethics Committee (HREC) requirements
- 5) Lack of clarity, consistency, transparency and timeliness of governance approvals
- 6) Inability for sponsor organisation to communicate directly with HREC or Research Governance Officer at sites
- 7) Inaccurate feasibility assessments and unclear accountability for delivering recruitment targets within institutions
- 8) Lack of awareness and support for clinical research in Australia.

E.4 CONCLUSIONS

Activities undertaken or initiated by the Department of Health, Department of Industry and Science, and/or the National Health and Medical Research Council (NHMRC) in response to recommendations from the 2011 Clinical Trials Action Group (CTAG) Report have gone some way to boosting Australia's profile as a preferred destination for conduct of clinical trials. However, examples of excellent and competitive timeframes for trial start up, and meeting or exceeding patient recruitment targets, were reported to be exceptions rather than the norm for clinical trials conducted in Australia over the past five years.

Inability to meet recruitment targets in many trials, which in some cases was impacted by relatively slow times to trial start up, was reported by companies to have a critical impact on future investment decisions in Australia as a clinical trial site. If Australia does not offer an advantage in terms of timeliness of trial start up and/or capacity to meet recruitment targets, our cost disadvantage is then factored into decision making and may impact choice of Australia as a site. Provision of quality data was still seen as an advantage for Australia by some project participants, although most participants saw it as a minimum requirement now which needs to be met by all countries.

Ongoing initiatives such as the streamlining of ethics and governance approval processes, and development of a consistent national approach to multi-jurisdictional clinical trials within Australia, whilst essential to help improve timeliness of trial start up in particular, have resulted in new delays. These include reluctance of sites to take on a lead role for ethics review due to increased administrative burden with this role, and risks associated with having

a single lead ethics site for multiple institutions if delays occur at that site. There is still a reported lack of consistency and transparency in governance approval scope, processes and timeframes, and concern that the current project to standardise clinical trial costs will need to represent 'fair market value' for Australia to remain competitive.

A key issue reported to be impacting patient accrual in particular, but also with the potential to impact start up times and data quality, is the perceived lack of significant investment by health departments or institutions in enhancing the profile of clinical research and involvement in clinical trial activity within the medical and broader communities. Where investment has been made in experienced and dedicated study coordinators at sites, this was reported to have had a significant impact on timely ethics and governance approvals, trial start up, honest and realistic patient recruitment estimates, capacity to achieve recruitment targets, and quality of data provided. Private institutions and ethics committees were considered to be better with respect to all these factors, although target patient pools at private sites usually need to be supplemented by involvement of public institutions or recruitment processes.

Capacity and reputation for recruitment to target, timely trial start up, provision of quality data, and costs which are not outside what is deemed fair market value, all impact decisions made by international and local pharmaceutical and medical device companies regarding investment in clinical trial activity in Australia. Importantly, trial delays and lack of awareness of or referral to clinical trials, also impacts patient access to new medicines and treatments. For some patients such as those with cancer, these delays have serious consequences.

1. INTRODUCTION AND BACKGROUND

The Australian Government Department of Health (the Department) appointed Health Outcomes International (HOI) in February 2015 to undertake a research project to conduct an in-depth analysis of recently conducted clinical trials in Australia to determine the critical success factors and/or reasons for failure of clinical trials in Australia. The focus of the research was on pharmaceutical and medical device clinical trials conducted within the last five years that were commercially funded, and conducted in more than one jurisdiction.

This chapter provides a background and overview of the clinical trials environment in Australia, the objectives of the current project, and the definitions of success and failure used in the project.

1.1 PROJECT BACKGROUND

1.1.1 PROJECT CONTEXT

Participation in clinical trials provides access to medications and devices for those patients that may otherwise have very limited access. Higher participation rates in trials can lead to faster and more robust trial data being available. Clinical trial research activity may also produce economic benefits such as encouraging skilled employment and attracting international business.

Competition to secure clinical trials is intense both within and between countries. Globally countries have been actively seeking to improve the environment and infrastructure to increase the number of clinical trials and patient participation and to generate more efficiency from existing infrastructures. There are reported inefficiencies resulting from the time and associated costs involved in obtaining separate ethics and governance approvals for each site of a multi-site trial in Australia (typically Phase 2 and 3 clinical trials). These delays in the approval process, in conjunction with issues related to patient recruitment, continue to affect Australia's competitiveness in the international market.

This section provides an overview of the Australian clinical trials environment, findings from recent reviews, and current initiatives to improve the clinical trials environment in Australia.

1.1.2 THE AUSTRALIAN CLINICAL TRIALS ENVIRONMENT

The Australian clinical trials environment is **complex**, involving various levels of responsibility across public and private hospitals, institutions, private organisations and companies, state/territory governments and the Australian Government. Clinical trials are **initiated and organised by sponsors** who may include multi-national companies, smaller Australian companies, individual doctors or researchers, or the institutions themselves. The focus of this project is on trials organised by multi-national or local pharmaceutical or medical device companies with trials conducted across more than one jurisdiction in Australia.

All jurisdictions support the *National Mutual Acceptance (NMA) of ethical and scientific review for multi-centre clinical trials conducted in public health organisations*¹. This allows public health organisations of participating jurisdictions to accept a single ethical and scientific review of multi-centre clinical trials conducted by an appropriate National Health and Medical Research Council (NHMRC) certified Human Research Ethics Committee (HREC). However, participation in the scheme is phased and currently only four jurisdictions have signed a Memorandum of Understanding (MOU) to introduce NMA (Victorian, South Australian and Queensland Departments of Health, and the NSW Ministry of Health)². There are also some research projects excluded from NMA due to state specific requirements. These include clinical trials involving persons in custody, trials specifically affecting the health and wellbeing of Aboriginal people and communities, trials requiring access to state-wide data collections, and trials involving access to coronial material.

Clinical trials are usually conducted in hospitals or other state/territory government organisations or by private institutions. Institutions are responsible for deciding whether clinical trials occur at that site, and rely on advice from HRECs as to whether the proposed clinical trial complies with the *National Statement on Ethical Conduct in Human Research (2007)* (the National Statement).³ The institution is also responsible for **research governance** and must ensure the capacity of the institution to undertake the trial, and that necessary contractual and insurance arrangements are in place⁴. In NSW under Part 5 of the *Guardianship Act 1987*, the NSW Civil and Administrative Tribunal must also approve clinical trials involving any adult who cannot consent to their own treatment⁵.

Once a sponsor has received ethics and governance approval, there is a requirement to notify the Therapeutic Goods Administration (TGA) of the intention to start a trial⁶. Clinical trials are considered experimental, and the goods do not have general marketing approval. There are a number of avenues in the Therapeutic Goods Legislation where “unapproved” goods may lawfully be supplied. The Clinical Trials Notification (CTN) and Clinical Trials Exemption (CTX) schemes provide two of these avenues for access.

- 1) **CTN Scheme.** Trial sponsors notify the TGA of their intention to conduct a clinical trial using an unapproved therapeutic good. In summary the CTN scheme involves:
 - Notification process
 - One step process to notify
 - Can be used for medicines, devices or biologicals
 - No TGA review of data prior to trial
 - Trial cannot commence without valid notification and fee paid

¹ [NMA factsheet on the QLD Health website](#)

² [Human Research Ethics Committee National Certification Scheme on the NHMRC website](#)

³ NHMRC (2014), [The Australian clinical trials environment on the NHMRC website](#)

⁴ Medicines Australia (2011). [Medicines Australia Occasional Paper Series - Paper 03. Keeping clinical trials in Australia: Why action is needed now.](#)

⁵ [Guardianship in clinical trials on the NSW Civil and Administrative Tribunal website](#), Accessed May 2015

⁶ Department of Health TGA (May 2015). [Introduction to changes to the TGA's Clinical Trial Notification process presentation on TGA website](#)

- Assurances pertaining to the trial conduct and protocol are provided by the sponsor, HREC, Primary Investigator (PI) and Approving Authority (AA)
 - Each additional trial site must be notified before commencing trial at that site
- 2) **CTX Scheme.** TGA conducts a review of information regarding the product and determines whether or not to approve the proposed Usage Guidelines of the product. In summary the CTX scheme involves:
- Approval process
 - Two step process – Part 1 (approval) Part 2 (notification)
 - Can be used for medicines, devices or biologicals but required for class 4 biologicals
 - TGA must evaluate the proposed Usage Guidelines
 - Trial cannot commence without Part 1 being approved
 - Assurances pertaining to the trial conduct and protocol are provided by the sponsor, HREC, PI and AA
 - May conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines
 - Each trial conducted must be notified to the TGA

Sponsors are also responsible for notifying the TGA of any serious and unexpected adverse drug reactions occurring during the trial, with clinical investigators responsible for notifying the approving ethics committee and the sponsor regarding these events⁷.

The **International Conference on Harmonisation Good Clinical Practice Guideline** (GCP Guideline) provides an internationally accepted standard for the design, conduct, recording and reporting of clinical trials. The GCP Guideline describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and independent review boards or ethics committees⁸. The TGA has adopted the GCP Guideline in principle, although has not adopted some elements relating to ethics review as they are overridden by the National Statement. The TGA has provided explanatory notes regarding local regulatory requirements for other elements including informed consent, retention of records and adverse drug reaction reporting.⁹

The **Australian Clinical Trial Handbook**¹⁰ provides a practical quick-reference guide for conduct of clinical research in Australia to GCP standards, and notes that TGA has the legislative power to seek further information regarding any aspect of a clinical trial, inspect trial sites and documentation, and stop a clinical trial if required on public safety grounds.

⁷ NHMRC (2014), [The Australian clinical trials environment on the NHMRC website](#)

⁸ [The International Conference on Harmonisation Good Clinical Practice Guideline on the ICH website](#)

⁹ TGA (2014), [Note for guidance on good clinical practice on TGA website](#)

¹⁰ Department of Health and Ageing: TGA (2006). *The Australian Clinical Trial Handbook: A simple, practical guide to the conduct of clinical trials to International standards of Good Clinical Practice (GCP) in the Australian context.* Commonwealth of Australia

1.1.3 RECENT REVIEWS

Following a decade of steady growth, clinical trials activity in Australia appears to have declined over recent years. It has been reported that in the three years to 2011 the number of new clinical trials conducted in Australia declined by an average of 13 per cent per year^{11,12}.

The **Clinical Trials Action Group (CTAG)** was established in 2009 as a subgroup of the Pharmaceuticals Industry Working Group with the task of boosting Australia's profile as a preferred destination for conduct of clinical trials. The recommendations of the 2011 CTAG Report were endorsed by the Australian Government and addressed key issues around timeliness of clinical trial approvals, benefits of e-health and information and communications technology (ICT) infrastructure to conduct of clinical trials, improving patient recruitment and support for clinical trials networks.¹³

The 2013 *Strategic Review of Health and Medical Research in Australia: Summary Report* (the McKeon Review)¹⁴ also recommended the acceleration of clinical trials reforms recommended in the CTAG Report as part of an overarching reform strategy to embed research activity in the health system. Additional recommendations from the McKeon Review included enhancing the existing consumer recruitment portal, establishing a fewer number of ethics committees, creating a research infrastructure funding vehicle to fund major infrastructure and key enabling technologies, accelerate development of national patient databases and clinical registry infrastructure, and development of a national biobank hub.

Medicines Australia has commented that in order to bring trials to Australia, the Australian subsidiary of a global company must compete against other subsidiaries on metrics for **cost, timeliness of trial start-up, capacity to reach recruitment targets, and quality of trial data**. Difficulties arising from a relatively small and geographically dispersed population, expenses associated with Phase 2 and Phase 3 trials, and multiple ethics and/or governance approvals, can impact the share of global clinical trial investment being made in Australia.¹⁵

1.1.4 RECENT INITIATIVES

Subsequent to the CTAG Report, the Australian Government is continuing to build upon previous work by undertaking initiatives **to improve the clinical trials environment in Australia to increase Australia's international competitiveness in clinical trials**. For example, the Department of Health, Department of Industry and Science, and the NHMRC are progressing initiatives and activities to support the following:

¹¹ Medicines Australia (2011), [Medicines Australia Occasional Paper Series - Paper 03. Keeping clinical trials in Australia: Why action is needed now.](#)

¹² It should be noted that the accuracy of this statistic may have been compromised during establishment of a new TGA database. The data published from September 2013 is considered to be correct for future reporting. Refer TGA website. [Inaccuracies in clinical trial statistics reporting for the period 2009-2012 report](#)

¹³ Australian Government (2011), *Clinical Trials Action Group Report – Clinically competitive: Boosting the business of clinical trials in Australia*. Commonwealth of Australia

¹⁴ Australian Government Department of Health and Ageing (2013), *Strategic Review of Health and Medical Research: Summary Report*. Commonwealth of Australia

¹⁵ Medicines Australia (2011), [Medicines Australia Occasional Paper Series - Paper 03. Keeping clinical trials in Australia: Why action is needed now.](#)

- streamlining of ethics and governance approval processes (including development of a generic human research ethics application form)
- development of a consistent national approach to multi-jurisdictional clinical trials within Australia (being progressed by the Clinical Trials Jurisdictional Working Group and covering priority areas of ICT metrics, ethics and governance approval processes, patient recruitment and strategies to position Australia as a preferred location for the conduct of clinical trials)
- development of a standard table of costs for clinical trial items
- development of a framework for safety reporting and monitoring of clinical trials
- development of training and education materials for clinical researchers and Research Governance Officers (RGOs)
- improvement in functionality of the Australian clinical trials website.¹⁶

With respect to the process for **development of a standard table of costs for clinical trial items**, a Ministerial Direction was issued to the Independent Hospital Pricing Authority (IHPA), dated 28th November 2012, to determine the national efficient price for a list of standard items (developed by the NHMRC) associated with conducting clinical trials in Australia. Subsequently in June 2013, IHPA produced a table of standard costs for conducting Clinical Trials in Australia¹⁷. These costs focused on the NHMRC list of items that was developed as a result of the CTAG process (that involved a high level of input from the pharmaceutical industry, but lower levels of participation from other commercial trial sponsors). The NHMRC list was largely focussed on pharmaceutical trials; as a result, it was considered that further work was required to ensure the applicability of the NHMRC list to medical device trials, and until such time as this work was undertaken, it has been noted that the table of standard costs should not be used for device trials.

Furthermore there was no mandated requirement to use the table of standard costs for negotiating trial budgets, as it was only intended to be used as a guide or reference point in this respect. Nonetheless, it is considered that there is considerable value in the Australian table of standard costs, particularly if users of the table have regard to the following factors in negotiating trial budgets:

- 1) **Standard care versus trial specific care.** It is important to note that the standard costs are intended to be applied only for those activities that are over and above standard of care i.e. the determined standard costs should not be applied to services that patients would have received in any case, if they had not been enrolled in a clinical trial.
- 2) **Type of trial.** Although, the standard costs have been developed without reference to the type of trial, there may be a need to consider adjustments to the standard costs depending on the nature of the intervention on trial (e.g. pharmaceutical trials, radiation oncology trials, surgical trials, service model trials, observational trials, etc.).
- 3) **Target population of trial.** Some trials will target populations where there will be different costs experienced relative to the typical adult population. This may require

¹⁶ Australian Government (2015), [NHMRC and Department of Industry and Science, Australian Government Clinical Trials Initiatives website](#)

¹⁷ Independent Hospital Pricing Authority (June 2013), [Development of a table of standard costs for conducting Clinical Trials in Australia report on Independent Hospital Pricing Authority website](#)

consideration of adjustments to the standard costs for trials that are likely to involve high proportions of participants from smaller target groups.

- 4) **Phase of trial.** Pharmaceutical trials are normally categorised into phases from Phase 1 through to Phase 4. The phase of the trial was found to impact on costs, so there may be a need to consider adjustments to the standard costs depending on trial phase.
- 5) **Trial setting.** Organisations conducting clinical trials represent a range of settings, from hospitals to primary and community services, through to purpose built facilities. The study found that there are different experiences of the cost of trials depending on the setting, so there may be a need to consider adjustments to the standard costs based on the setting in which the clinical trial will be conducted.
- 6) **Location of trial sites and participants.** Some trial sites are located in regional/ rural areas, where there may be higher cost experiences. Also, metropolitan area-based trials may provide access to participants residing in regional/rural areas through the use of tele-health technology, or subsidised travel to and from the regional/rural location. Accordingly, there may be a need to consider adjustments to the standard costs for trials where the trial site and/or the trial participants are in located in regional/rural areas.
- 7) **Trial complexity.** There are potentially a number of factors associated with trial complexity that may impact on cost. It is considered that the judgement about trial complexity needs to be made in context as general rules are too difficult to develop, but it may be relevant to consider an adjustment to the standard costs based on trial complexity.

Although the project to develop a table of standard costs highlighted widespread support for this to occur, there were a few stakeholders who expressed concerns about the possible negative impact of the initiative. The Commonwealth subsequently agreed to undertake further work to refine the table of standard costs for clinical trial items and at the time of writing, this work is in progress.

1.2 PROJECT OBJECTIVES

As outlined above, the Department has been involved in supporting a range of initiatives aimed at strengthening the effectiveness of conducting clinical trials across the health sector. The current project focuses on **assessing the enablers and barriers** for a selection of Australian pharmaceutical and device clinical trials in an attempt **to extrapolate these findings to increase Australia's clinical trial participation and competitiveness.**

The objectives of this project were to identify critical success or failure factors for recently conducted, commercially sponsored pharmaceutical treatment and device trials, and more specifically to identify:

- 1) The key barriers or reasons for failure leading to:
 - a sponsor's decision not to place a commercial trial in Australia, and/or
 - a trial conducted in Australia that fails to deliver either agreed participant numbers or high quality data

- 2) The key enablers leading to successful completion of a commercial clinical trial in Australia (e.g. a trial that either meets or exceeds the sponsor's expectations).

1.3 DEFINITIONS OF SUCCESS

An analysis of how success should be defined for the purposes of this project was conducted at the project outset. Several definitions of success proposed by various authors were reviewed for their applicability, and these are outlined below.

- 1) **Operational success.** This refers to the extent to which trials can be successfully operated in Australia and includes metrics by which Australia is compared with other countries as a potential trial site (e.g. cost, timeliness of trial start-up, capacity to reach recruitment targets, and quality of trial data). Operational success includes not only the ability to successfully execute the protocol (including site feasibility and capacity planning, site selection, investigator recruitment, patient recruitment and retention, data collection, management and analysis)^{18,19}, but also includes other factors such as ethics and governance approval processes or safety reporting processes which must be complied with to operate in the Australian environment. Current initiatives to enhance the environment for clinical trials in Australia are focussed on improving operational success, and this was also **a key focus for this project**.
- 2) **Scientific or protocol design success.** This refers to the extent scientific risks are considered and addressed in the protocol design. It includes factors such as:
 - clinical relevance of the question being addressed
 - appropriateness of the patient population or assessment techniques
 - appropriateness of the data being collected
 - whether the right hypotheses, product dose, outcomes or study power have been incorporated into protocol design.¹⁹

Protocol design factors may also impact the operational success of a trial in the Australian context. For example, if investigators do not perceive the trial to be clinically relevant or if data collection requirements are unnecessarily complex or restrictive, it may impact investigator, site and patient recruitment. Hence protocol design factors, where they impact operational success, **were also considered in the current project**.

- 3) **Program success.** This is also referred to as clinical strategy success¹⁸ and focuses on the success of planning and decisions occurring prior to and during product development phases to inform clinical strategies for the compound. For example, it includes factors such as the extent of investment in terms of time and money in Phase 2 trials considering different doses or dose-response in different subpopulations, or assessment of comparative effectiveness as well as safety and efficacy of the compound²⁰. Whilst these

¹⁸ Silverman M (2011). [Article on clinical trial success: how do you define success on the BioStrategics Consulting Ltd Blog](#)

¹⁹ Customised Improvement Strategies, L.L.C (2009), [Protocol development article on Customised Improvement Strategies website](#)

²⁰ Park T and O'Hara B (2013). A Maturity Model for Clinical Trial Design: Harnessing the power of modelling and simulation. Tessella Technology and Consulting.

factors may have an impact on both scientific and operational success, they are **not the focus of the current project**.

- 4) **Product success.** This refers to the safety and efficacy of the product itself, and its comparative effectiveness (including cost-effectiveness). An analysis of product success per se is **not within the scope** of this project.
- 5) **Asset management strategy success.** This refers to the success of organisation policy and portfolio decisions regarding ongoing development of different compounds at various points in product development phases. For example, if a product does not enter Phase 3 trials by a particular date, investment may be transferred to an alternative product within the portfolio. Whilst this may be impacted by operational and product success, assessment of asset management strategy success per se is **not within the scope** of this project.

The scope of success for this project included all operational factors, and selected protocol design factors which either enable or act as barriers to operational success. Other definitions of success in terms of product success, program success and asset management strategy success were not within the scope of this project.

1.4 STRUCTURE OF THIS DOCUMENT

The Draft Final Report comprises five chapters as follows:

| | |
|------------------|---|
| Chapter 2 | Presents a discussion of the methodological design and data collection techniques that were applied to undertake the project. |
| Chapter 3 | Provides a discussion of findings from the literature and preliminary consultations regarding critical success and failure factors for conducting commercially sponsored clinical trials in Australia in the past five years. |
| Chapter 4 | Presents a discussion of the findings of the case studies and articulates the reasons for selecting Australia as a trial site; experience regarding start up times; patient recruitment to the trial and data quality; and the reasons for success or failure of these trials in Australia. |
| Chapter 5 | Presents a summary of findings and conclusions from the project encompassing the preliminary stakeholder consultations; literature scan; and the nine case studies to address the specified project objectives. |

2. PROJECT METHODOLOGICAL DESIGN

This chapter presents a discussion of the methodological design and data collection processes that were applied to undertake the project.

2.1 OVERALL PROJECT DESIGN

The primary data collection method for the project was a series of nine case studies conducted using semi-structured interviews with nominated representatives of pharmaceutical or medical device companies in Australia. These companies needed to be able to identify and discuss a clinical trial or trials which had been conducted in Australia in the past five years, and which highlighted key contributors to decisions regarding clinical trial investment in Australia as well as barriers/enablers to successful conduct of trials in Australia. The name of the drug/device under investigation did not require disclosure.

Case study discussion questions were informed by an initial environment scan including literature scan pertaining to factors critical to the success or failure of pharmaceutical clinical trials in Australia, and preliminary consultations with AusBiotech, Bellberry Limited, the George Institute for Global Health and three jurisdictional representatives nominated by the Clinical Trials Jurisdictional Working Group²¹. Organisations and individuals approached by HOI for involvement in preliminary consultations were identified by the Department. The process for identification and selection of case study participants is presented in the following section.

Preliminary consultations occurred in late April to early May 2015, and case study discussions occurred from 1-15 June 2015.

2.2 STAKEHOLDER CONSULTATIVE PROCESSES

This section provides an overview of the stakeholder consultation processes that were undertaken to support the collection and analysis of the pre-requisite data.

2.2.1 CONSULTATION FRAMEWORKS

Two consultation frameworks were prepared and approved by the Department for distribution to selected stakeholders involved in preliminary consultations and case studies. These frameworks included discussion guides relevant to these different project stages. Appendix A and Appendix B of this document contain discussion guide questions used for the preliminary consultations and for the case studies respectively.

²¹ Note that Medicines Australia was invited to participate in preliminary consultations but was unable due to staff availability within project timeframes. The Medical Technology Association of Australia (MTAA) was not invited to participate in preliminary consultations as the scope of the project was not expanded to include devices until after preliminary consultations had been conducted.

Discussion guides were reviewed by the Department prior to finalisation and distribution.

2.2.2 CASE STUDY SITE SELECTION

The initial process planned for identification and recruitment of up to ten case study participants was via a search of clinical trials listed on the Australian New Zealand Clinical Trials Registry (ANZCTR) meeting the following selection criteria, as agreed by the Department:

- examples of both pharmaceutical treatment and medical device trials
- conducted in the last five years (2010-2015)
- commercially funded
- a range of Australian jurisdictional involvement (i.e. small number to multiple jurisdictions, including single and multiple sites within jurisdictions)
- a range of trial phases
- a range of disease/conditions
- mix of health care settings or organisations involved (e.g. public/private)
- at least one case study from an AusBiotech member organisation
- examples of trials listed on ANZCTR as well as those not listed on this Register.

In order to meet the final selection criterium (i.e. find examples of trials not listed on ANZCTR as well as those listed on ANZCTR) and the timeframes for the project, a second process to identify potential trials was initiated. This involved representatives from Medicines Australia and AusBiotech sending a request to participate to member organisations and/or other organisations with whom they were involved. Based on this latter recruitment process, sufficient participant organisations were identified early in the project to meet the selection criteria, and this became the sole process for recruitment of case study sites. Organisations selected the most appropriate representative(s) to participate in the case study following review of questions in the discussion guide.

2.2.3 CASE STUDY PARTICIPANTS

A total of nine organisations participated in the project including seven pharmaceutical companies, one medical device company, and one contract research organisation (CRO) specialising in biopharmaceuticals, medical devices and diagnostics. All organisations are global, with two having global headquarters in Australia and seven having global headquarters overseas. Table 2.1 below presents an overview of case study organisations and selected trials against the required selection criteria. Note that two organisations presented case studies on two trials each in order to showcase examples of successful and less successful conduct. The participating CRO did not select a particular trial for discussion but discussed broad issues impacting multiple trials for which they have been responsible over the past five years.

Organisation representatives participating in the case studies included heads of global clinical research operations, heads of Australian or regional clinical research operations, heads of clinical trial start up operations, senior clinical research managers and clinical trial managers.

Table 2.1: Characteristics of case study participating organisations (n=9)*

| Domain | Option | No. of case studies |
|--|---|----------------------------|
| Organisation type | Pharmaceutical | 7 |
| | Medical device | 1 |
| | CRO | 1 |
| Industry organisation membership | Medicines Australia member organisation | 7 |
| | AusBiotech member organisation | 4 |
| | Medical Technology Association of Australia member organisation | 1 |
| Trial phase | Phase 1 | 2 |
| | Phase 2 | 2 |
| | Phase 3 | 5 |
| | Phase 4 | 1 |
| Disease/conditions | Cancer | 4 |
| | Cardiovascular | 3 |
| | Diabetes | 1 |
| | Urology | 1 |
| | Infectious diseases | 1 |
| Number of sites in Australia | Range | 1-over 20 |
| States/territories involved in Australia | Victoria | 9 |
| | New South Wales | 8 |
| | Queensland | 8 |
| | South Australia | 7 |
| | Western Australia | 4 |
| | Tasmania | 2 |
| | Australian Capital Territory | 2 |
| Health care setting | Public institutions only | 3 |
| | Public and private institutions | 7 |
| Register listing | Clinicaltrials.gov | 8 |
| | ANZCTR only | 1 |

*Note that some case study organisations presented more than one trial for discussion, and/or were members of more than one industry organisation

2.3 ANALYSIS AND PRESENTATION OF FINDINGS

A thematic analysis of findings from the preliminary consultations and literature scan of factors critical to the success or failure of pharmaceutical and/or device clinical trials in Australia was presented in the project *Stocktake Analysis Report* provided to the Department on 13 May 2015. These findings are summarised again in Chapter 3 of this Report. Findings from the case studies were presented in the Case Study Analysis Report provided to the Department on 19 June 2015, and are presented again in Chapter 4 of this Report. Triangulation of findings from the preliminary consultations and each of the case studies was conducted to prepare overall project findings which are presented in Chapter 5.

3. ENVIRONMENT SCAN FINDINGS

This chapter provides a discussion of the Environment Scan aimed at identifying the factors impacting on the critical success and failure for conducting commercially sponsored pharmaceutical and/or medical device clinical trials in Australia in the past five years from the following sources:

- literature scan
- preliminary consultations with AusBiotech, Bellberry Limited, the George Institute for Global Health and three jurisdictional representatives nominated by the Clinical Trials Jurisdictional Working Group (CTJWG)²².

3.1 WHAT DOMAINS ARE WE COMPETING IN?

Medicines Australia has commented that in order to bring trials to Australia, the Australian subsidiary of a global company must compete against other subsidiaries on metrics for **cost, timeliness of trial start-up, capacity to reach recruitment targets, and quality of trial data**²³. The importance of these factors is borne out by the following comments from various participants in the preliminary consultations:

"When making investment decisions in head offices, costs come into it after discussion regarding regulatory and clinical considerations (e.g. available patient populations). So after choosing US and European sites, decisions regarding Australia, Southeast Asia, Bulgaria, and Brazil etc. are taken by looking at balancing costs against data quality."

"Australia is becoming less crucial due to increased capacity in Asia and Latin America. There are increasing numbers of companies choosing to not invest in Australia."

"We are at a tipping point at the moment in Australia, with a lot of trials in recent years failing to reach recruitment targets, and a lot of companies choosing to not invest in Australian sites. We are at the point of questioning whether we continue to run clinical trials in Australia."

3.2 KEY DRAWCARDS FOR CONDUCT OF CLINICAL TRIALS IN AUSTRALIA

The key drawcards for Australia as a choice of clinical trial investment given by participants in the preliminary consultations relate to ability to provide **quality data** and **timeliness of trial start up**. Drawcards include the following:

- 1) **Excellent research reputation and provision of quality data**. It was reported that Australian researchers involved in commercially sponsored clinical trials have a

²² Note that Medicines Australia was invited to participate in preliminary consultations but was unable to due to staffing changes at the time. MTAA was not invited to participate in preliminary consultations as the scope of the project was not expanded to include devices until after preliminary consultations had been conducted.

²³ Medicines Australia (2011). [Medicines Australia Occasional Paper Series - Paper 03. Keeping clinical trials in Australia: Why action is needed now.](#)

recognised history of compliance with GCP Guidelines and trial protocols. This results in excellent documentation and quality data being provided compared with some other countries between whom choices are being made.

- 2) **CTN/CTX Scheme.** The CTN scheme for trial notification to the TGA following ethics and governance approvals was reported to allow some of the *"swiftest start up times in the world"*. However one respondent commented that *"although the CTN scheme is incredibly positive, these benefits are now largely irrelevant due to bloated ethics and governance timeframes."*
- 3) **Research and development (R&D) tax incentive.** The R&D tax incentive provides a tax offset for eligible R&D activities particularly those that benefit Australia. This incentive was reported to be particularly important by AusBiotech for early phase studies when considering Australia as an investment site.
- 4) **Good reputations of dedicated research teams and key opinion leaders.** The availability of dedicated research teams at some sites, investigator networks (e.g. Kidney Trials Network), sophisticated understanding of products, and the quality of staff on research teams (e.g. key opinion leaders as principal investigators, dedicated clinical research nurses) was cited as a reason for investment in Australia compared with some other countries.
- 5) **Willingness of population to be involved in research.** Research conducted by the Department of Industry and Science found that Australians had a significant willingness to be part of a clinical trial and that this increased with age. Only 15% of Australians surveyed said they would be unwilling to take part in a clinical trial in the future.²⁴ It is worth noting that findings from case studies conducted for this project appear contrary to this, with several case study organisations reporting a lack of awareness and/or willingness to participate in clinical trials by the medical community and the Australian public more broadly. Reasons for this difference are unclear, but may reflect that with increased awareness and understanding of the importance of clinical trials, willingness of primary care practitioners and the general public to participate in trials may increase.

Other reasons given less commonly as drawcards for Australia include a clear process for licensing and reimbursement, use of the English language, regulatory recognition by the Food and Drug Administration (FDA) and sponsor company compared with regulatory approvals from some developing countries, and our location in the southern hemisphere allowing year round studies by United States of America (USA) or European companies for seasonal illnesses.

3.3 KEY DRAWCARDS FOR CONDUCT OF CLINICAL TRIALS IN PARTICULAR AUSTRALIAN INSTITUTIONS

The key drawcards for sponsors to choose particular institutions within Australia were also related to ability to provide **quality data** and **timeliness of trial start up**, and also to the

²⁴ Australian Government Department of Industry and Science (2012). [National survey on attitudes towards clinical trials on Australian Government Department of Industry and Science website](#). Accessed April 2015

expected **capacity to reach recruitment targets**. Specific reasons for choosing particular institutions include:

- 1) **Reputation and experience of key opinion leaders and institution**. The reputation of key opinion leaders and the institution, not only in the particular area of research but also in the conduct of clinical trials, are key factors affecting choice of site.
- 2) **Predictability of achieving recruitment targets**. The history of the institution and/or investigator in meeting stated recruitment targets is critical to decisions regarding choice of site. Literature also supports that inability to meet recruitment targets is one of the key reasons for failure of a trial at a particular site or overall²⁵, and that this is also an issue in Australia²⁶.
- 3) **Available patient population**. The ability to meet recruitment targets depends not only on the ability to accurately estimate the potential patient pool and recruit patients, but also on the actual patient pool available. Certain hospitals may be chosen based on the size of the relevant potential population (e.g. specialised cancer or cardiac hospitals).
- 4) **Governance and ethics requirements of particular institutions**. Streamlined governance and ethics approval processes are essential to limit delays to trial start up.
- 5) **'Research readiness'**. Institutions doing the most research are reportedly the ones who not only have a strong belief in the importance of research, but are also commercially ready to support operation of trials at their site (e.g. clear governance processes, rates for investigators, available resources and infrastructure etc).

3.4 KEY BARRIERS TO CONDUCT OF CLINICAL TRIALS IN AUSTRALIA

The key reasons for Australian and international pharmaceutical companies **not** choosing Australia as a preferred clinical trial site location cited by stakeholders during the preliminary consultations relate to **cost, timeliness of trial start up** due to governance approval processes, and small population size limiting **recruitment for some population groups**.

Specific barriers to conducting clinical trials in Australia include the following:

- 1) **Cost**. A number of stakeholders reported that Australia is a more expensive location in which to conduct clinical trials compared with Southeast Asia and Latin American sites, although cost considerations are balanced against timeliness of start up, capacity to recruit, and quality of data.
- 2) **Small population size**. Compared with other countries that may be considered as alternative trial sites, the relatively small population size in Australia limits the recruitment pool for certain target population groups, particularly for Phase 2 and 3 trials.
- 3) **Lengthy governance/ethics approval processes**. Initiatives to streamline ethics approval processes over the past five years have led to considerable improvements in time taken for ethics approval in Australia. However, governance approval is still required

²⁵ Farrell B, Kenyon S, Shakur H. Managing clinical trials. *Trials* 2010;11:78, [Managing clinical trials article on BioMed Central website](#)

²⁶ Grand M and O'Brien PC. Obstacles to participation in randomised cancer clinical trials: A systematic review of the literature. *Journal of Medical Imaging and Radiation Oncology* 2012 Feb;56(1):31-9

and specific to each institution, and can be a lengthy process. It was noted by several participants in preliminary consultations that the simplified ethics process which has been introduced in recent years has actually unmasked a very ad hoc and inconsistent approach to governance within institutions. Timelines for governance approval was reported to range from *“very quick to ridiculously slow, resulting in an approval process which is no longer quick, efficient and effective but now slow and bureaucratic.”* This issue was also raised by Davis and Chew (2013)²⁷ who reported that whilst the Harmonisation of Multi-centre Ethical Review (HoMER) initiative has been a significant step forward to allow a single ethical review process, the same had not occurred for governance.

- 4) **Poor research infrastructure and accountability.** It was reported during consultations that the engagement of public sector sites has become more difficult in recent years, with clinical investigators and/or institutions not having accountability for the extent to which they are engaged in research nor in meeting research protocol requirements including recruitment targets. Unlike countries such as Korea, Hong Kong and Taiwan, it was reported that Australia has not made a significant or strategic investment in dedicated clinical trial centres of excellence within institutions.

3.5 FACTORS CONTRIBUTING TO SUCCESS OR FAILURE OF CLINICAL TRIALS IN AUSTRALIA

Factors contributing to success or failure of Australian clinical trial sites given by participants in the preliminary consultations relate primarily to poor patient accrual within timeframes and delayed time to trial start up. Contributing factors to **delayed timeframes** and **poor patient accrual rates** were reported as the following:

- 1) **Estimation of potential patient population.** Over-estimation was reported to occur as a result of inadequate questions being asked by the sponsor organisation in the feasibility study, inconsistent medical records systems requiring a ‘best guess’ rather than fact-based estimate of patient numbers, and/or motivation of researcher regarding involvement in the study. It was reported during consultations that other countries are investing heavily in **patient electronic records** which allow a more accurate estimation of potential recruitment pools.
- 2) **Patient participation.** McMahan et al (2011)²⁸ reported that enabling factors for patient trial participation in Australia include a perceived health benefit, sufficient information regarding condition and clinical trial process, direct referral by their physician, and perceived positive outcomes for individual or society. Whilst patient willingness to be involved in trials was not reported to be an issue during preliminary consultations, it was reported that timely patient recruitment would be substantially enhanced by national patient databases for both healthy subjects and target populations. Establishment of national patient databases to enhance patient recruitment has also been supported by

²⁷ Davis ID and Chew DPB. Clinical effectiveness research: a critical need to health sector research governance capacity. MJA 2013;198(4):191-2

²⁸ McMahan VA, Matthews S, Capper H, Chudleigh JB, McLachlan CS. Understanding decision and enabling factors influencing clinical trial participation in Australia: a view point. Asian Pacific J Cancer Prev 2011;12:3153-6

other Australian researchers²⁹ and as previously noted, was also a recommendation from the McKeon Review³⁰

- 3) **Timely ethics and governance approval processes.** As previously discussed, delays in local site ethics and governance approval processes can cause significant delays in time to trial start-up, and may even result in discontinuation of the site.
- 4) **Site 'research readiness'.** The ability of the site to undertake the research successfully may not have been adequately assessed during the feasibility study. Lack of research readiness or accountability can impact **patient recruitment and data quality**, and may manifest as lack of site resources (e.g. clinical research nurses available 24/7), competing priorities for staff, overworked staff, or lack of senior management commitment to the particular clinical trial or to clinical research more broadly within the institution or health service.

"With no accountability to anyone for research delivery, recruitment is poor in Australia and there is a substantial risk of no clinical trials being conducted in Australia in the future."

- 5) **Appropriateness of site selection.** Poor site selection in multicentre randomised clinical trials can lead to delayed start-up, delayed or insufficient participant recruitment, and poor data quality or research integrity³¹. Rigorous feasibility studies to inform appropriate site selection are therefore critical. Harper and Zuckerman (2006)³² suggest that the following factors should be carefully considered during a **site feasibility study** to inform appropriate site selection:

- Site interest, enthusiasm and buy-in to study design and rationale
- Site experience (clinical research and therapeutic area)
- Site staffing, resources, workload and time commitments
- Site personnel skills and abilities
- Staff turnover rates
- Functional responsibilities of site personnel
- Access to subject population with the required eligibility criteria
- Technical facilities and equipment
- Reasonable and fair study budgets
- Ethical and governance review policies and procedures
- Institutional legal procedures
- Site training and standard operating procedures

²⁹ De Roach JN, McLaren TL, Paterson RL, O'Brien EC, Hoffmann L, Mackey DA, Hewitt AW, Lamey TM. Establishment and evolution of the Australian Inherited Retinal Disease Register and DNA bank. *Clin Experiment Ophthalmol* 2013 Jul;41(5):476-83

³⁰ Australian Government Department of Health and Ageing (2013). *Strategic Review of Health and Medical Research: Summary Report*. Commonwealth of Australia

³¹ Berthon-Jones N, Courtney-Vega K, Donaldson A, Haskelberg H, Emery S, Puls R. Assessing site performance in the Altair study, a multinational clinical trial. *Trials* 2015 Apr;16:138

³² Harper BD and Zuckerman D. Critical success factors for planning for site selection and patient recruitment planning. *BioExecutive International* 2006;2(6):S16-28

- GCP compliance and inspection history
 - Past enrolment performance metrics
 - Flexibility of clinic hours
 - Site security and storage facilities
 - Role and accountability of clinical research associate in managing site and subject enrolment.
- 6) **Protocol design.** Other contributing factors to poor patient accrual reported during preliminary consultations and evidenced in the published literature related to protocol design rather than operational factors. These include:
- failure of patient eligibility criteria to keep pace with current medical practice
 - inability to meet USA Food and Drug Administration (FDA) or other international recruitment timeframes (e.g. patient recruitment over December-January in Australia is difficult)
 - perceived lack of value of study question
 - inaccurate prevalence estimates and/or restrictive eligibility criteria³³
 - sample size requirements, or protocol requirements being too complicated³⁴.

³³ Biotext. Review of the literature on participation in clinical trials: barriers and incentives for health care practitioners and consumers. Biotext, March 2012, [Review of the literature on participation in clinical trials report, on the Department of Industry, Innovation and Science website](#) Accessed April 2015

³⁴ Foster JM, Sawyer SM, Smith L, Reddel HK, Usherwood T. Barriers and facilitators to patient recruitment to a cluster randomised controlled trial in primary care: lessons for future trials. BMC Medical Research Methodology 2015;15:18, [Barriers and facilitators to patient recruitment to a cluster randomised controlled trial in primary care article on BioMed Central](#)

4. CASE STUDY FINDINGS

This chapter presents a discussion of the findings for each of the case studies and articulates the reasons for selecting Australia as a trial site; experience regarding start up times; patient recruitment to the trial and data quality; and the reasons for success or failure of these trials in Australia. It is important to emphasise that the definition of success in this context is where a trial met or exceeded sponsor expectations in terms of conduct and recruitment, and the definition of failure is where a trial failed to meet recruitment targets and/or provide high quality data.

4.1 CASE STUDY 1: PHASE 2 PHARMACEUTICAL TRIAL

This was a global Phase 2 pharmaceutical trial involving multiple Australian sites **across several jurisdictions**, including a **mix of public and private** institutions. Despite timely ethics approvals, the trial faced challenges with respect to start up times at some sites and with patient recruitment, resulting in closure of the majority of sites in Australia.

4.1.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conducting this trial based primarily on the **reputation and enthusiasm of the key opinion leaders** and institutions who indicated their interest in participating, and on findings from the **feasibility assessment** indicating that sites would have the capacity to recruit.

Cost of trial conduct was factored into the investment decision after consideration of the above factors. It was reported that Australia is becoming much more expensive as a place to run clinical trials, second only to Switzerland and more expensive than the USA. From this perspective there is an urgent **need to standardise costs** to assist in negotiations with clinical trial outlier items in particular.

In the past, Australia has been more involved in Phase 3 research for this organisation, although it is becoming increasingly chosen as a site for Phase 2 and Phase 1 trials. This is as a result of improved internal capacity and advocacy for conduct of earlier phase trials in Australia, and the **attractiveness of the CTN scheme** in contributing to timely trial start up.

4.1.2 TRIAL START UP EXPERIENCE

Several ethics submissions were required for sites involved in this clinical trial to cover public sites under the NMA, public sites in jurisdictions not under the NMA, and private sites. The company reported that whilst ethics approval was timely for this trial, and the NMA has “helped enormously” to expedite this process, **sourcing a lead site was difficult** due to a lack of dedicated clinical trial staff at institutions and a reluctance by sites to take on this additional administrative burden.

Although ethics approval for this trial did not delay start up times, obtaining **governance approval caused delays** at some sites of up to three months. Issues with governance approvals arose with this and other trials due to the following:

- a reluctance by Research Governance Officers (RGOs) to consider governance in parallel with ethics
- the sponsor company being unable to directly contact RGOs to discuss the contract or issues being raised, but rather having to rely on an often busy or under-resourced investigator or study coordinator as the conduit for all communication
- a lack of transparency or clarity regarding the requirements and timeframes for governance review and approvals
- a lack of standardised costs for public health institutions requiring the sponsor to seek budget approvals from head office for sites that varied from fair market value.

“Whilst the NMA has helped enormously in fast tracking the ethics approval process, it has failed regarding governance. Organisations will not conduct governance reviews in parallel as they are reluctant to commit resources until after ethics approval. Submitting to governance is like submitting to a black hole and instead of taking 2 weeks post ethics to finalise, it can take up to 6 months. If we could get both ethics and governance in a 30 day time frame we would be competitive with the US. We should at least be able to do it within six weeks.”

The company reported that they always aim to choose one private site if possible and submit this first in order to fast track the time to trial start up and first patient enrolled.

4.1.3 PATIENT RECRUITMENT EXPERIENCE

Recruitment to this trial did not go as expected. Although this has been a global issue, **Australia fared particularly poorly and the majority of Australian sites were closed** after not recruiting any patients to the trial.

The key issue impacting inability to meet recruitment targets for this trial was that despite initial enthusiasm, **investigator excitement waned** as the product was not seen as “novel” enough and there was **no accountability at the investigator end for delivering on estimated recruitment numbers**. The pharmaceutical sponsor company reported that despite amending recruitment estimates to only 25% of those originally estimated by sites (and submitting this amended figure in the feasibility assessment for Australia), sites had still fallen well short of recruitment targets. Poor recruitment was also attributed to a relatively small eligible population for this particular trial in Australia due to the high standard of screening and provision of health care for this particular disease/condition. However, this was clear in the questionnaire completed by site investigators as part of the feasibility assessment, and should have been factored into patient estimates by sites.

4.1.4 QUALITY OF TRIAL DATA

It was reported that whilst Australia is generally well regarded for quality of trial data, there are occasional situations where due to lack of resources at the site, data have not been entered in a timely manner (i.e. within five weeks) with potential impacts on patient safety. It was reported that there is a lack of clarity as to who is accountable for poor data entry and quality in these situations.

4.1.5 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- The CTN scheme is very attractive to investors in clinical trial activity in Australia
- Single ethics review expedites the ethics review and amendment process but is still not in place nationally or currently recognised between public and private sectors
- Research governance is valuable and important, despite current processes being unclear and inconsistent.

4.1.6 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of this and other clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- Lack of understanding and engagement of the Australian population in the importance of research, and lack of awareness regarding available clinical trial options for the general public
- Lack of consistent and 'fair market value' approach to trial costs between institutions and between studies impacts start up times due to time taken for head office approvals and contract negotiations with sites
- Governance approval is currently not conducted in parallel with ethics and there is a lack of transparency, consistency and clarity regarding scope, requirements and timeframes for governance review
- Lack of accountability at an institution level for meeting recruitment targets and trial timeframes.

4.2 CASE STUDY 2: PHASE 3 PHARMACEUTICAL TRIAL

This was a global Phase 3 pharmaceutical trial involving multiple Australian sites **across several jurisdictions**, including a **mix of public and private** institutions. The trial faced challenges with respect to start up times, and with patient recruitment.

4.2.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conduct of this trial based on **potential recruitment population**, a lengthy history and **experience** in conducting trials in this disease area compared with other Asia Pacific sites, history of good quality data, and being English speaking. It was noted that despite our current advantage of being more experienced in conduct of clinical trials within the Asia Pacific region, we are likely to lose this advantage in the near future as other countries increase their clinical trial activity.

When considering whether differences in choice of country for clinical trial investment differs by trial phase, it was reported that for this organisation, decision-makers for Phase 1 trials are different to those for later phases. Decisions for Phase 1 trial locations are made based on quality of Phase 1 units/facilities and investigators in the conduct of these trials; agreements

are put in place with these units to conduct trials for the organisation. Work is currently underway to establish agreements with additional Australian sites to conduct Phase 1 trials, but it was noted that other countries such as Korea are well recognised for excellent Phase 1 units and facilities.

Choice of sites within Australia for this trial was based on internal knowledge regarding adequacy of clinical trial resources at sites, and previous experience with these sites regarding governance and start up timelines. In addition, the organisation has **stipulated 'fair market value' regulations** which restrict activity with institutions whose requested costs are beyond fair market value. All sites chosen need to remain within these corporate guidelines. It was reported that if standardised costs within Australia start to rise, we will no longer remain a competitive or attractive site for clinical trial investment.

"We are an expensive country and things are in place to tighten up the budget in our organisation. We have fair market value stipulations which mean that we are unable to work with outliers beyond what is deemed fair market value. Thus whilst the project to standardise clinical trial costs is a great initiative, if standardised costs are too high this will negatively impact the extent of clinical trial investment in Australia by our organisation."

4.2.2 TRIAL START UP EXPERIENCE

It was reported that the biggest issue impacting the successful conduct of clinical trials in Australia is delays in the timeliness of start up. This is influenced by delays in ethics and governance approvals rather than delays in budget and contract negotiations, as the latter are often initiated prior to ethics submissions and conducted in parallel.

Despite advances from the NMA in streamlining ethics approval processes, **Australia still does not have a nationalised system for ethics approval**; thus requiring multiple ethics submissions and approval processes. For this trial, several ethics submissions were required to cover public sites under the NMA, other public sites, and private sites. **For sites under the NMA, two ethics submissions were actually made to split the risk** in case delays were experienced at one site. In addition, finding a lead site is also difficult as there is **increasing reluctance by NMA sites to take on the role of lead site** due to a lack of resources to manage the increased administrative burden associated with this role. **Timing of HREC meetings** was also reported to be an issue impacting start up times. Public ethics committees generally don't meet more often than monthly, unlike other countries such as the UK which have 11 national ethics committees which rotate to ensure weekly meetings. Bellberry has also implemented a model that offers weekly ethics review meetings for private trial sites. In addition, at many sites **communication cannot occur directly between the site and the pharmaceutical company** but must go via the study coordinator, adding delays to the process.

In addition to relatively lengthy ethics approval processes, it was reported that **governance approval can take up to 90 days (3 months) following ethics**, as these **processes are not conducted in parallel**.

"It should not be unrealistic for us as a country to aim for 3-4 months in total for trial start up if ethics and governance requirements can be considered in parallel, as we already have the CTN scheme which expedites regulatory approval. Governance approval should take no

longer than two weeks to finalise post ethics approval. This would be hugely attractive for Australia as a clinical trial investment site."

The impact of start up delays in a competitive recruitment trial is that Australian sites risk not being able to recruit target participant numbers, which not only impacts access to new medicines by Australian patients, but is also an expensive exercise in terms of start up costs. This can impact future investment decisions in Australia.

4.2.3 PATIENT RECRUITMENT EXPERIENCE

Recruitment to this trial was less than expected primarily due to a lack of robust feasibility assessment, lack of national databases for many conditions requiring investigators to base estimates on 'gut feel', and a **lack of referrals to clinical trials**. This latter issue was reported to be a key issue for Australia compared to other countries which have good infrastructure and clinical trials networks to capture and refer patients to trials. In Australia, it was reported that doctors are reluctant to hand over care of patients for the period of the trial, so do not refer. An example was cited of an app that has been recently developed by a haematology network in Australia to share information regarding current trials and facilitate referral of patients – it was reported that this was a very positive initiative to increase awareness both within the medical and patient community regarding relevant clinical trial activity.

4.2.4 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- The CTN scheme is very attractive (although there are some "hiccups" reported with the electronic form)
- Adequate resourcing at some sites with experienced study coordinators and good clinical oversight
- Good feasibility assessment at some sites, and a commitment to deliver on what has been agreed.

4.2.5 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of this and other clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- No national system of ethics and governance – processes to improve timeliness of ethics and governance approvals are required, including a standardised format and templates used across sites, and a parallel ethics and governance process
- Lack of resourcing and support for clinical research and clinical trials activity at an institution level – support for study coordinators by the institution is essential
- Lack of standardised clinical trial costs between institutions and between studies impacts start up times due to time taken for head office approvals and contract negotiations with sites.

"We'll never be cheap, although we do need to stay competitive with respect to costs. However, we do have the potential to significantly improve start up times to make us more attractive for investment – we used to be awesome. Start up delays are primarily due to

serial rather than parallel governance and ethics approval processes – governance should take no longer than 2 weeks post ethics approval to finalise, but can currently take up to 3 months.”

4.3 CASE STUDY 3: PHASE 3 PHARMACEUTICAL TRIAL

This was a global Phase 3 pharmaceutical trial involving multiple Australian sites **across several jurisdictions**, including a **mix of public and private** institutions. This was reported to be *“a positive case study, which is a huge exception to the rule”*.

4.3.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conduct of this trial based primarily on the **reputation of investigators to provide honest recruitment numbers**, the reputation of investigators in being able to **work with site research governance officers to expedite start up times** and investigators who are **passionate about the subject** areas and keen to get patients access to new medicines. Australia, and the investigators chosen, also had a good reputation with respect to provision of quality data.

Another key reason for selecting Australia and the choice of particular sites was the **quality of study coordinators at the sites chosen**. It was reported that these study coordinators are very experienced in trial conduct, know the patients, know the system and receive a lot of support and autonomy within the institution to conduct multiple trials. However, this was described as the exception rather than the rule, with other trials having major issues with lack of resourcing, support and availability of study coordinators dedicated to trial operation.

4.3.2 TRIAL START UP EXPERIENCE

There were **no issues with timeliness of ethics or governance approval** for this trial, which was reported to be **attributable to excellent and experienced site study coordinators and keen investigators driving the process**. Ethics approval for the private site was achieved in 2.5 weeks, and provisional approval for the public sites was achieved **within one month**. Governance approval following ethics occurred in **less than two days** at one site, with the longest site taking only two weeks. The investigators involved in the trial were aware that they were in a competitive recruitment trial which meant that any delays had the potential to limit patient recruitment in Australia (i.e. once global trial targets were reached, the trial would be closed to recruitment), and they worked with ethics and governance officers to ensure that submissions were considered in a timely manner.

Several approaches for choice of site for ethics submission were planned based on potential dates by which all necessary internal documentation would be received. Sites were considered based on their history of short turn-around times for ethics and governance approvals, and their available HREC submission dates. For this trial, only one ethics submission was made for public sites under the NMA, but it was reported that **usually more than one submission is made in order to share risk and lessen the burden on lead sites** as per the comment below.

“The downside of the NMA is that most sites (or particular departments within sites) do not want to be the lead as there is too much additional work involved. In theory you should just do one ethics submission for NMA sites, but in practice we usually do more than one as sites will only agree to be the lead for no more than three sites. Also, we need to share the risk across sites. For example, in another trial a site said they’d be the lead then didn’t deliver as the investigator went on leave and no-one else would sign the documentation.”

Although timeliness of governance approval was excellent for this trial, it was reported that **governance is usually the biggest cause of delayed trial start up**. Whilst in theory governance should be able to occur in parallel with ethics, in practice RGOs do not want to commit to reviewing documentation prior to ethics approval. This may be due to a lack of clarity and consistency regarding the scope and role of RGOs, as it was reported that some of them are asking questions that fall under the remit of ethics committees.

4.3.3 PATIENT RECRUITMENT EXPERIENCE

Target recruitment numbers for all sites were **achieved within very short timeframes**. This was reportedly due to the particular condition and patient inclusion criteria for the trial (i.e. *“patients were waiting for treatment for this condition, whereas in other trials you are waiting for patients to show up”*), but also critically due to **feasibility studies** conducted as part of site selection. Sites were chosen based on their databases indicating a high number of patients suitable for recruitment to the trial, and on their history of **providing correct patient estimates** and delivering on these estimates in a timely manner. Comment was made that for most feasibility studies, estimates provided by investigators are adjusted down particularly for new therapeutic areas where it is a bit of a ‘judgement call’, but for this study numbers were not adjusted as the investigators had a history of delivering as promised. The investigator **“enthusiasm factor”** in this case ensured that recruitment targets were met even within short timeframes, although it was noted that in most cases this enthusiasm factor usually leads to overestimation of potential recruitment numbers which in practice cannot be met.

4.3.4 QUALITY OF TRIAL DATA

Quality of trial data in Australia was reported to be of a generally high standard. However issues can arise if site staff are inexperienced or if recording databases are complex. The site investigator is responsible for ensuring that there are no protocol deviations and in providing trial oversight. The site study coordinator is responsible for ensuring that all data are collected as per protocol, and is also responsible for data entry. The latter may require the ability to learn new data systems and requirements for each trial.

4.3.5 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- An attractive product and research question
- An available population pool for recruitment
- Enthusiastic investigators and study coordinators who can drive the ethics and governance approval processes to occur in a timely manner

- Reputation of investigators to deliver target recruitment numbers (i.e. not just their reputation as a key opinion leader in the field, but more specifically their reputation in delivery of recruitment targets in clinical trials)
- The CTN scheme helps to expedite start up times
- Dedicated study coordinator at the site.

4.3.6 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

Although this trial successfully met expectations, key barriers or reasons for failure of other clinical trials to meet recruitment and/or data quality expectations in Australian sites were identified as:

- Lack of reliable and fast ethics approval processes and timeframes, with no national single site review and multiple submissions still made for sites under NMA in order to share risk and reduce additional administrative responsibility for lead sites
- Lack of consistent and transparent governance approval processes, which currently vary in scope and requirements for each site and are generally not conducted in parallel with ethics
- Lack of understanding and engagement of the Australian population and the medical community in the importance of research, resulting in a reluctance of both patients and medical practitioners to become involved in trials or refer patients to trials

"We have a small population here anyway, and a lack of willingness to refer patients to trials makes it even harder to recruit. We have had situations where the specialist has referred the patient for enrolment in a trial, then the patient has spoken to their GP and been told to not participate. This may be due to a lack of understanding of the value of trials by GPs, or a reluctance to hand over patient care to the clinical trial investigator. We need to embed in the medical and broader community that being involved in a clinical trial is a good option."

- Lack of consistent and 'fair market value' approach to trial costs means that we are now seen as one of the most expensive countries in which to conduct trials
- Lack of accountability or understanding at an institution level regarding the importance of meeting recruitment targets and trial timeframes

4.4 CASE STUDY 4: PHASE 3 PHARMACEUTICAL TRIAL

This is a global Phase 3 pharmaceutical trial involving multiple Australian sites **across several jurisdictions**, with the majority of sites being **public** institutions and one private. The trial faced challenges with respect to start up times, and with patient recruitment.

4.4.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conduct of this trial based primarily on the **reputation of the key opinion leaders** and the institutions who indicated their interest in participating in the trial, and on findings from the **feasibility assessment** indicating that sites would have the

capacity to not only recruit to the trial, but also to ensure that patients could be followed up³⁵.

Other contributing factors included our IT infrastructure, English language and reputation regarding data quality. It was commented that researchers being familiar with GCP is an expectation of all countries and does not place Australia at an advantage, and that we are *not* renowned for timeliness of trial start up or meeting recruitment targets.

4.4.2 TRIAL START UP EXPERIENCE

Although the process for ethics approval was reported to have improved over recent years, **inherent risks associated with single site ethics approval** became apparent in this trial, and ethics approval took a total of **six months**. Although notification of ethics approval was received within three months from the original lead site (which covered all other public institution study sites across several jurisdictions), due to changes at the original site a second lead site had to be identified and the whole ethics submission and approval process repeated.

Following ethics approval, governance approval at each of the sites **ranged from two weeks to three months**. There was **wide variation in the documentation required** by different RGOs, and a **lack of clarity regarding the scope** of the governance approval process. For example, it was unclear and inconsistent as to what aspects of the protocol need to be reviewed and approved by governance bodies, compared to aspects that may only need to be notified to governance following ethics approval. Generally sites will not progress governance approval until ethics approval has been received, as they are currently reviewing a lot of the same material and do not want to 'waste time' if there are changes made during the ethics approval process. This company is **seeking a national approach for governance committees with clear and agreed documentation regarding scope, steps and requirements** for governance approval at institutions to allow the process to be expedited and conducted in parallel to ethics approval processes.

"The ethics approval process is improving in Australia. However, the separation of governance, whilst it has taken the burden off ethics committees regarding contract agreements and legalities, has done the opposite of its intended purpose to improve approval timelines. The original intent was to submit governance in parallel to ethics but in practice this rarely happens. There is now an additional administrative process, and it is very disheartening to get ethics approval and then have to wait another eight weeks or more to get governance approval."

It was noted that relevant clinical trials networks may be useful in recommending key sites for inclusion in trials, and also to advise on and negotiate payments with sites based on knowledge of costs across different sites for the same activities in similar trials.

4.4.3 PATIENT RECRUITMENT EXPERIENCE

The ability to meet recruitment targets was reported by this organisation to be the key driver for choice of country for future clinical trial activity.

³⁵ This was an end point study so if patients were lost to follow up they were recorded as deceased, which had the potential to impact study findings

“Not meeting recruitment targets will put investment in clinical research in Australia by this organisation on the chopping block.”

This study **did not meet recruitment targets** in Australia primarily due to a reported lack of rigour in the feasibility assessment process on the part of both the commercial sponsor organisation and the site investigators, with a resulting overestimate of patient recruitment numbers. Another issue impacting patient recruitment was the ‘human factor’ involved in study conduct and coordination; for example, study coordinator taking leave during the trial without replacement of position.

Despite this organisation having a procedure in place to close down sites if they are not recruiting in a timely or expected manner (i.e. as per their contractual arrangements), in reality this was reported to rarely occur as these decisions have potential future commercial impacts in terms of product endorsement and use by key investigators. Rather than being accountable to the sponsor company therefore, it was suggested that it may be preferable for investigators to have some accountability to the site where the trial is being conducted for delivery of quality and timely clinical research.

4.4.4 QUALITY OF TRIAL DATA

Whilst Australia is generally well regarded for quality of trial data, this organisation commented on the increasing importance of timely data entry as per the quote below. Whilst responsibility for prioritising timely data entry falls on sites and study coordinators, it was recognised that pharmaceutical companies have responsibility for the adequacy of data entry tools and support systems provided to sites to fulfil this role.

“What is becoming absolutely imperative is data entry. Previously study coordinators have not had to prioritise data entry, but it is now essential that this is done in a timely manner in line with risk based monitoring being rolled out by sponsor companies. Monitors are now going out to sites less often, and companies rely on centralised monitoring groups to review data. For this to occur, the data needs to be entered in a timely manner. However, sites do not always understand the critical importance of this particularly with respect to patient safety. This is a number one priority for sites.”

Particular issues with data quality which are commonly seen by this company were reported to be around the provision of verifiable source documentation and accurate informed consent documentation. For example, it was commented that common issues with informed consent documentation include use of documents not yet approved; use of the incorrect document (e.g. previously approved version); updated consent forms not provided to previous patients; and forms not being properly completed or signed by patient and/or doctor.

4.4.5 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- The involvement and engagement of the Primary Investigator as per the following comment: *“If the Primary Investigator is motivated and wants the trial to succeed then it will.”*

- Relationship between the sponsor company and the site, and provision of support by the sponsor organisation to help the site succeed wherever possible
- Realistic feasibility assessment in terms of the expected recruitment population and the adequacy of site resources to achieve recruitment numbers

4.4.6 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of this and other clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- Insufficient support at both a company level and an institution level to conduct realistic feasibility assessments to more accurately inform estimated patient recruitment numbers and ensure resources are available at a site level to support this recruitment
- Lack of understanding and engagement of the Australian population in the importance of research, resulting in a reluctance of both patients and medical practitioners to become involved in trials (e.g. participants still perceived as “guinea pigs”)
- Lack of truly national approach to ethics review impacts trial start up times
- Lack of consistency and transparency in approach for governance reviews impacts trial start up times
- Lack of consistent and ‘fair market value’ approach to trial costs between institutions and between studies impacts start up times due to time taken for head office approvals and contract negotiations with sites.

It was suggested that Australian Government provision of guidelines for clinical research sites would be beneficial in addressing some of the above issues. These may include standard operating procedures (SOPs) for such items as how to conduct a feasibility assessment, negotiate with pharmaceutical or medical device companies, conduct trial start up, obtain informed consent and a one-two page document outlining governance responsibilities and scope.

4.5 CASE STUDY 5: PHASE 1-2 PHARMACEUTICAL TRIALS

The clinical trials presented as a case study by this pharmaceutical company were a series of **Phase 1 and 2 pharmaceutical trials**. **Phase 1 trials were conducted only in Australia** across two jurisdictions, and provide an example of successful trial conduct. The global Phase 2 trial has only faced minor challenges and involves multiple Australian sites across several jurisdictions, with all sites being **public** institutions.

The trial was listed on **ANZCTR** prior to first patient recruited in order to make the information publicly available in Australia. The company also registers trials on **Clinicaltrials.gov** if there are any USA sites and on the European Union registry if there are European sites.

4.5.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conduct of **Phase 1 studies** due to our **positive regulatory environment (CTN scheme) and established Phase 1 units** with a good reputation for successful Phase 1 trial conduct. The first-in-human Phase 1 trials were conducted by Phase 1 research units in two Australian jurisdictions. These units were reported to be operated as businesses, and are realistic in their ability to deliver required patient numbers within the project timeframes (noting that Phase 1 trials generally require healthy volunteers, where numbers are known up front).

Australia was chosen as one of the sites for conduct of the global **Phase 2 study based on the reputation** of the country lead researcher, the experience and expertise of other Australian researchers in this field, and the fact that we are English speaking. Most importantly, a very **strict and robust feasibility assessment** was conducted to identify that we had the required recruitment population, and to understand the extent to which investigators had overpromised during their original estimations. It was reported that in some trials for rare diseases requiring drug-naïve patients, Australia is not chosen because our high standard of healthcare means that the number of drug-naïve patients is low in an already rare disease, in an already small population in Australia compared to other countries (e.g. Eastern Europe and South America).

"It is really important that we take the time and discipline to conduct robust feasibility assessments particularly for rare disease populations. We then apply this same discipline to conduct feasibility assessments for trials in more common diseases or conditions. We look not only at patient numbers, but also at the experience of the institution and clinician in running successful trials, as running a trial is very different to provision of clinical care."

Choice of sites within Australia was based on recommendation of the Australian country leader and by the global steering committee as to which sites had experience in conduct of trials, did not have a reputation for lengthy ethics or governance approval processes, could recruit as per identified targets, and were able to deliver quality data based on an appropriate level of resourcing and support by the institution for clinical trial activity.

4.5.2 TRIAL START UP EXPERIENCE

It was noted by this organisation that the ethics approval process is a changing game in Australia, with a number of recent positive initiatives. However, **single site ethics approval is still not available** and the Phase 2 trial in this case study required more than one ethics submission for the public sites involved. The different ethics committees had different questions and different requirements for response, with one committee requiring responses to be reviewed by the full committee and others not. Changes to protocol required by one ethics committee also had to be submitted to other ethics committees for approval. The **ethics approval process took 3-4 months** for this trial.

"If we had the choice to go to Bellberry for all ethics submissions we would. They are resourced to conduct these in a timely manner – that's their job. It would be great if we could get a commercial arm on public HRECs that would speed up the process for commercially sponsored trials – companies would pay for improved timeframes."

Following ethics approval, governance approval took a minimum of 4 weeks at sites, with all sites undertaking governance approval processes linearly rather than in parallel. It

was reported that the governance process in Australia varies between institutions, and can require not only consideration of contractual and indemnity arrangements, but in some cases also require review of trial design which has already been approved by the ethics committee. Delays of 3-6 months are not uncommon as budgets are negotiated prior to submission of documentation for governance approval, particularly where each hospital or institution costs things differently for the same service (e.g. xray).

The **impact of delayed start-up** for some sites in the Phase 2 trial has been both short and long term. In a competitive recruitment trial, site delays mean that they may **miss the opportunity to recruit** if international recruitment targets are met. Also, other countries on the waiting list for participation will be offered the chance to participate if Australian sites do not get up and running. The longer term impact of poor recruitment is that **other countries will be chosen ahead of Australia** for conduct of future trials.

4.5.3 PATIENT RECRUITMENT EXPERIENCE

The Phase 1 trials experienced no issues with recruitment. Recruitment was not yet complete for the Phase 2 trial. The organisation commented that despite robust feasibility assessment, one barrier still existing for recruitment was the attitude toward clinical trial activity which still exists in Australia.

"We need to change the attitude to clinical research in Australia. We need a big media campaign similar to the campaign around organ donation to change the attitudes of the general public, medical community and institutions towards involvement in trials."

4.5.4 QUALITY OF TRIAL DATA

Whilst our ability to produce high quality clinical trial data was reported to be Australia's greatest enabler ten years ago, it is now not seen as a competitive advantage but more as a cost of entry which other countries are now meeting.

The greatest influence on continued good quality data provision in Australia was reported to be the level of site resourcing. Pharmaceutical companies are paying for study coordinators at sites, but are unclear the proportion of time spent by these coordinators on trial activity or the number of trials being coordinated by these funded positions.

4.5.5 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- Expertise of clinical investigators in the therapeutic area
- Good knowledge of your patient population and rigorous feasibility assessments using real data to determine expected recruitment population and the adequacy of site resources to achieve recruitment numbers

4.5.6 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of this and/or other clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- Complexity and variability of ethics and governance approval processes, and time taken to negotiate contracts with sites, impacts start up times
- Lack of understanding and engagement of the Australian population in the importance of research, resulting in a reluctance of both patients and medical practitioners to become involved in trials

"Australia is falling behind in our acceptance of clinical trial participation at a general community level. As a country we do not do a good job of promoting the benefits of clinical trials compared to countries like UK, USA, Asia and Europe. People still see involvement as being like guinea pigs in an experiment."

- Lack of investigator networks which can improve level of referral to trial (i.e. compared to big networks in the USA and Europe)
- Poor access by patients to information regarding clinical trial activity (e.g. portals and registers such as ANZCTR are not easy to navigate for the general public)
- Lack of clear national documentation on how to navigate the Australian system for organisations involved in, or considering increasing their involvement in, clinical trials (i.e. no national Clinical Trials Centre or hub assisting hospitals, commercial sponsors, patients and jurisdictions to meet clinical trials needs).

4.6 CASE STUDY 6: SHOWCASE OF TWO TRIALS

Two clinical trials were presented by this organisation to showcase both a 'successfully conducted' trial and one that faced more challenges. The successfully run trials were a series of **Phase 1 pharmaceutical trials**, with the majority of these conducted in public institutions in Australia. The less successfully conducted trial was a global **Phase 4 pharmaceutical trial** in multiple **Australian sites across several jurisdictions**, including a **mix of public and private** institutions.

4.6.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conduct of both these trials based on the attractiveness **of our CTN scheme** in limiting the regulatory hurdles impacting start up times in other countries, and feasibility studies indicating the capacity to meet the **required patient accrual targets**. Sites for the Phase 4 trial were chosen based on numbers estimated by specialists, and also on the available infrastructure required.

It was also reported that the Australian subsidiary of this pharmaceutical company has been advocating the **benefits of conducting Phase 1 trials in Australia**, and that this activity has led to an increase in choice of Australia for Phase 1 trial activity by the organisation. For this particular Phase 1 trial there was also an unmet need in Australia, and key international experts with expertise and experience in conduct of trials in this therapeutic area were Australian based.

When considering whether there are differences in corporate decisions regarding investment in Australia as a clinical trial site based on trial phase, it was reported that the primary reason for choice is based on patient volumes. These are dependent on the disease/condition under investigation and the particular patient inclusion or exclusion criteria. For Phase 3 trials in some conditions, Australia would always be considered. For Phase 2 trials, we may not be considered as we do not have the required patient population, or ethics committees may be unlikely to support the choice of comparator for the trial. For Phase 1 trials, Australia is seen as an attractive location due to our CTN scheme and the capacity at a hospital level to conduct these trials.

Whilst **relatively high cost** is not necessarily a deciding factor for choice of Australia as a site for conducting clinical trial activity as long as other factors are favourable ("*We are expensive but if we still deliver on patient numbers we will be considered favourably*"), the Australian subsidiaries do receive questions asking for justification of high costs associated with trial activity. There are occasions where Australia is *not* chosen based on comparatively high costs of clinical trial start up and conduct. There was some concern expressed that although the **current project underway in Australia to standardise costs** associated with clinical trial activity is a positive initiative, if these costs are standardised "too high" it could have a negative impact on research budgets in Australia.

4.6.2 TRIAL START UP EXPERIENCE

The **Phase 1 trial received ethics and governance approval from a public institution within six weeks**. This was attributed to the enthusiasm of key opinion leaders, and in

particular the Primary Investigator in Australia, to deliver a product with the possibility of meeting a key unmet need.

Ethics approval timeframes for the Phase 4 trial took eight weeks for private sites and ranged from 2-3 months at public sites. Separate ethics submissions were required for sites in jurisdictions not part of the NMA, and also at sites requiring individual submissions despite their jurisdiction being a signatory to the NMA. It was noted that the single site review process still had a long way to go, and that an issue now arising is the difficulty engaging a site willing to act as the lead site due to additional administrative responsibilities for which the site does not feel that they are adequately resourced despite the company agreeing to cover costs.

Combined ethics and governance review timeframes ranged from 3 months to 8 months, with almost all of this **variability due to differing governance approval processes and timelines.** Following ethics approval, it was reported that actually getting approved documentation can take from one day to one month, depending on the experience and availability of the study coordinator at the lead site. A lack of clarity was reported in governance approval processes and requirements.

"We need to simplify and standardise the governance process and make it transparent. The current complexity is absorbing too much of the limited time resources of study coordinators. We need to work out what the requirements are for governance approvals, and provide institutions with a good incentive or reason to change their current processes if required."

Delayed ethics and governance approval timeframes have the **potential impact of limiting timeframes for patient recruitment** to the trial, and therefore impacting future investment decisions in Australia as a clinical trial site. It was reported that there is a huge cost imposition involved in trial start up at each site, and delays impacting patient recruitment are therefore not viewed favourably.

4.6.3 PATIENT RECRUITMENT EXPERIENCE

Whilst the Phase 1 trial for which there was an identified unmet need had no difficulty with recruitment, the Phase 4 trial faced major challenges.

A key challenge was a reported **reluctance by GPs to refer** identified patients to the trial and a lack of awareness amongst GPs and the general population about clinical trials and their importance. Part of the issue also was that despite the eligibility criteria being clear in protocols available for the original feasibility assessment, clinical researchers may not have read the details in the questionnaire, and are not held accountable for **lack of rigour in patient recruitment estimates.**

The impact of poor recruitment is both short term and long term. In this trial, **some sites were closed**, and there was an additional **huge cost imposition** and delay in looking for and starting up new sites. Longer term, this **impacts the future investment decisions** of the corporation in clinical trial activity in this area in Australia.

"There were huge costs associated with starting up the original sites, followed by additional sites when the first did not deliver. The output was very few patients. If I was in head office, I would have said 'what a waste'."

4.6.4 QUALITY OF TRIAL DATA

This company reported that good quality data is now an entry requirement for conduct of trials, and that there was no issue with quality of data collected for these trials.

4.6.5 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for these and other clinical trials reported by this organisation include:

- Positive impact of the CTN scheme on timely regulatory approval compared with other countries
- Leading researchers and ability to deliver against protocol requirements at some sites and in some therapeutic areas

4.6.6 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- Lack of reliability and predictability around start up times due to variability in ethics, governance and budget negotiation processes

"If I could put my hand on my heart and say to headquarters that we can have all sites through ethics, governance, budget and contract negotiations within 45 days, this would be a HUGE advantage."

- Lack of understanding and engagement of the Australian population and general practitioners in the importance of research, resulting in a reluctance to become involved in trials
- Insufficient support for or value placed on clinical research at an institution, health department and government level – institutions need to believe that conduct of clinical trials is part of their core business
- Lack of consistent and 'fair market value' approach to trial costs
- Lack of integrated e-health system to make patients aware and allow practitioners to recruit eligible patients to clinical trials – *"other countries are way ahead of us on this"*.

4.7 CASE STUDY 7: SHOWCASE OF PHASE 3 PHARMACEUTICAL TRIALS

Two clinical trials were presented by this organisation to showcase both a 'successfully conducted' trial and one that faced more challenges. Both were global **Phase 3 pharmaceutical trials** in different disease areas conducted in multiple Australian sites **across several jurisdictions**. One trial included a **mix of public and private** institutions and the other included only **public** institutions.

4.7.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

Australia was chosen as a site for conduct of these Phase 3 trials for different reasons.

For the first trial, Australia was initially approached by the international corporation to present a feasibility assessment based on internal review of **prior experience and performance of different countries** in this therapeutic area (i.e. number of patients previously recruited to trials in this area, ability to meet recruitment targets, timeliness of recruitment). Australia was then chosen as a site for conduct of this trial based on the original **feasibility assessment** completed by the Australian subsidiary and presented to international headquarters.

For the second trial, Australia was not initially chosen due to our low overall population numbers and estimated recruitment population for this particular study. However, due to poor recruitment internationally, Australia was subsequently chosen as a "**rescue country**" to assist in meeting overall recruitment targets (note that although this trial will now meet recruitment targets overall, Australia has fallen well short of its estimated recruitment population – see further discussion below).

When considering whether there are different influences on choice of country based on trial phase, this organisation commented that for **Phase 1 trials** requiring smaller populations, the choice of country and site is based more on research capability and experience in the therapeutic area than on patient populations. It was also reported that whilst cost is not a key issue in site consideration for Phase 1 trials, it becomes a consideration for later phase trials *after* consideration of country experience and recruitment populations. In these situations, **cost can influence final choice** of country location, and Australia has missed being chosen as a site as we are seen as an expensive country where approval often needs to be sought from head office for site budgets which are not considered to represent 'fair market value'.

4.7.2 FACTORS INFLUENCING CHOICE OF SITE(S)

The major factors influencing choice of site within Australia is one or more of the following:

- reputation of the Principal Investigator in the therapeutic area
- previous experience of working with the Principal Investigator and study coordinator at the site, particularly with respect to study conduct, data quality, and ability to meet recruitment targets, and/or
- feasibility study including site visit to determine likely recruitment population and, in circumstances where the company has not previously worked with site staff, an assessment of likely study conduct, data quality, and ability to meet recruitment targets.

Consideration of ethics and governance approval timeframes at particular institutions is made after consideration of the above.

4.7.3 TRIAL START UP

The two trials discussed by this organisation were chosen to showcase different experiences with trial start up times.

The **first trial involved several different ethics submissions** to cover NMA sites, jurisdictions not part of NMA, sites where jurisdictions are part of NMA but still require separate submissions, and submission for private sites. There were no issues reported for ethics or governance approval processes for this trial, and **time to first site opening was 12 weeks** (this included ethics and governance approvals, and contract negotiations/finalisation). This was quicker than the average time reported for first site start up for trials conducted by this organisation in Australia. Other public sites took between 15 and 18 weeks, although one took considerably longer than this due to delays with governance approvals. Private sites took between seven and 10 weeks.

The **second trial involved two ethics submissions for the public trial sites**, including one group and one separate submission. The majority of sites took around **30 weeks (7 months)** to trial start up, with one site taking even longer at 40 weeks (over 9 months). Delays were primarily administrative around **governance approvals and contract requirements**. Patient recruitment for this trial has also been an issue (see discussion below), and delays in start-up times have only exacerbated this problem.

Key factors reported to have positively influenced trial start up times for the first trial were:

- Timing of submission for ethics approval to coincide with monthly meeting date
- An improved and clear process for combined ethics and governance review in one jurisdiction (not part of NMA)
- Single site ethics review for sites under the NMA has expedited the timeframes for adding new sites and/or amendments
- An excellent study coordinator at trial sites who is responsible for facilitating, coordinating and managing ethics and governance submissions and communication, and for meeting requirements for contract negotiations and finalisation
- Internal organisational structures and responsibilities around clinical trial management.

Key factors reported to have negatively influenced trial start up times for trials in Australia are:

- Inexperienced study coordinator, lack of dedicated study coordinator, or change of study coordinator at sites who is not familiar with and/or held accountable for all aspects of study coordination including ethics, governance and contract approval process requirements
- Senior management within institutions does not place a high priority on clinical research activity nor provide adequate resources to support clinical trial coordination and research within the institution – there is a lack of accountability for study coordinators and

researchers to meet both contractual requirements regarding research activity, but also to meet pre-contractual start up requirements

- Difficulty recruiting a lead site for sites under the NMA, with sites reporting lack of resources to take on this additional administrative role despite receiving additional payment for this activity
- Multiple ethics submissions required for sites not under the NMA or still requiring separate submissions, which then require notification and review of all amendments requested by other ethics committees.

4.7.4 PATIENT RECRUITMENT

Capacity to meet recruitment targets was reported to be a key factor influencing future investment by international and Australian based pharmaceutical companies in Australia.

The first trial was not only able to exceed average start up times, but also exceeded its commitment regarding patient recruitment to the extent that it received permission to open additional sites to assist in meeting global recruitment targets. The second trial on the other hand has not been able to meet and had to reduce recruitment targets. If global recruitment targets are met prior to Australian sites meeting targets, these sites will close to recruitment if they are not recruiting well.

"The [first] study was not a complicated study or a particularly special drug, so we cannot attribute quick start up and excellent recruitment to excitement about the product – it was rather due to pure operational excellence. We always see a difference at sites with dedicated study coordinators and committed doctors who see the importance of research. At sites with a commitment to achieve what they said they would do, we are able to meet and exceed patient recruitment targets and also take more patients when other international sites are slower."

The key issue impacting inability to achieve recruitment targets for the second trial was the overestimation of patients during the feasibility study. Despite the fact that the company halved the original estimates from site investigators, recruitment has still been less than promised during feasibility. Reasons for poor estimation were reported to include a lack of time and resources at the site level, in some instances a lack of patient databases, and a lack of accountability at the site level.

"We haven't got as big a population as some other countries, so we need to get our patient estimates correct during feasibility or we will under-achieve."

Short and longer term impacts of delayed start up combined with poor patient accrual include:

- patients potentially miss out on early access to new medications
- significant costs associated with start up of each of these sites, even where patient recruitment is less than target and in some cases zero, and
- international corporations consider this performance (cost, timeliness of start up and capacity to reach recruitment targets) when making decisions regarding future investment in clinical trial activity in Australia.

4.7.5 QUALITY OF TRIAL DATA

It was reported that despite Australia's reputation for quality of data, this organisation has noticed a trend over the past two years around issues with some Primary Investigators being unwilling to provide an adequate level of oversight for clinical trial activity at their sites. This is a serious concern as it can lead to non-compliance with protocols and poor data quality. In the short term, it results in companies not choosing those sites for future trial activity, but longer term it has the potential to impact investment in Australia as a site for trial activity if quality data cannot be relied upon.

4.7.6 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for these and other clinical trials reported by this organisation include:

- Experience of sites in clinical trial operation
- Timely approval of ethics and governance, where this occurs, can result in short start up times in conjunction with CTN scheme
- Good study coordinators and Primary Investigators, with adequate resources and established processes at a site level, can result in short start up times and capacity to meet or exceed recruitment targets
- Access to the required patient population
- A collaborative approach at the trial site with a focus on problem solving to meet study objectives.

4.7.7 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- There is still not a single ethics review process across Australia – in at least one state which is a signatory to NMA, some institutions require their own ethics review process.
- Difficulty in securing a lead site for ethics submissions under the NMA – sites who do agree are getting overloaded
- Single review for NMA means that study coordinators may be managing several trials at their site which have all been reviewed by different lead sites with differing reporting requirements (e.g. forms required for reporting of adverse events, annual progress reports)

"Sites now have different studies approved by different lead ethics committees that all have different reporting requirements. What a waste of time and resourcing for study coordinators to have to manage all these different processes and risk things not being reported, or not reported in a timely manner."

- Lack of accountability at an institution level to deliver on targets

"If public clinical trial sites could manage themselves like a small business with respect to clinical trial management (managing performance and metrics around trials), companies would pay the unit or institution, and any profit could be invested back into their own research."

4.8 CASE STUDY 8: MEDICAL DEVICE TRIAL

This was a global medical device trial with **multiple sites in Australia across several jurisdictions**, including a **mix of public and private** institutions. The trial faced challenges with respect to start up times and with patient recruitment, although Australia was the highest recruiter compared with other international sites.

4.8.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

This medical device trial was initiated in one Australian jurisdiction, and then expanded to other Australian sites and overseas in order to recruit sufficient patients. The Primary Investigator at the first site was a key opinion leader who had a good relationship with the company. Subsequent sites were chosen based on the recommendation of the Primary Investigator, and on feasibility studies to review patient numbers and ensure that clinicians at the site had the necessary experience in conducting the particular procedure involved. The availability of an experienced study coordinator, particularly with respect to *“handling the ethics process”* was also important, as was the history of the site in provision of ethics and governance approvals in a timely manner.

4.8.2 TRIAL START UP EXPERIENCE

Multiple **ethics submissions were required** to cover states under the NMA, states/territories not under the NMA, institutions under the NMA but requiring separate submission, and private institutions. Other than the obvious **duplication, costs and risks** of error involved in the process of ensuring that all ethics committees were informed of and approved all changes requested by different HRECs, delays were also incurred in **trying to source a lead site** for the submission covering public sites under the NMA, as sites are reluctant to take on this additional responsibility.

“Multiple ethics submissions and sourcing a lead site is our biggest hurdle. The process has been slowed down rather than accelerated due to the number of acknowledgements and approvals required. It also costs more as we have to pay lead ethics committees for their additional responsibilities, and pay for submission of all amendments to all HRECs.”

Governance approval timeframes **ranged from two to six months after ethics** approval was received, and the process was reported to be very hospital dependent. The **governance process was not consistent or transparent**, with some RGOs reportedly requesting similar information to ethics, and one delaying consideration of the submission to a subsequent meeting due to a “backlog of requests”.

“At least with ethics you know the timelines and requirements. For governance, we don’t know exactly what they do or their timelines. The submission goes in and you don’t know what happens.”

The impact of these delays is that patients do not have timely access to new treatments. In this case, these were patients with [a disease] where delayed access to new treatments can have a serious impact on survival.

4.8.3 PATIENT RECRUITMENT EXPERIENCE

Although Australia ended up being the highest recruiter overall for this trial compared with other international sites, some of the sites within Australia were slow to recruit or did not recruit at all. The company reported that this was due partly to lack of systematic approach and an inexperienced internal team conducting the feasibility assessment, but also to investigators “*not taking the questionnaire seriously*” and overestimating numbers in order to get commercial funding for a study coordinator at the site. It was reported that although investigators sign a legal contract indicating target recruitment numbers, there is no accountability for reaching these targets, and sponsor companies are unlikely to take legal action as there may be future commercial implications for getting key opinion leaders off-side.

“For new therapy or intervention areas, it is currently a trial and error approach as to which sites will deliver in terms of recruitment targets, even after numbers have been adjusted down to account for over-estimation. This is costly as we still pay start up fees and annual site administration fees even if no patients are recruited.”

4.8.4 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- Primary investigators who are advocates of the treatment and keen for the trial to be conducted successfully
- Good internal clinical team and excellent collaboration between the sponsor and the sites

4.8.5 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of this and other clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- Inexperienced internal team in undertaking feasibility assessments and site selection
- Lack of truly national approach to ethics review impacts trial start up times
- Lack of consistency and transparency in approach for governance reviews impacts trial start up times
- Lack of consistent and ‘fair market value’ approach to trial costs between institutions and between studies impacts start up times due to time taken for head office approvals and contract negotiations with sites

4.9 CASE STUDY 9: ISSUES IMPACTING MULTIPLE TRIALS

This case study was with a global CRO specialising in biopharmaceuticals, medical devices and diagnostics. Rather than discussing a particular trial, the case study covered broad issues impacting multiple trials for which this CRO has been responsible over the past five years in Australia.

4.9.1 FACTORS INFLUENCING CHOICE OF AUSTRALIA

The key factors reported to positively influence choice of Australia as a country in which to conduct pharmaceutical and/or medical device clinical trials are:

- The CTN scheme – this was reported to be particularly important to facilitate quicker start up of Phase 1 trials compared to other countries
- Seasonal differences compared with northern hemispheres for trials involving seasonal illnesses (e.g. influenza)
- English speaking
- Quality of data.

The key barriers to choice of Australia as a site are:

- Slower timelines to trial start up due to delays in budget finalisation, ethics and governance approvals – it was reported that median time from site qualification to activation is 100 days in the USA compared to 170 days in Australia (although private sites in Australia can do in 100 days)
- We are an expensive site with respect to start up costs, administrative fees, and site costs, although per patient costs were reported to be comparable.

4.9.2 TRIAL START UP EXPERIENCE

Although the NMA in principle aims to expedite the ethics approval process, in practice there is still **no single site ethics review**, and governance committees still require different things which need site specific submissions. One of the biggest issues identified by this CRO is that HRECs are **working under guidelines** (i.e. the *NHMRC National Statement on Ethical Conduct in Human Research*) rather than mandated requirements. Thus whilst some states mandate use of the NHMRC template for informed patient consent for example, others do not.

“It is embarrassing and a nightmare having to try and report to international clients how time lapses have occurred due to the varying requirements of different states and territories with respect to ethics documentation and governance approvals.”

Governance approval processes were reported to vary enormously and have different requirements across different jurisdictions and within different institutions. The key issues causing delay in governance approval timeframes were reported as:

- RGOs will generally not consider governance in parallel with ethics, but require ethics approval prior to submission for governance approval
- Poor communication between lead ethics sites and RGOs at other institutions (i.e. sending required documentation),
- Inability for sponsor organisation to communicate directly with RGO but rather having to go through the Primary Investigator at the site – this can significantly add to timeframes for getting queries addressed and governance approvals finalised
- Lack of transparency and consistency in processes and requirements, with amendments in many circumstances having to go to both HRECs and RGOs for approval.

This CRO reported that they always look to incorporate private sites in order to meet activation targets, and public sites where needed in order to meet recruitment targets.

The **impact of delayed start up** in trials with competitive recruitment is that **sites may close to recruitment** if patient targets are reached internationally; and patients may therefore miss out on involvement in the study. The CRO cited one example of a study with very competitive recruitment, where a site in one Australian jurisdiction missed enrolling any patients due to delays with the lead ethics committee in another jurisdiction.

4.9.3 PATIENT RECRUITMENT EXPERIENCE

Ability to meet recruitment targets is largely tied to the targets estimated in the **feasibility assessment**. This involves an initial assessment questionnaire sent to investigators at sites. Following this, a pre-study visit is conducted by the CRO or sponsor company to have a robust discussion with the investigator regarding the full trial protocol and patient exclusion/inclusion criteria. The CRO or sponsor company apply an **"inflation factor"** to account for original over-estimation, unless recruitment targets are clearly based on robust patient databases or registries that exist for certain conditions (e.g. respiratory diseases).

4.9.4 QUALITY OF TRIAL DATA

Having multiple ethics and/or governance reviewing organisations means that all changes (even minor changes such as correction of a spelling error), require all sites to be informed and to carefully manage version control of materials. This risks administrative errors in data.

4.9.5 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

The key enablers of successful conduct for this and other clinical trials reported by this organisation include:

- CTN scheme
- NHMRC templates (e.g. patient information consent forms)
- Good partnership and communication between the site and the sponsor organisation
- Provision of realistic recruitment targets by sites
- Some excellent ethics committees, sites, study coordinators and research facilities which should be recognised as such

4.9.6 KEY BARRIERS OR REASONS FOR FAILURE TO MEET EXPECTATIONS

The key barriers or reasons for failure of this and other clinical trials to meet expectations in terms of recruitment and/or data quality in Australian sites were identified as:

- Lack of mandated ethics and governance requirements (i.e. currently guidelines only)
- Inability for sponsor organisations to communicate directly with ethics committees and RGOs but having to go via the Primary Investigator as a middle man
- Lack of truly national approach to ethics review and approval across all jurisdictions and both public and private sites
- Lack of accountability for trial delivery, with no measurement of deliverables at a health service level (noting that private sites are generally better at delivering targets as they operate with a business philosophy)

5. SUMMARY OF FINDINGS AND CONCLUSIONS

This chapter presents a summary of findings and conclusions from the project encompassing the preliminary stakeholder consultations; literature scan; and the nine case studies to address the specified project objectives. These findings have been categorised based on the following key themes:

- Reasons for investment in Australia for placement of commercial pharmaceutical or medical device clinical trials in the past five years
- Key enablers of successful clinical trial conduct in Australia
- Key barriers or reasons for failure of clinical trials in Australia in terms of delivery of agreed participant numbers and/or high quality data
- Overall project conclusions

5.1 REASONS FOR INVESTMENT IN AUSTRALIA

The key reasons outlined in case studies, and supported by the preliminary consultations and literature scan, for investment by global pharmaceutical and medical device companies in conduct of clinical trials in Australia were:

- 1) **Reputation of investigators to achieve recruitment targets.** Reputation of, and previous experience with, Primary Investigators and/or institutions in conduct of clinical trials where recruitment targets have been met or exceeded and quality data have been provided, were reported to be critical to decisions not only regarding choice of institution but also choice of country for trial placement.
- 2) **Available patient population.** A feasibility assessment indicating that Australia has the required patient population and will be able to meet recruitment targets, including an adjustment factor to account for investigator overestimation where deemed necessary, is also critical to investment decisions. The recruitment pool for some target population groups is small in Australia compared to other countries, and in these circumstances Australia will only be chosen based on excellent patient accrual in previous trials and/or an extremely robust feasibility assessment.
- 3) **Reputation of Australia and/or institutions for timely trial start up.** The CTN scheme for trial notification to the TGA following ethics and governance approvals was reported during both the case studies and preliminary consultations as a very positive contributor to swift regulatory approval in Australia. However, in many cases overall start up is being delayed by lengthy ethics and governance approval processes in public institutions (see discussion regarding 'key barriers' below), despite introduction of the NMA which has reduced the number of ethics submissions required for many clinical trials. Institutions with a history of timely ethics and governance reviews, often driven by dedicated and experienced research teams and study coordinators, do exist in Australia and are a key reason for investment in clinical trials in those institutions.

- 4) **Dedicated research teams.** It was mentioned by several case study participants that dedicated and experienced investigators and study coordinators who are well supported by the institution, contribute significantly to timely trial start up, capacity to meet recruitment targets, and quality of trial data provided. These institutions are then considered very favourably for future investment in clinical trials. In addition, clinical trial networks or investigator networks were also cited as a reason for investment in Australia where these networks are able to assist with patient accrual.

It is worth noting that **cost** was also reported to be a consideration for choice of country, but only after consideration of the above factors. However, **Australia is seen as an expensive place in which to conduct trials**, and although this is currently balanced by other factors such as data quality, timeliness of start up and capacity to recruit, it may become a deciding factor if we do not remain ahead of other countries in these other factors. As many trials operate under competitive recruitment, trials that do not recruit or do not meet recruitment targets due to delayed start up or other factors, are costly to the organisation as money is invested in start up costs for little or no return. Also, unless **standardised costs** are developed which remain competitive, cost may become a key reason for not choosing Australia as a site for future investment.

It was reported that whilst critical, provision of **quality data** is now seen as a **minimum requirement** rather than a competitive advantage in most cases. The fact that we are **English speaking** was also mentioned by some project participants as a key contributor to choice of Australia as a site for clinical trial conduct.

5.2 KEY ENABLERS OF SUCCESSFUL CLINICAL TRIAL CONDUCT IN AUSTRALIA

Success in this context is defined as a trial that has met or exceeded sponsor expectations in terms of conduct and recruitment. The key enablers of successful conduct of clinical trials in Australia identified during the case studies and supported by the preliminary consultations and literature scan were the following:

- 1) **CTN scheme.** The CTN scheme enables quick regulatory timeframes compared with other countries.
- 2) **National Mutual Acceptance Scheme.** The move towards single ethics approval has reduced duplication in ethics approval documentation and in particular, has expedited the process for seeking and obtaining approvals for protocol amendments including additional site approvals. However, the NMA has not yet been fully implemented and new issues have arisen, such as difficulty engaging a lead site and site coordinators currently having to manage multiple HREC requirements (see barriers to successful conduct below).
- 3) **Short ethics review timeframes for private sites.** Companies reported that they often chose private sites in order to expedite time to trial start up, as ethics review through private ethics committees can take under one month.
- 4) **Experienced researchers and site study coordinators.** Experienced Primary Investigators and site study coordinators, particularly where they are passionate about

the therapeutic area and are supported by the institution (e.g. adequately resourced), have a significant positive impact on timely ethics and governance approvals, patient recruitment and provision of quality data.

- 5) **Standardised costing or corporate 'fair market stipulations'**. Budget negotiations in some cases were reported to be protracted, with this process being easier in cases where the company has clear regulations on what is an acceptable 'fair market cost'. It was noted that standardisation of costing should further help these negotiations to ensure fair market value (unless standardisation is considered 'too high').
- 6) **Robust feasibility assessments and honest patient recruitment estimates**. In situations where companies invest time and effort in conducting a thorough feasibility assessment including initial investigator questionnaire, site visit, and analysis of patient databases where available, and where investigators understand the importance of taking the time to provide accurate patient recruitment estimates and feel accountable to deliver on these estimates, capacity to deliver target recruitment numbers is greatly improved.
- 7) **Established referral networks and national patient databases**. Patient awareness regarding clinical trials, and willingness of GPs to refer patients to clinical trials, were reported as barriers to recruitment in many cases, with the ANZCTR and Clinicaltrials.gov sites not being seen as 'patient friendly'. However, where national patient databases exist, and/or where local networks are establishing their own clinical trials information sites and referring patients within these networks, capacity to meet recruitment targets was reported to be enhanced. Examples of these initiatives include:
 - Development of hospital organisational cultures to support clinical research and innovation that focuses on properly conducted clinical research as an important standard of care
 - The availability and retention of a strong independent clinical trials research sector as represented by Clinical Cooperative Trial Groups (CCTGs) to enhance the skilled clinical trials workforce available to industry to conduct trials as well as providing networking and sharing of resources
 - Mechanisms for increasing patient recruitment have been established by CCTGs and their state-based networks. This includes promotion of the benefits/availability of trials through wider clinical networks, general practice, health consumer groups etc. to increase recruitment
 - The availability and retention of a skilled clinical trials workforce including world class medical and scientific researchers, trial co-coordinators, data managers and biostatisticians
 - The collaborative development and sharing of key infrastructure and resources that is aimed at supporting and enhancing clinical research in Australia. An example is the development of a national model for biobanking of specimens from participants in clinical trials that can be used for further research.

Researcher understanding and compliance with GCP is an enabler of successful clinical trial conduct, but was reported to be a minimum requirement rather than a competitive advantage in most cases. Therefore any lack of compliance with GCP, particularly where it

leads to poor data quality, will be seen as a real barrier to future clinical trial investment in Australia.

5.3 KEY BARRIERS OR REASONS FOR FAILURE OF CLINICAL TRIAL CONDUCT IN AUSTRALIA

Failure in this context is where a trial has failed to meet recruitment targets and/or provide high quality data. The key barriers to, or reasons for failure of, successful conduct of clinical trials in Australia identified during the case studies and supported by the preliminary consultations and literature scan were the following:

- 1) **No national single ethics approval process is yet established.** Only four states are current signatories to the NMA, and even within some of those states (e.g. Victoria), there are institutions which require their own separate ethics submission. Thus companies are required to still often submit to multiple HRECs which may include a group submission for sites under the NMA, one or more other submissions for states/territories not under the NMA, a separate submission for institutions recognised under the NMA but who still require a separate submission, and a submission for private sites. This duplication not only impacts study timeframes and costs, but can impact data quality due to the multiple approvals required for all ethics documentation and amendments, and the risk of incorrect document versions being used.
- 2) **Reluctance of sites to become lead sites for ethics submissions.** The majority of case study participants reported that under the NMA, it was now difficult to engage a lead site for ethics submissions, as sites were reluctant to take on the additional administrative responsibilities associated with this role despite the additional payment. Some sites will only take on the role for up to three other sites, so more than one lead site and ethics submission must be prepared for trials with a greater number of sites in participating jurisdictions. Securing a lead site can add to the timeframes for trial start up.
- 3) **Risk associated with single ethics submission.** Companies reported that even in situations where single ethics review was possible (i.e. where all sites are under the NMA), a second lead site will often be identified and utilised in order to spread the risk for public sites. Several companies identified situations where ethics approval and subsequent governance approvals had previously been delayed due to issues at a single lead site (e.g. Primary Investigator went on leave, site closed its research facility, poor or delayed communication from lead site to other sites).
- 4) **Lack of consistency in HREC requirements.** Previously, when ethics and governance reviews were undertaken by each institution or recognised within a jurisdiction, site study coordinators would be familiar with the reporting requirements of that ethics committee. Under the NMA, study coordinators need to be familiar with and comply with differing requirements of what may be multiple HRECs acting as lead sites for different trials for which the study coordinator is responsible. This lack of consistency has the potential to impact data management and quality.
- 5) **Lack of clarity, consistency, transparency and timeliness of governance approvals.** It was reported that in almost all situations, governance approval is not conducted in

parallel with ethics approval processes, adding timeframes of 3-6 months or more after ethics approval. The fact that there are examples where governance approvals were granted in ≤ 2 weeks post ethics indicates that there is opportunity for this to be the norm rather than the exception. The reason for reluctance to conduct governance reviews until after ethics approval was unclear, but was thought to result from a lack of clarity regarding the scope of the RGO role versus the HREC role (i.e. many RGOs were reported to be asking for similar things to ethics) and therefore an unwillingness to commit scarce resources until ethics had been finalised.

- 6) **Inability for sponsor organisation to communicate directly with HREC or RGO.** Sponsor organisations are required to communicate with HRECs and RGOs via the Primary Investigator. This was reported to result in significant delays in addressing issues raised by HRECs or RGOs when the Primary Investigator is busy, absent, under-resourced, or does not prioritise clinical research activity.
- 7) **Inaccurate feasibility assessments and unclear accountability for delivering recruitment targets.** The ability to achieve recruitment targets is a key factor impacting future investment by companies in Australian clinical trial activity. Even when companies halve or quarter estimates provided by investigators, these targets are often not reached. Some responsibility for more accurate patient recruitment estimates lies with companies to ensure adequate time and care is taken to conduct robust feasibility assessments. However, a key issue was reported to be the lack of care or time taken by investigators to provide honest recruitment targets, and the subsequent lack of accountability for meeting these targets. Although these targets are recorded in contracts, commercial sponsors are unlikely to take legal action because of the future commercial implications for their products. Organisations commented that they believed investigators need to be held more accountable by the institution for clinical trial activity.
- 8) **Lack of awareness and support for clinical research.** It was reported that difficulties with patient recruitment arose in many cases due to a lack of referrals from GPs, and a lack of awareness about relevant clinical trials in the general community. It was felt that clinical research was seen by the broader community and also the medical community as secondary to clinical care, and that the Australian Government had not significantly invested in promoting the benefits of clinical trials and involvement in clinical research.

With respect to availability of information regarding clinical trials on ANZCTR, the seven case studies with overseas head offices all stated that it was company policy that global trials are listed on clinicaltrials.gov with these decisions made at the international head office level, and that responsibility for updating information also lay with central operations. The two case studies with Australian head offices also register on clinicaltrials.gov as it is seen as a bigger registry that covers international sites, although these companies register on ANZCTR if only Australian sites are involved. One case study participant stated that company policy requires information to be updated every six months by central office, although other participants did not know how often information was updated. One participant felt that *"we need to do better especially in light of the NHMRC website for patients, as the quality of information available from clinicaltrials.gov may not be that good"*, and another stated that *"I haven't found that it's been easy to find your trial via ANZCTR even though information should also be available via ANZCTR when registered with clinicaltrials.gov ... ANZCTR may not be delivering*

according to its intent at this stage". The other seven case studies did not have any further comment to make on ANZCTR or its usefulness.

Other contributing factors to poor patient accrual reported during consultations and in the published literature relate to protocol design rather than operational factors. These included patient eligibility criteria not reflecting current medical practice or being too restrictive, a perceived lack of value of the study question or product, and/or protocol requirements being too complicated.

5.4 CONCLUSIONS

Activities undertaken or initiated by the Department of Health, Department of Industry and Science, and/or the NHMRC in response to recommendations from the 2011 CTAG Report have gone some way to boosting Australia's profile as a preferred destination for conduct of clinical trials. However, examples of excellent and competitive timeframes for trial start up, and meeting or exceeding patient recruitment targets, were reported to be exceptions rather than the norm for clinical trials conducted in Australia over the past five years.

Inability to meet recruitment targets in many trials, which in some cases was impacted by relatively slow times to trial start up, was reported by companies to have a critical impact on future investment decisions in Australia as a clinical trial site. If Australia does not offer an advantage in terms of timeliness of trial start up and/or capacity to meet recruitment targets, our cost disadvantage is then factored into decision making and may impact choice of Australia as a site. Provision of quality data was still seen as an advantage for Australia by some project participants, although most participants saw it as a minimum requirement now which needs to be met by all countries.

Ongoing initiatives such as the streamlining of ethics and governance approval processes, and development of a consistent national approach to multi-jurisdictional clinical trials within Australia, whilst essential to help improve timeliness of trial start up in particular, have resulted in new delays. These include reluctance of sites to take on a lead role for ethics review due to increased administrative burden, and risks associated with having a single lead ethics site for multiple institutions if delays occur at that site. There is still a reported lack of consistency and transparency in governance approval scope, processes and timeframes, and concern that the current project to standardise clinical trial costs will need to represent 'fair market value' for Australia to remain competitive.

A key issue reported to be impacting patient accrual in particular, but also with the potential to impact start up times and data quality, is the perceived lack of significant investment in enhancing the profile of clinical research and involvement in clinical trial activity within the medical and broader communities. Where investment had been made in experienced and dedicated study coordinators at sites, this was reported to have had a significant impact on timely ethics and governance approvals, trial start up, honest and realistic patient recruitment estimates, capacity to achieve recruitment targets, and quality of data provided. Private institutions and ethics committees were reported to be noticeably better with respect to all these factors, although target patient pools at private sites usually need to be supplemented by involvement of public institutions or recruitment processes.

Capacity and reputation for recruitment to target, timely trial start up, provision of quality data, and costs which are not outside what is deemed fair market value, all impact decisions made by international and local pharmaceutical and medical device companies regarding investment in clinical trial activity in Australia. Importantly, trial delays and lack of awareness of or referral to clinical trials, also impacts patient access to new medicines and treatments. For some patients such as those with cancer, these delays have serious consequences.

It was suggested by one organisation that prior to implementing any changes, it will also be crucial to seek the perspective of institutions and investigators on these same questions regarding ethics, governance, and study conduct for commercially funded pharmaceutical and medical device trials in Australia. In particular, feedback should be sought on what can be done to help with realistic and transparent feasibility assessments and ability and accountability for meeting recruitment targets.

APPENDIX A – PRELIMINARY CONSULTATION DISCUSSION GUIDE QUESTIONS

- 1) Based on your recent experience, what are the key drawcards for choosing Australia as a preferred location for the conduct of pharmaceutical clinical trials (i.e. what is contributing to the successful operation of clinical trials in Australia)?
- 2) Based on your recent experience, what are the key drawcards for choosing particular institutions within jurisdictions as preferred sites for conduct of pharmaceutical clinical trials in Australia (i.e. what is contributing to the successful operation of clinical trials at particular sites within Australia)?
- 3) Based on your recent experience, what are the key reasons for Australian and international pharmaceutical companies NOT choosing Australia as a preferred location for the conduct of clinical trials?
- 4) Based on your recent experience, what are the key reasons for failure of clinical trials within Australia? In this context, 'failure' is where the trial has not progressed or has been terminated, withdrawn or suspended for reasons other than scientific/clinical (e.g. reasons other than safety or efficacy concerns), or where data are of poor quality. For example, a trial may have failed because of lengthy or protracted approvals processes, because it did not achieve recruitment targets within agreed timeframes, or because of feasibility issues.
- 5) Based on your recent experience, what are the key reasons for failure of pharmaceutical clinical trials at particular institutions within Australian jurisdictions (if different to responses provided for previous question)? For example these may include, but not be restricted to, a culture which is not supportive of clinical research; a lack of senior management commitment to clinical research or an inadequate research structure.
- 6) Please identify up to six commercially-funded pharmaceutical trials conducted in the past five years which may be appropriate for inclusion as case study sites. These will include at least two completed trials and two trials which did not progress or were suspended, withdrawn or terminated for non-clinical reasons.

Note that case studies do not require the drug name or trial findings to be disclosed, but will be focussed on the processes and infrastructure impacting on the operational success or failure of trials within the Australian environment. In addition, we are happy to work with sponsors to ensure information is appropriately and sufficiently de-identified.

Note also that HOI is happy to take the lead in contacting potential case study organisations and participants once identified (i.e. as part of Stage 3 of the project to follow). However, should clinical trial contacts or other participants from these preliminary consultations wish to seek permission from trial sponsors before nominating trials as potential case studies, HOI can assist with provision of appropriate correspondence as required.

APPENDIX B – CASE STUDY DISCUSSION GUIDE

QUESTIONS

BACKGROUND INFORMATION ON TRIAL BEING USED IN CASE STUDY

- Trial type:
- Trial phase:
- Disease/condition:
- Start date (approximate):
- Completion or termination/withdrawal date (approximate):
- No. of clinical trial sites and jurisdictions in Australia:
- Any international sites:

INVESTMENT DECISIONS

- 1) **Choice of Australia.** Why was Australia chosen or not chosen as a site for conduct of this clinical trial? You may wish to consider the extent to which factors listed in the Appendix influenced this decision.
- 2) **Differences.** In your experience, to what extent do decisions to invest in Australia as site for clinical trials differ by trial phase, whether the funding organisation or sponsor is Australian owned or international, and whether the trial is for a pharmaceutical product or a device?

NOTE THAT IF THE TRIAL BEING DISCUSSED WAS CONSIDERED BUT NOT CONDUCTED IN AUSTRALIA, GO STRAIGHT TO Q14 NOW.

TRIAL STATUS

- 3) **Completed/terminated.** Was this trial completed at Australian site(s) or was it terminated, withdrawn or suspended for operational reasons (i.e. NOT due to efficacy or safety reasons, or corporate decisions to not continue with the product program)? If the trial was terminated, withdrawn or suspended at any/all sites for operational reasons, what contributed to this decision?

TRIAL START UP

- 4) **Ethics approval.** How was the decision made regarding choice of Human Research Ethics Committee(s) (HREC) in Australia for this trial, and did it qualify for single ethical review? Approximately how long did ethics approval take, and did this impact time to trial start

up? If this was a multi-site / multi-jurisdictional trial, what was your experience in obtaining approvals or navigating processes across different states and territories?

- 5) **Choice of site(s)**. How was the decision made regarding choice of site or institution(s) in which to conduct the trial in Australia?
- 6) **Governance approval**. Approximately how long did governance or other approval processes take, and did this impact time to trial start up?
- 7) **Changes/delays**. If delays or changes to the trial were required based on the HREC and/or specific site assessment process, what were the key reasons for delays and/or how did changes add value to the project?
- 8) **ANZCTR**. How was the decision made to list this trial on the Australian New Zealand Clinical Trials Registry (ANZCTR) or other clinical trials registry? Did you find ANZCTR (or other register) useful and did you continue to update the information? Why / why not?

PATIENT RECRUITMENT

- 9) **Recruitment targets**. Were recruitment targets in Australia met for this clinical trial within the expected timeframes, and what were the barriers and enablers to meeting these targets? Consider both protocol design and operational barriers and enablers.
- 10) **Feasibility assessment**. What was the nature of the feasibility assessment conducted at the outset of the trial? Who conducted the feasibility assessment and who was involved (i.e. lead clinicians, site administrators etc)? Was it useful / accurate?
- 11) **Slow recruitment**. If the trial was slow to recruit, was consideration given to shutting it down? Why / why not? If it was shut down, how was this done?

QUALITY OF DATA

- 12) **Data quality**. What factors impacted the ability of Australian sites to collect quality data for this clinical trial? Consider both barriers and enablers.

OVERALL COMMENTS

- 13) **Successful conduct**. What were the key factors contributing to the successful or unsuccessful conduct of this trial in Australia (where 'success' refers to the ability to meet or exceed sponsor expectations in terms of cost, data quality, time to start up, patient accrual etc)? You may wish to consider factors listed in the Appendix.
- 14) **Looking forward**. If you could change up to three things to improve the attractiveness of Australia as a site for conduct of clinical trials what would they be, and do these differ by trial phase?
- 15) What initiatives or structures/processes should be continued in Australia and supported or promoted to improve awareness of Australia as an attractive site for clinical trial investment?

APPENDIX: POSSIBLE FACTORS INFLUENCING INVESTMENT DECISIONS AND SUCCESSFUL CONDUCT OF CLINICAL TRIALS IN AUSTRALIA

Australian environment

- location of funding organisation
- CTN/CTX scheme
- R&D tax incentive
- research environment or culture in Australia
- regulatory approval processes
- pricing and reimbursement processes
- cost of trial operation (e.g. CRO, investigators, other research staff, pharmacy, transport etc)
- IT infrastructure including e-health
- English language

Approval processes

- ethics approval processes
- governance approval processes
- other approval processes

Trial management

- dedicated clinical trial managers and/or research teams
- reputation or availability of Contract Research Organisations (CROs)
- time to trial start up (expected/actual)
- communication and reporting processes

Researchers/institutions

- reputation of research institution
- reputation of investigators or key opinion leaders
- researchers familiar with Good Clinical Practice (GCP) Guidelines
- investigator or research networks
- dedicated research centres of excellence
- quality of data (expected/actual)

Participant accrual

- potential population pool
- willingness and awareness of Australian population to participate in clinical trials
- patient, biobank, and/or healthy subject databases
- time to first patient recruited (expected/actual)
- ability to meet recruitment targets (expected/actual)

Other

- any other factors