CLINICAL TRIALS JURISDICTIONAL WORKING GROUP

FRAMEWORK FOR NATIONAL AGGREGATE STATISTICS (NAS)

SECOND ACTIVITY REPORT ON CLINICAL TRIALS IN AUSTRALIAN PUBLIC HEALTH INSTITUTIONS

2015–16

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Acronyms

AU RED	Australian Research Ethics Database
COAG HC	Council of Australian Governments Health Council
CRO	Commercial Research Organisation
CTJWG	Clinical Trials Jurisdictional Working Group
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
FTIH / FTIP	First Time In Human / First Time In Patient
NHMRC	National Health and Medical Research Council
HREC	Health Research Ethics Committee
HPC	Hospitals Principal Committee
NAS	National Aggregate Statistics
NMA	National Mutual Acceptance
SSA	Site Specific Assessment
TGA	Therapeutic Goods Administration

Glossary & definitions

Glossary terms	Definitions
Administrative clock	A measure of the ethics or SSA timeline which includes the time that the ethics or SSA application is with the investigator/trial coordinator/sponsor/CRO.
Clinical Trial	Interventional research involving a drug/device trial, radiation therapy, surgery, treatment or diagnostic procedure and studies associated with ongoing activities relating to trials that have been conducted. This may include post-trial activities such as observational research and evaluation of a trial, developing a registry and other post-marketing surveillance activities.
Collaborative Group clinical trial	The Collaborative Group is an academic and/or non-commercial collaborative research group responsible for sponsoring, initiating, managing, developing and coordinating the study.
Commercial trial	Commercial trials are conducted by organisations that typically own or have a financial interest in the intellectual property related to the intervention being tested. Commercial organisations such as pharmaceutical companies or clinical research organisations use the information obtained from the trial to support the application to obtain licences or subsidies to sell their product.
First Time In Human (FTIH)	First time an unapproved product is administered to a healthy human.
First Time In Patient (FTIP)	First time an unapproved product is administered to a human with a medical condition.
Investigator – initiated clinical trial	Investigator – initiated clinical trials are trials that are developed and conducted by individual independent clinicians and/or academic researchers. The institution, through the principal investigator, is responsible for the initiation and conduct of the study at the study site(s) which is/are under the control of the Institution.
First NAS Report	*First National Aggregate Statistics Report on Commercially Sponsored Clinical Trials in Australia*, 2014–15.
National Mutual Acceptance (NMA)	A single ethical review framework for multi-jurisdictional research projects. To participate, jurisdictions are required to co-sign a Memorandum of Understanding.
Phase 1	Phase 1 clinical trials involve the first administration of the medicine to humans, usually to small numbers of healthy volunteers. Phase 1 clinical trials determine the safety of the medicine, how it works and how well it is tolerated. These clinical trials also identify preferred routes of administration (e.g. tablet, liquid or injection) and help determine the appropriate doses for later studies. Phase 1 clinical trials are usually undertaken in centres appropriately equipped for the specialised monitoring and the high degree of surveillance needed.

Glossary terms	Definitions
Phase 2	Phase 2 clinical trials are normally the first trials of the medicine in patients suffering from the condition for which the medicine is intended. The principal aim of these clinical trials is to determine effectiveness and safety. These clinical trials are undertaken in a small number of closely supervised patients and conducted by researchers regarded as specialists in the particular disease or condition and its treatment.
Phase 3	Phase 3 clinical trials involve greater numbers of patients and are undertaken for the purpose of determining whether the medicine confers clinical benefit in the disease/s for which effectiveness was demonstrated in Phase 2 clinical trials. They also determine the nature and likelihood of any side effects. Phase 3 clinical trials are undertaken if the Phase II clinical trials indicate the medicine has potential benefit that outweighs the hazards.
Phase 4	Phase 4 clinical trials are those clinical trials undertaken after the medicine has been approved for the treatment of a particular disease. Phase 4 clinical trials are undertaken to compare a new medicine to a wider range of existing medicines/therapies and to investigate the use of the medicine in the normal clinical setting of the disease. Such clinical trials are used to establish where, in the range of treatment options, the new medicine is best used.
Public Health Organisation/ Institutions	A statutory health corporation or affiliated health organisation in respect of its recognised establishments and recognised services.
Regulatory timeline	Refers to ethical review and approval of a human research project and SSA/ site assessment authorisation. These steps must comply with legislative requirements, adherence to national guidance and other jurisdictional policy. On completion the research may start at the study site.
Site Specific Assessment (SSA)	Refers to the Site Specific Assessment Form. The SSA Form is linked through coding to the trial HREC/ethics application form.
Sponsor type	An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial. In this report, major sponsor type refers to either ‘commercially sponsored’, ‘collaborative group’, ‘investigator – initiated’, ‘institution’, or ‘other’.
SSA/site assessment	The process conducted by a research governance officer to assess the SSA form and documentation for authorisation by the chief executive or delegate for an organisation to participate as a trial site.
With Clock	Clock either on or off to measure time intervals (time between request and receipt of further information) for HREC approval.
Without Clock	No measure of intervals when the clock is stopped and re-started for HREC approval and SSA/site assessment processes.

Executive summary

This report contains clinical trials conducted in public health institutions (hospitals). These trials include commercially and non-commercially sponsored, multi-site and single-site studies. National Mutual Acceptance (NMA) has provided the framework that underpins the metrics in this report through the cooperative efforts of jurisdictions in reporting cross-jurisdictional clinical trials since 2011. NMA participating jurisdictions are: Australian Capital Territory (from 2016), New South Wales, Queensland, South Australia and Victoria. In addition to the NMA jurisdictions, Northern Territory has contributed intra-jurisdictional clinical trial information (both single-site and multi-site review).

Clinical trials represent activity in publicly funded health institutions although this will include trial sites at some private health organisations and universities that accept the ethical review under NMA. Private health and university sectors may not be directly captured in this report as the SSA/site assessment process is locally managed and is not entered in the information management platform operated by public health institutions. Clinical trials conducted in a primary care setting are unlikely to be represented in this report, unless the trial is connected to a public health institution.

This is the second report produced under the cross-jurisdictional Clinical Trials Jurisdictional Working Group (CTJWG) National Aggregate Statistics (NAS) Framework. The First NAS Report included commercially sponsored trials in public hospitals in six jurisdictions, for the year 2014–15. Direct comparison with the findings from the First NAS Report are not presented in this analysis, as the samples for the two years are different. While both draw data from public health organisations, the First NAS Report included commercially sponsored trials only in six jurisdictions (n = 335), while this current report includes all trials in five jurisdictions (n = 718). This includes multi-site trials across and within jurisdictions, and single-site trials within a jurisdiction.

There are 718 new clinical trials reported in the year 2015–16, of which 86 per cent of applications have been approved by a Human Research Ethics Committee (HREC). There are 491 multi-site (68 per cent) and 227 single-site (32 per cent) trials. Eight hundred and forty seven (89 per cent) of SSAs/site assessments are authorised.

It is important to note that individual data elements (metrics) were missing in some of the 718 trials in the data set. Findings for individual metrics in this report reflect the proportion of the trials reporting that *particular data element*. Of the trials where clinical trial phase was reported, the majority are in Phase 3 (43 per cent) followed by Phase 2 (25 per cent). Earlier phase trials (Phase 1 and earlier) are significant with 53 of the 247 (21 per cent) trial applications that reported clinical trial phase. There has been discussion around the future potential for Australia to focus on early phase trials. While no direct comparison is possible with results from the First NAS Report, the expanded coverage of data collection in this Second Activity Report indicated a higher proportion of earlier phase trials in public health organisations than the first report. Analysis of phase results in this report is limited by low responses, with 34 per cent of the 718 trials reporting a trial phase.

Major sponsor type was reported in 82 per cent of all trials (583 out of 718). Australia's clinical trials activity in public health organisations is predominantly associated with commercially sponsored clinical trials, contributing 63 per cent of trials that recorded sponsor type. This highlights the importance of industry interaction with the medical research sector in Australia. In comparison, a third (33 per cent) of trials that recorded sponsor type were associated with non-commercial investigator – initiated (16 per cent), collaborative groups (5 per cent), institutions (12 per cent) and other (4 per cent) sponsored trials (see Metric 1a). There may be some variation between jurisdictions in designation of the sponsor type 'investigator – initiated' and 'institution' for non-commercial trials.

Analysis of metrics for ethics approval included 605 records of the total trial number (718) reported and represents 84 per cent of trials in the time period. The residual trials had not completed the approval process but will be included in a future update. Ethics (HREC) approval Metric 4a indicates that almost half (46 per cent) of ethics applications are approved between 0–60 days and 88 per cent within 120 days, without the clock. This compares to Metric 4b with the clock operating and a benchmark set for NMA of 60 days. In this case 89 per cent of ethics applications met a 60 day benchmark for ethics approval in the NAS data set.

International comparison of targets is available for the following countries regarding ethics approval time: 60 days in Europe and England; 30 days in United States, Canada and Korea; and 145 days in China[1]. The degree to which targets in these countries are achieved is not available in the KPMG Report.

Sponsors have emphasised that global competitiveness to locate clinical trials relies on timelines, for both the regulatory approval, site authorisation, study start-up and first patient recruited. The overall study start-up timeline has been estimated by measuring the regulatory process: from ethics application submission closing date to date of first site authorisation. It was not feasible to use the date of Clinical Trial Notification or Clinical Trial Exemption (CTN or CTX) notification as an end-point, nor is there data currently accessible on date of first patient recruited to a trial. Mechanisms to collect data on first patient recruited are being considered and actively progressed.

The report shows the total timeline for the regulatory process to first site authorisation for trials that recorded ethics approval and authorisation at a site, was 19 per cent within 60 days, and cumulatively 62 per cent within 120 days, measured without a clock. An aspirational target of 12 weeks (84 days) has been put forward by commercial industry sponsors for study start-up to make Australia internationally competitive. Currently 37 per cent of reported trials would meet this target which is a sound baseline from which to improve performance in Australian public health organisations.

Analysis of components of the regulatory process and the administrative clock

These metrics analyse a single component of the regulatory process, whereas in the above metric the overall study start-up requires completion of both the parallel ethics/HREC and SSA/site assessment processes.

Metric 3 addresses the entire regulatory process, as does Metric 2, overall study start-up timeline. However Metric 3 introduces the use of an administrative clock that allows distinction of responsibility for time between the administering organisation and the investigator/trial coordinator/sponsor/CRO. When a further information request is made to the investigator/trial coordinator/sponsor/CRO, the clock stops as the response is not an administrative office responsibility. Once there is a response provided to ethics/HREC, the clock re-starts.

Without a clock operating for study start-up timeline, there is a significant shift to a longer time period as the response time is included for the investigator/trial coordinator/sponsor/CRO.

1 KPMG, *Assessment of the value of clinical trials to Victoria and development of a strategy for delivering reform of Victoria's clinical trial system,* October 2014 (unpublished).

HREC approval timeline

By comparison, ethics/HREC approval when measured with the clock reflects the timeliness of the reviewing organisations' administration only. Eighty nine per cent of applications completed the ethics/HREC process within 60 days and a total of 98 per cent by 120 days.

- **With the clock**, ethics/HREC approval time has been benchmarked at 60 days by NMA, jurisdictions and in the United Kingdom. This report shows 89 per cent of clinical trials meet this benchmark with the administrative clock operating.
- **Without the clock** ethical review and approval is 46 per cent of clinical trials within a 60 day period. Cumulatively, 88 per cent of trials complete the ethics/HREC process within 120 days. In general, timelines are longer for ethics/HREC approval without the clock as indicated by a lower percentage of applications being approved within 60 days.

Further analysis is needed to better understand the reasons for delayed responses to HREC requests for more information. It is critical that this delay is addressed, and the issue will form an important element of continuous improvement strategies to be developed. Investigators, trial coordinators, sponsors, and CROs will be key stakeholders to work with in the future.

SSA/site assessment timeline

SSA/site assessment is another element of the regulatory process and occurs at each trial site where authorisation to conduct the trial must be provided.

For consistency, an administrative clock is not used in this analysis as research governance officers do not uniformly stop and re-set the clock in processing SSA applications. More importantly, there is no defined start point for the SSA process as there is no prescribed submission date. A SSA application can be submitted at any time before or after the ethics submission closing date and submission is dependent on the readiness to provide relevant documentation by the sponsor/CRO. It is important to note that a sponsor may be an institution, investigator or a commercial industry company which has overall responsibility for the trial.

Two process steps have been identified as a starting point for analysis and they are: time from the ethics/HREC approval date and the date of validation of the SSA application (see Diagram 1).

- **The ethics/HREC approval date** is a logical start point as it is a critical requirement before SSA/site assessment can be finally authorised by the organisation that will conduct the trial. It also allows continuity of the overall regulatory timeline in that the SSA assessment should be occurring in parallel and be completed as soon after ethics/HREC approval as possible. Metric 5a indicates that half of SSAs are authorised within 60 days of ethics/HREC approval. This suggests that the investigator/trial coordinator may be delaying preparation of the SSA documentation.
- **SSA validation date** is the first date that appears in the Australian Research Ethics Database (AU RED) for SSA applications. This is not related to the ethics/HREC process. Validation date can be an extremely variable decision making step i.e. a SSA application may be complete or incomplete with additional documents to be submitted at a later date but the SSA form can be considered valid. However, Metric 5b indicates that once a SSA application is validated the majority (92 per cent) are authorised within 60 days.

In conclusion the report lays out the current activity of clinical trials in five jurisdictions across Australia. There are measures that can be compared to international benchmarks and industry targets. Some learning can be gleaned from this report to inform future directions for improvement of timelines and to promote Australia as a location for global clinical trials.

This second NAS Report includes collaborative group, investigator – initiated and institution sponsored clinical trials which represents Australia's activity in non-commercial trials as well as the majority that are commercially sponsored. Participation of more jurisdictions, and the longer term intention to expand NAS to add other universities and to include private sites, will give a more complete picture for clinical trials.

Introduction

Clinical trials benefit patients, advance medical knowledge and are estimated to be worth around $1 billion to the Australian economy each year[2]. The environment in which clinical trials are conducted is complex, often occurring across multiple jurisdictions, involving multiple sites and with every study needing ethics and governance approvals before commencement. Internationally, selection of location for clinical trials has become increasingly competitive.

The challenges and issues facing clinical trials have been well documented. The Australian Government and jurisdictions, in consultation with the clinical trials sector, have responded by implementing a number of activities aimed at a significant and sustained improvement in Australia's ability to initiate and deliver clinical trials.

The CTJWG was established in 2014 under the auspices of the then Standing Council on Health. The CTJWG consists of senior level health officials and includes representatives of all jurisdictions' health agencies, the Therapeutic Goods Administration (TGA) and the National Health and Medical Research Council (NHMRC). The purpose of the CTJWG is to identify and address barriers and enablers to multi-jurisdictional clinical trials within Australia, to promote national consistency and enhance Australia's attractiveness as a place to conduct clinical trials.

The CTJWG identified four key priority areas for inclusion in its work program:

- information technology – interoperability and metrics;
- consistency of processes for pre-approval: ethics and governance;
- recruitment / accruals (retention) of clinical trials participants; and
- positioning Australia as a preferred place to conduct clinical trials.

These priorities also support a broader agenda for improving the clinical trial sector in Australia. In April 2016, the Council of Australian Governments (COAG) Health Council agreed to look at new approaches to organising sites to improve administrative efficiencies, better engage sponsors and improve trial start-up times and outcomes. The CTJWG is currently working up options for consideration, a process that will include jurisdictional and industry consultations. The report back to COAG Health Council will occur in early 2017. NHMRC is also working to streamline the approval process for clinical trials, and to recognise sites that are able to conduct high quality efficient clinical trials.

To both support and measure the effectiveness of activities designed to improve the environment for clinical trials in Australia, the CTJWG agreed to a Framework for NAS. This Framework was approved by the Hospitals Principal Committee (HPC), the Australian Health Ministers Advisory Council (AHMAC) and the COAG Health Council in 2015. For the first time, when fully implemented, national data will be available across a set of key strategic and operational objectives to drive quality improvement within the sector and to position Australia as a preferred location for clinical trials.

2 Australian Government, Clinical Trials Action Group Report, *Boosting the Business of Clinical Trials in Australia*, 2011.

In late 2015, Victoria prepared the *First National Activity Report on Commercially Sponsored Clinical Trials in Australian Public Health Organisations* (the First NAS Report) using data from almost all jurisdictions for the year 2014–15, in accordance with the agreed data set for NAS. The First NAS Report was endorsed by all jurisdictions in March 2016, HPC in April 2016 and AHMAC in May 2016. It represented a key step forward in understanding Australia's performance in the clinical trials sector, and the committed cooperation of all jurisdictions in its development.

This current report (the *Second National Aggregate Statistics Report on Clinical Trials in Australia*) has been prepared under the same NAS framework, for CTJWG. It has been prepared by Victoria, using data from almost all jurisdictions for the year 2015–16. Like the First NAS Report, it includes data for clinical trials conducted in public health organisations, but has expanded to include trials from *all* sponsor types (not just commercially sponsored trials). This report provides the most reliable and comprehensive national picture to date for clinical trials in public health organisations in Australia. The information in the report was made possible by the effective collaboration and effort of jurisdictions.

University trials that involve clinical treatment within hospitals is already captured in this existing data set as researchers either have both clinical and university appointments or are required to seek health institution ethics review. However, some university research that relates to an out-patient setting, and trials that rely on General Practices, are not captured.

Purpose of National Aggregate Statistics

Collecting national data on clinical trials activity will provide greater clarity around the number and type of trials occurring nationally, and can also be used to identify areas where there are opportunities for improvement. Developing and implementing a national system to assess the timeliness and efficiency of clinical trials, and promoting interoperability of information technology across jurisdictions, are key priorities for the CTJWG.

The NAS represent the essential metrics to gain a measure of number and timelines for clinical trial approvals and time to commencement in Australia, to evaluate the success of clinical trials improvement initiatives and to promote Australia as a preferred global destination. NAS will assist in identifying strengths, gaps and barriers to the efficient and effective conduct of clinical trials. It will provide a means to share lessons learnt, and facilitate a quality improvement approach in the sector. The Framework will also inform strategic and targeted promotion of Australia as a preferred global location for clinical trials. To this end, the NAS should inform strategic and operational objectives to improve timelines in the regulatory stage before trial start-up.

As part of this framework, the CTJWG identified a set of eight metrics for clinical trials:

1. number of new trials and breakdown by trial phase, and by sponsor type
2. overall study start-up timeline (regulatory timeline)
3. ethics and governance approval timeline
4. Human Research Ethics Committee (HREC) approval timeline
5. SSA/site assessment timeline
6. trial recruitment: actual and planned number of participants recruited
7. site recruitment: actual and planned number of participants recruited
8. total inbound (internal and external) investment annually.

These eight metrics were approved as the foundation of the NAS by HPC, AHMAC and COAG HC in 2015. The first reporting period was 1 July 2014 through to 30 June 2015 (the First NAS Report), and this second reporting period was 1 July 2015 through to 30 June 2016. As noted above, direct comparison with the findings from the First NAS Report are not presented in this analysis, as the samples for the two years are different. While both draw data from public health organisations, the

First NAS Report included commercially sponsored trials only in six jurisdictions (n = 335), while this current report includes all trials in five jurisdictions (n = 718).

Clinical trials overview

The regulatory timeline begins with the submission of an ethics application to the reviewing HREC and this review is in parallel with site assessment. In each process there is allowance for the reviewing administrator to request further information from the lead investigator and others that may be involved (could include the trial coordinator/sponsor/Contract Research Organisation (CRO)). The end-point is the authorisation of SSA/site assessment at the trial site and this can then trigger the initiation of a trial at that site.

This report does not include:

- timelines for compliance with a regulatory body such as the Therapeutic Goods Administration;
- data relating to the conduct of the trial at sites, which would include the actual number of participants recruited and retained in a trial; and
- the funds expended by sponsors for the conduct of the trial.

A flow diagram of the ethics and SSA/site assessment processes

The flow diagram below illustrates the two processes, ethics/HREC review and SSA/site assessment, required for a clinical trial. The two processes occur with separate administration but in a parallel timeframe.

The initiation point for a clinical trial is the submission closing date for the ethics application.

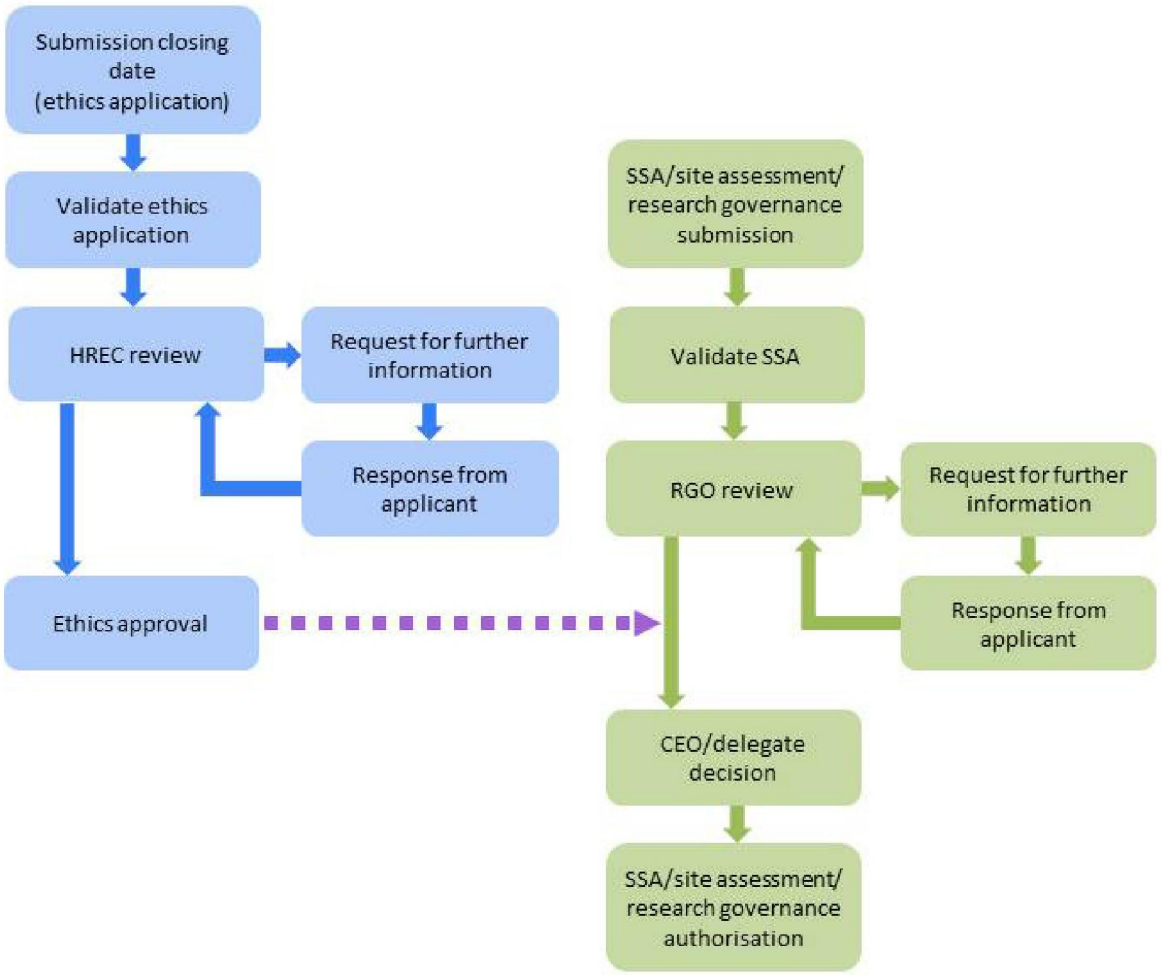
The end-point is the authorisation of SSA/site assessment.

Metric 2 and 3 capture the total of Diagram 1 below – overall study start-up timeline 'without clock' and 'with clock' respectively.

Metric 4 captures time taken for the ethics section of Diagram 1 below – HREC approval timelines. This includes submission closing date, validation, HREC review, request for further information, responses from applicants, and final ethics approval.

Metrics 5 and 6 capture time taken for the SSA process of Diagram 1 below – SSA/site assessment. This includes submission, validation, Research Governance Officer (RGO) review, request for further information, responses from applicants, Chief Executive Officer (CEO)/delegation decision, and SSA/site assessment/research governance authorisation.

Diagram 1: Flow diagram of ethics and SSA processes for clinical trial regulatory requirements.



Overview of data collection

This report contains an aggregate of data collection for all clinical trials. Development of data definitions, data collection templates and analysis has been led by Victoria, in collaboration with contributing jurisdictions, and was endorsed by the CTJWG in March 2016. CTJWG agreed that all NAS data would be obtained through jurisdictional data systems as access to other government or commercial sources was not feasible.

The data presented in this report has some limitations and these should be taken into account when interpreting the information provided.

The data captured is:

- part of routine practice for clinical trial regulatory processing of ethics and SSA/site assessment applications at publicly funded health organisations;
- provided by contributing jurisdictions as noted in this report; and
- an under-representation of clinical trials as some jurisdictions currently have limited capacity to report in the NAS format, others have an incomplete data set for single-site clinical trials and some jurisdictions do not conduct an SSA process *per se*.

For successive reports jurisdictions will be actively working to report more comprehensively regarding additional data and current gaps in some data sets.

Data collection process

Data contained in this report is based on a template developed by the CTJWG and in accordance with agreed data definitions. The data relates to all trials i.e. trials that are funded by commercial organisations such as pharmaceutical or device companies and non-commercial, including investigator – initiated, collaborative group, institution and other multi-centre and single-site clinical trials.

This *Second National Activity Report on Commercially Sponsored Clinical Trials in Australian Public Health Organisations* has been drafted using data for one year from 1 July 2015 to 30 June 2016. Contributing jurisdictions include: New South Wales, Northern Territory, Queensland, South Australia and Victoria. It is intended that future reports will contain data from all jurisdictions as reporting capacity, against agreed metrics, grows.

The data captured in this second NAS report shows 718 new clinical trials occurring in Australian publicly funded hospitals in 2015–16. The total number of new trials is somewhat underestimated due either to some jurisdiction data sets being incomplete (e.g. single-site trials), some jurisdictions not contributing data as yet, and those jurisdictions contributing, but not yet participating in National Mutual Acceptance (NMA), having limited data sets due to current information management systems. These limitations will improve as the NAS concept is adopted more broadly and further refined.

Data sources

The NMA framework operating between five participating jurisdictions has provided the infrastructure for NAS data collection and analysis and has been established since 2011. Jurisdictions that operate the Australian Research Ethics Database (AU RED) are New South Wales (including Australian Capital Territory), Queensland, South Australia and Victoria. AU RED is a specialist information platform that integrates the ethics/HREC and SSA/site assessment application steps for investigators with the administrative management of these applications. Processing both these document flows results in completion of regulatory approval requirements, except for the CTN/CTX systems under the Therapeutic Goods Administration (TGA).

NMA involves linking cross-jurisdictional applications so each jurisdiction hosting a trial site has a record of ethical review in another jurisdiction. Bringing together NMA and state-only AU RED records in this report is an important step and has relied on cooperative relations between jurisdictions. The Northern Territory provided clinical trial information collected from other data sources or a stand-alone database as AU RED is not currently used.

Features of research projects enable identification of clinical trials and their characteristics such as Study Type (e.g. clinical trial as opposed to health research, social research), Sponsor Type (commercial sponsored, collaborative group, investigator – initiated, institution and other), Trial Phase (e.g. First Time In Human (FTIH), First Time In Patient (FTIP), Phase 1, 2, 3 and 4), and Application Type (e.g. multi-site, single-site, site specific assessment).

The unique identifier for an ethics/HREC application ensures that duplication of applications in reports is eliminated, and more importantly, it links the HREC and SSA/site assessment applications for a trial to measure the overall study start-up timelines.

AU RED has a clock system whereby it is possible to measure timelines and also time intervals when applications are or are not the responsibility of administering organisations. Calculations can be made to measure both the administrator activity and the time for actions carried out by the investigator/trial coordinator/sponsor/CRO.

AU RED records dates regarding decisions and document flow actions and these dates together form a comprehensive picture of the key time points in the ethics and site assessment processes.

The data source, AU RED, provides a comprehensive view of the regulatory timeline but does not include details of a trial product or the actual conduct of the trial where participants are involved. There is a clear distinction of AU RED data, including features and regulatory process dates, compared to a data set required for a trial registry.

Next steps

In the future, reporting capability will be improved in jurisdictions as more data becomes available through cooperative learning, and will lead to more comprehensive data analysis for Australian clinical trials in public health organisations. The CTJWG is working on a strategy to expand reporting to include private health sector data. Opportunities to partner with the industry sector to harness commercial sector data sources are also actively being pursued.

Metrics report

The ethics process is discrete and measured between submission of the ethics application to approval. A common benchmark for process of ethics applications is 60 days. However, at this stage, there are two statistical mechanisms to measure this metric and that involves use of an administrative clock or not.

With the operation of the clock the metric measures the administrator timeliness. The clock measures the time that the trial application is with the administrator processing the application. The clock stops when the application leaves the administrator and is the responsibility of the investigator, trial coordinator, sponsor or CRO to provide further information about the application. The clock re-starts when a response is received from the investigator/trial coordinator/sponsor/CRO.

Without the application of the clock the metric measures timeliness of both the administrator and investigator, trial coordinator, sponsor or CRO. That is, the interval(s) when the investigator/trial coordinator/sponsor/CRO has responsibility for the application is included in the overall time measurement.

The reasons for the HREC to request information from the investigator, trial coordinator, sponsor or CRO have not yet been explored but lack of quality of the application is often encountered. Observations of HREC members suggest that the participant information and consent form associated with trials frequently requires revision. Participant information is crucial to gain consent to participate in a trial with a clear understanding of the nature of the trial and requirements of the participant. Research merit and integrity (quality explanation of the science, methodology and compliance requirements) and respectfulness (adequate risks, safety and privacy consideration) reflected in the information form have been identified as deficiencies.

A significant amount of time is being expended when a trial application is in the hands of the investigator, trial coordinator, sponsor or CRO. The reasons for such time loss (e.g. due to communication between multiple parties) in responding to a request from the HREC are important to understand to improve performance for ethics and overall study start-up timelines.

Metric 1: Number of new trials per trial phase

For the annual period commencing from 1 July 2015 – 30 June 2016 there are 718 new clinical trials reported from five (5) jurisdictions that submitted data. Of these, 247 trials reported trial phase[3]. The low response is largely the result of one of the six jurisdictions not reporting trial phase.

Phase 1 trials determine the safety of the medicine in humans and helps determine the appropriate doses for later studies such as phase 2 trials that determine effectiveness and safety. Phase 3 trials are conducted to determine whether the medicine confers clinical benefit for a disease and involves a greater number of participants in the trial. After a medicine is approved for treatment of a particular disease/condition, Phase 4 trials are conducted to compare a new medicine against a wider range of existing medicines/therapies or to investigate the use in a normal clinical setting. Refer to the Glossary & definitions for a fuller explanation of trial phase.

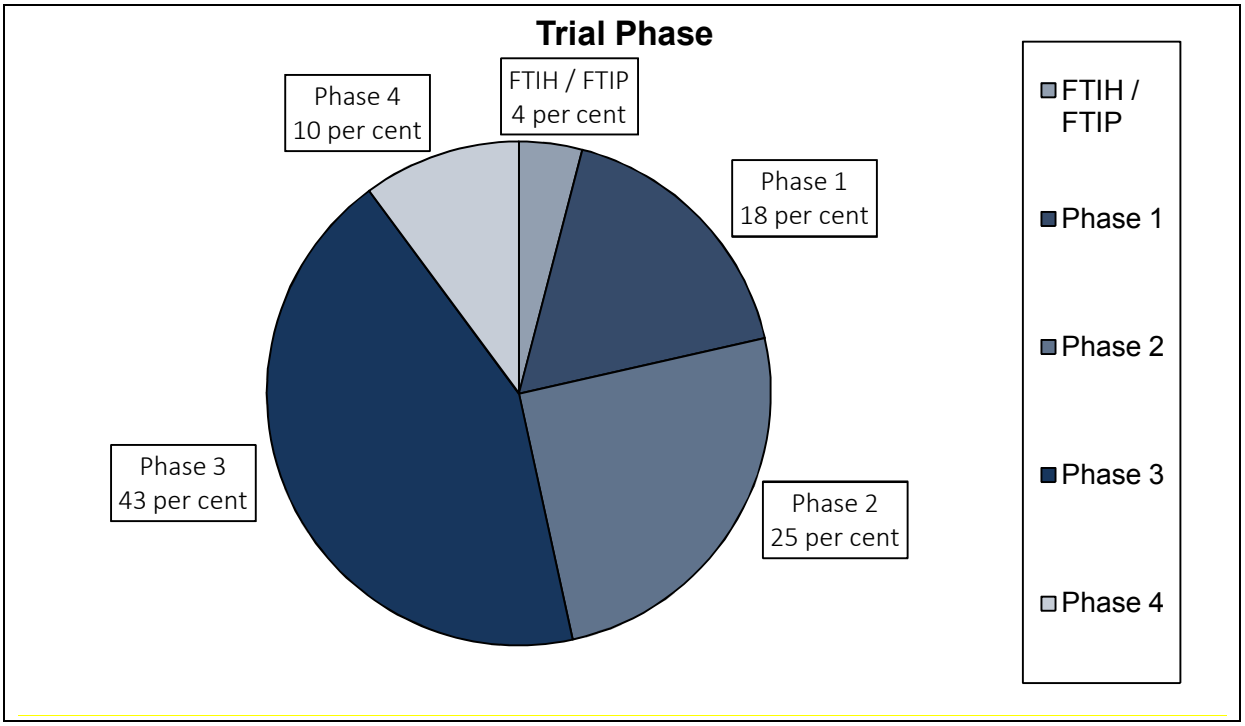
As shown below, 43 per cent of the 247 trials that reported trial phase are in Phase 3, followed by 25 per cent in Phase 2 trials. Phase 1 represent 18 per cent, and phase 4 are 10 per cent of trials undertaken in this reporting period. This suggests that the majority of trials in public hospitals are phase 2 and 3.

Figure 1: Number of Clinical Trials (medicines) by trial phase

Trial phase	No.	Per cent
FTIH / FTIP	10	4
Phase 1	43	18
Phase 2	62	25
Phase 3	107	43
Phase 4	25	10
Total	247	100

Note: Jurisdictions represented are: Northern Territory, Queensland, South Australia and Victoria. The 'Clinical Trial Phase' field is not reported in some jurisdictions or for individual trials or may be 'not applicable' (e.g. device trial). Therefore the number of trials by phase (n=247) only represents a fraction of the overall number of clinical trials (n=718).

3 Trial phase reported for trial type 'medicine' only.



The clinical investigations pathway for medical technology/devices differs from the clinical trial pathway for medicines. While phases 1, 2, 3 and 4 apply to medicines, for medical technology/devices the clinical trial pathway is represented by the following stages: Stage 1 – feasibility or “first in man” (FIM) clinical trials conducted in a small number of patients with the disease to be treated, with assessment of the safety being the main focus; Stage 2 – pivotal clinical trial is usually conducted in a large number of patients with the disease to be treated, with assessment of performance and safety being the main focus; Stage 3 – post-market clinical trial is conducted after satisfying the pre-market regulatory requirements, with the focus being to collect additional clinical data to assess a variety of end-points.

There is no data recorded for device trial stages but overall there are 84 device trials reported in this data set (12 per cent of total trials).

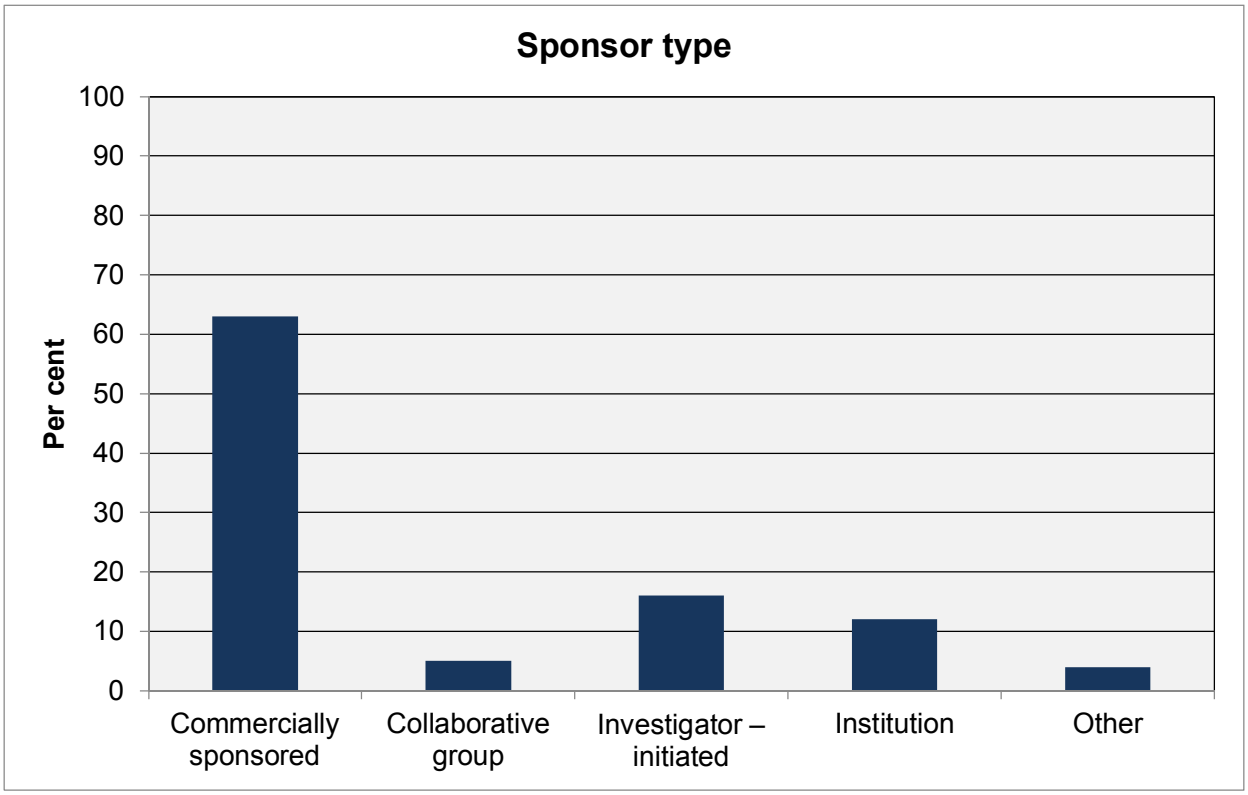
Metric 1a: Number of new trials per sponsor type

Commercially sponsored clinical trials are predominant in Australia with 63 per cent of the 583 trials reporting 'sponsor type' indicating they were sponsored by industry. Investigator centred trials, including collaborative groups, investigators and institutions represent a third of trials (33 per cent).

Figure 2 Number of Clinical Trials by sponsor type

Sponsor Type	No.	Per cent
Commercially sponsored	370	63
Collaborative group	31	5
Investigator – initiated	91	16
Institution	70	12
Other	21	4
Total	**583**	**100**

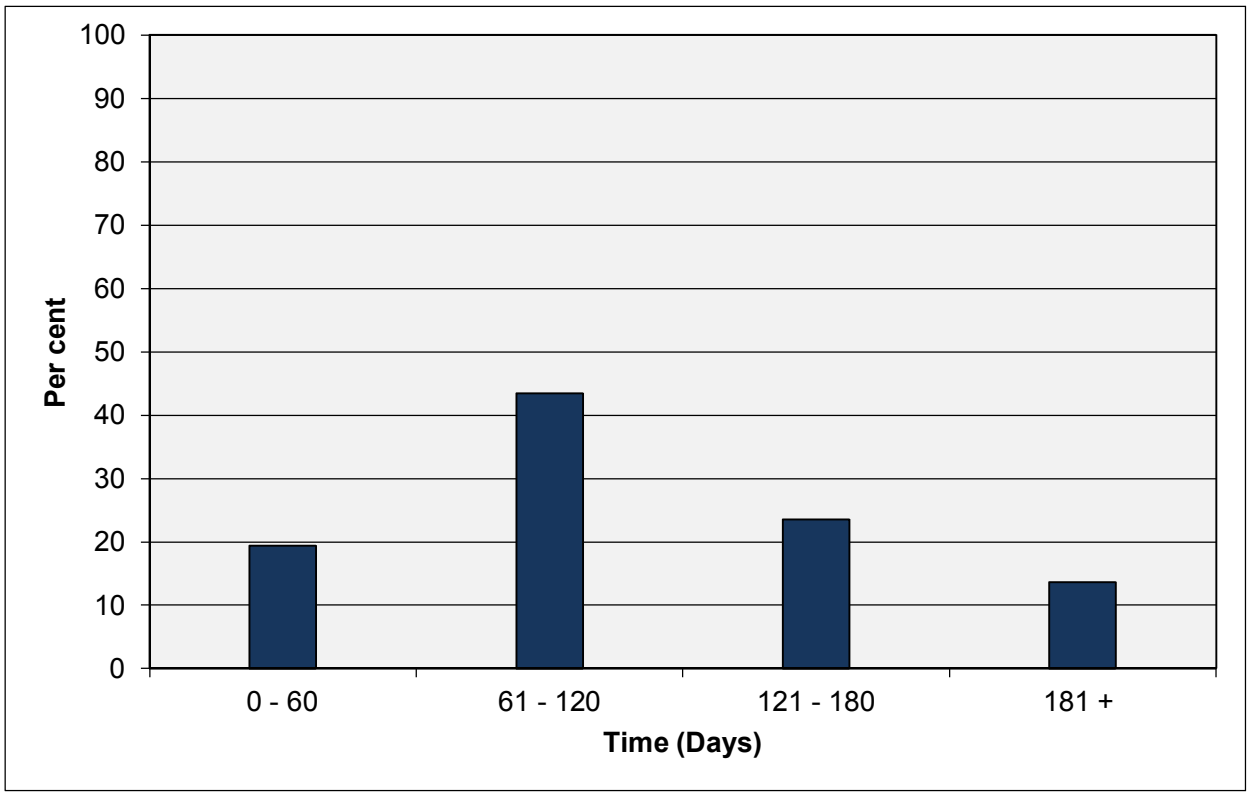
Note: Jurisdictions represented are: New South Wales, Northern Territory, Queensland, South Australia and Victoria. The 'Sponsor Type' field is not reported in some jurisdictions or for individual trials. The number of trials by sponsor type (n=583) represents a high proportion of the overall number of clinical trials (n=718).



Metric 2: Overall study start-up – 'Without clock'

Measuring the overall study start-up is an important metric for commercial sponsors in determining location of clinical trials globally. In this reporting period, there are 417 clinical trials reported for this measure. The period commences at ethics submission and the date for the first SSA/Site assessment authorisation is the end-point. This measure gives a real indication to sponsors of the time from submission of ethics application to possible site initiation and trial commencement.

The international target metric for time to recruit the first patient into a trial often used by industry is 12 weeks. Here, 37 per cent of trials meet a 12 week (84 days) target for regulatory approval, however this will not include some steps that commercial sponsors may measure in the international metric, as data on time to recruit the first patient is not yet available.



Almost 20 per cent of clinical trials complete the regulatory process in 60 days or less, and a total of 62 per cent of trial applications are processed within 120 days. The remainder of trials take 120 days or more (over 180 days) to reach the end-point of the regulatory process.

Time (Days)	0–60	61–120	121–180	181+	Total
No.	81	181	98	57	417
Per cent	19	43	24	14	100

Note: Jurisdictions represented are: New South Wales, Queensland, South Australia and Victoria. N=417 of the 718 trial applications. Some clinical trials did not meet the criteria for this metric as they were either approved but an SSA was not yet authorised or there were reporting errors.

Metric 3: Ethics and SSA/Site assessment timeline – 'With Clock'

This reflects overall study start-up but it has an administrative clock which distinguishes the responsibility for time between the administering organisation and the investigator/trial coordinator/sponsor/CRO. The start of the process is the submission closing date and the completion is the date of the first site authorisation (see Diagram 1).

This metric measures the overall regulatory process, and is the same as the information in metric 2 but with clock in use (for HREC time only) and the interval when the responsibility for the application is with the investigator/trial coordinator, sponsor/CRO is deducted. Therefore this is a measure of administration time. The measure includes the ethics review and time to the first SSA authorisation at the first site.

Administration of the ethics/HREC and authorisation of the first SSA/site assessment is completed within 60 days for 46 per cent of applications, and 83 per cent of applications fall within 120 days. The proportion falling under either 60 or under 120 days is higher in Metric 3 than in metric 2 as the time taken to provide a response to the ethics committee is not measured.

Time (Days)	0–60	61–120	121–180	181+	Total
No.	190	154	56	17	417
Per cent	46	37	13	4	100

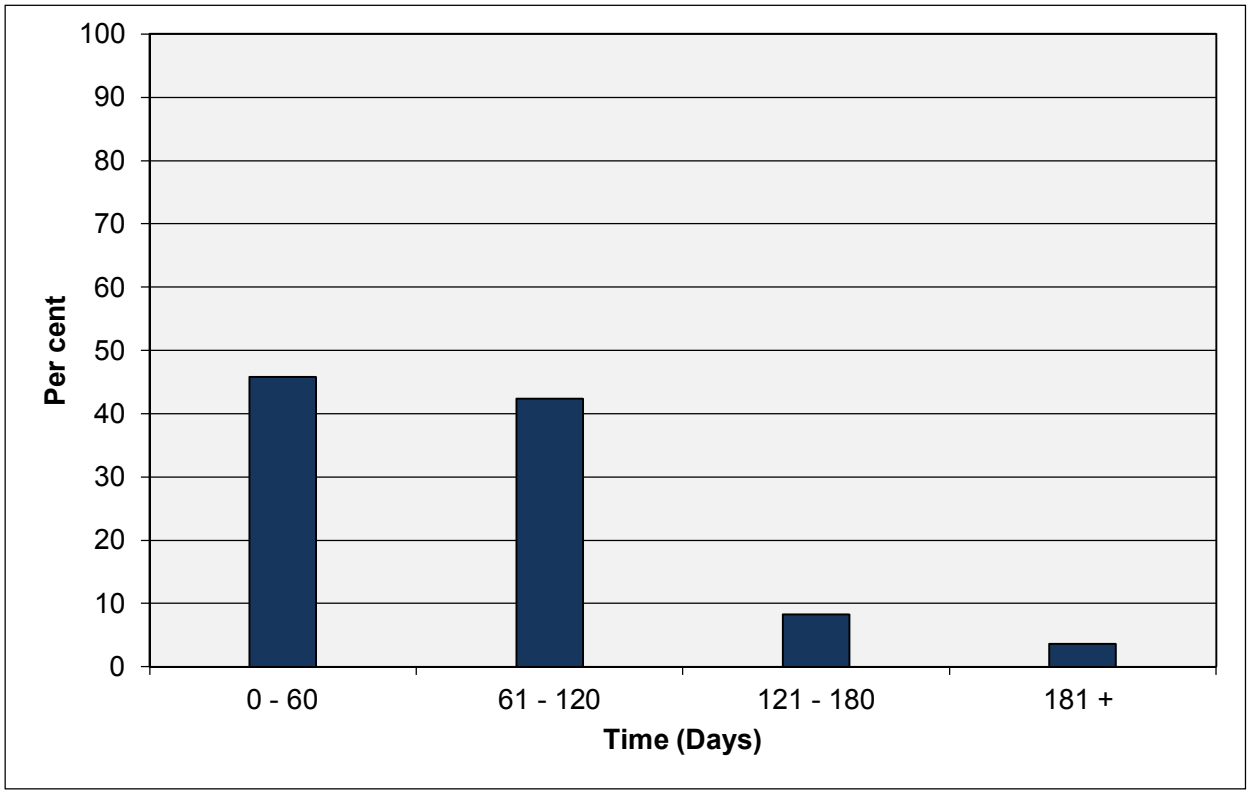
Note: Jurisdictions represented are: New South Wales, Queensland, South Australia and Victoria. N=417 of the 718 trial applications. Some clinical trials did not meet the criteria for this metric as they were either approved but an SSA was not yet authorised or there were reporting errors.

Metric 4: Ethics approval timeline

4a HREC approval timeline – 'Without Clock'

Time in days from Cut-off Date/Submission Closing Date to the Approval Clock Stop Date 'Without Clock' operating.

This does not measure intervals when the clock is stopped and re-started during HREC review.



Without operation of an administrative clock 46 per cent of trials complete the ethics process within a 60 day period which is a commonly used benchmark for the ethics process in Australia and the United Kingdom. The majority of trials had an ethics approval timeline within 120 days.

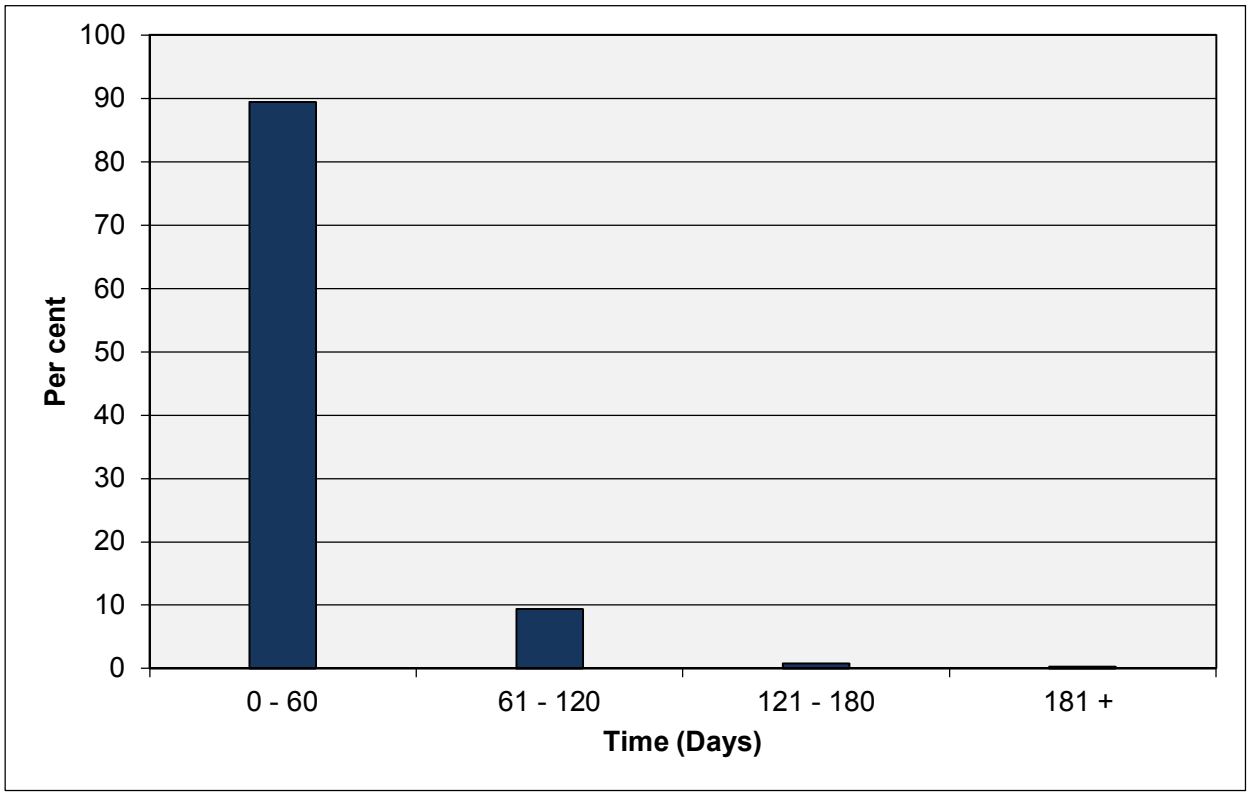
Time (Days)	0–60	61–120	121–180	181+	Total
No.	277	256	50	22	605
Per cent	46	42	8	4	100

Note: Jurisdictions represented are: New South Wales, Northern Territory, Queensland, South Australia and Victoria.
N= 605 of the 718 trial applications. Of the applications meeting the criteria, some clinical trials were eliminated because of reporting errors and time could not be calculated.

4b HREC approval timeline – 'With Clock'

Time in days from Cut-off Date/Submission Closing Date to the Approval Clock Stop Date.

With Clock measures the time intervals between request and receipt of further information from investigator/trial coordinator/sponsor/CRO and this interval is deducted from the overall time period.



The majority (89 per cent) of ethics/HREC applications were reviewed and approved within a 60 day benchmark, with operation of an administrative clock. This measures the administrating organisations' timeliness for the ethics process.

Time (Days)	0–60	61–120	121–180	181+	Total
No.	541	57	5	2	605
Per cent	89	9	1	0	100

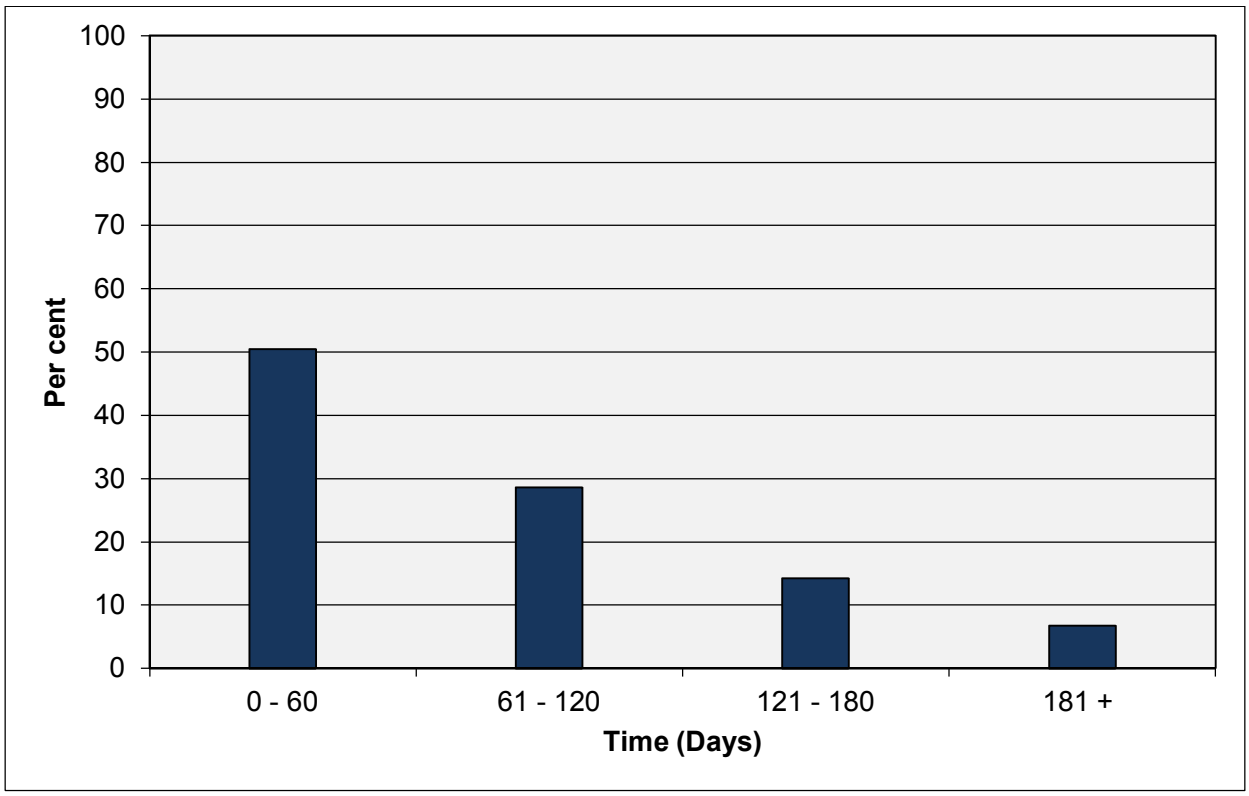
Note: Jurisdictions represented are: New South Wales, Queensland, Northern Territory, South Australia and Victoria.
N= 605 of the 718 trial applications. Of the applications meeting the criteria, some clinical trials were eliminated because of reporting errors and time could not be calculated.

Metric 5: SSA/Site Assessment Timeline – 'Without Clock'

The timeline for the SSA site authorisation process can be measured from different start points. For instance from ethics/HREC approval date (Metrics 5a) or from SSA validation date (Metric 5b).

5a SSA/Site Assessment Timeline – from HREC Approval Date 'Without clock'

Time from Date of HREC approval to Authorisation Clock Stop Date, 'Without Clock' operating. There is no deduction of intervals when the clock is stopped and re-started for the SSA/site assessment authorisation process. There is inconsistent use of the stop and re-start clock function across jurisdictions and sites and therefore the clock was not used in the SSA process measure for this report.



Half of the SSA applications completed the SSA/site assessment process within 60 days following the ethics/HREC approval date.

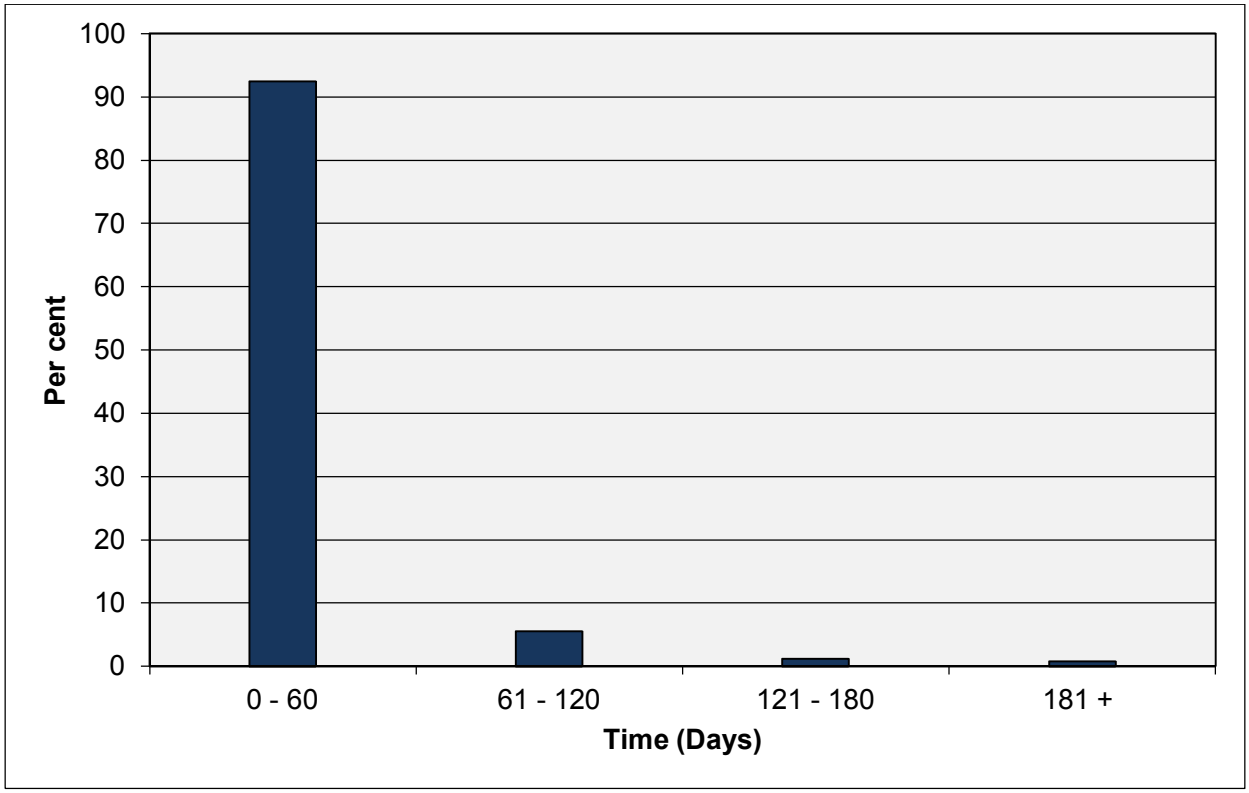
Time (Days)	0–60	61–120	121–180	181+	Total
No.	406	230	115	54	805
Per cent	50	29	14	7	100

Note: Jurisdictions represented are: New South Wales, Queensland, South Australia and Victoria. N=805. The HREC application must be approved before an SSA/site assessment can be authorised/completed. Applications with data errors are not reported.

5b SSA/Site Assessment Timeline – from SSA Validation Date 'Without Clock'

Time from SSA validation Date to Authorisation Clock Stop Date, 'Without Clock' operating.

There is no deduction of time intervals (clock stop and re-start) for the SSA/site assessment process. There is inconsistent use of the stop and re-start clock function across jurisdictions and sites and therefore the clock was not used in the SSA process measure for this report.



Ninety two per cent (92 per cent) of applications completed the SSA/Site assessment process within 60 days following the validation of an SSA by the administrator.

Time (Days)	0–60	61–120	121–180	181+	Total
No.	750	45	10	6	811
Per cent	92	6	1	1	100

Note: Jurisdictions represented are: New South Wales, Queensland, South Australia and Victoria. N=811. The HREC application must be approved before an SSA can be authorised/completed. Applications with data errors are not reported.

SSA/Site Assessment Timeline 'With Clock'

This data is not collected to date. Not all clinical trial site administrators record time between request and receipt of further information for SSA/site assessment by stopping and re-starting the clock. Similarly, site administrators do not routinely use the clock between validation and authorisation of an SSA.