Clinical Trials in Australian Public Health Institutions 2016-17 (NAS 3 report)

A comparison over 3 years from 2014 to 2017

Framework for National Aggregate Statistics (NAS) - Third Activity Report

Clinical Trials Project Reference Group (CTPRG)

Disclaimers

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Contents

Acronyms

ACSQHC	Australian Commission on Safety and Quality in Health Care
ANZCTR	Australian New Zealand Clinical Trials Registry
AU RED	Australian Research Ethics Database
COAG HC	Council of Australian Governments Health Council
CPC	Clinical Principal Committee
CRO	Commercial Research Organisation
CTN	Clinical Trial Notification
CTPRG	Clinical Trials Project Reference Group
CTX	Clinical Trial Exemption
ERM	Ethics Review Manager
FTIH / FTIP	First time in human / First time in patient
HMR	Health and Medical Research
NHMRC	National Health and Medical Research Council
HREC	Health Research Ethics Committee
HPC	Hospitals Principal Committee
NAS	National Aggregate Statistics
NMA	National Mutual Acceptance
REGIS	Research Ethics and Governance Information System
RGS	Research Governance System
SSA	Site Specific Assessment
TGA	Therapeutic Goods Administration

Executive summary

Health and Medical Research (HMR) is the backbone of health system delivery and continuous improvement, and clinical trials are a key part of the Australian HMR sector. They benefit patients, advance medical knowledge and for every dollar invested in clinician-driven clinical trials it is estimated that $5.80 is returned in health benefit[1]. All jurisdictions are collaborating to improve the Australian clinical trials environment with a view to improving health outcomes and increasing international investment in Australia.

Ensuring efficient government investment in these reform efforts is critical. In 2015, all Health Ministers agreed to a Framework for National Aggregate Statistics (NAS) and annual collection of NAS data, to be facilitated through the Clinical Trials Project Reference Group (CTPRG). The NAS Framework is being progressively implemented by all jurisdictions, to inform strategic and targeted promotion of Australia as a preferred global location for clinical trials, and operational objectives to improve approval timelines.

This current report, the *Third National Aggregate Statistics Report on Clinical Trials in Australia* (NAS 3 Report) was produced by Victoria on behalf of all jurisdictions, through the CTPRG, and approved for publication by AHMAC in 2019 (pending). 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. This report is the second NAS report to be made publically available, following public release of the NAS 2 Report (2015-16 data) in 2017[2].

The NAS 3 Report represents all new clinical trials in 2014-15 (NAS 1), 2015-16 (NAS 2) and 2016-17 (NAS 3) in public health organisations from 6 jurisdictions[3]. In total, between 807 and 861 new clinical trials were reported each year. Some data sets were incomplete, and therefore not all NAS metrics include data from all 6 jurisdictions (for example trial phase is not recorded in New South Wales). It includes data on total clinical trial activity (including number and sponsor type), and timelines for ethics approval and SSA/site assessment. This report has a time-series and includes updated NAS 1 and NAS 2 data, and NAS 3 data.

Key findings from the report indicate that in public health organisations in Australia[3]:

- The majority of clinical trials were multi-site (between 66 and 70 per cent), Phase 3 (between 46 and 50 per cent), and commercially sponsored (between 53 and 61 per cent).
- There were improvements in *average* approval times:
    - Total time (without clock) for approval of ethics applications decreased from 86.6 days (2014-15) to 77.7 days (2016-17)[4];
    - Time taken to administer approval of ethics applications (with clock) decreased from 38.2 days (2014-15) to 31.2 (2016-17)[5]; and
    - Time for SSA/Site assessment authorisation of all sites in a trial decreased, regardless of which of the two NAS metric start-dates were used[6].

[1] http://www.clinicaltrialsalliance.org.au/wp-content/uploads/2018/08/Economic-evaluation-of-investigator-initiated-clinical-trials-conducted-by-networks.pdf
[2] http://www.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials
[3] Excluding Tasmania and Western Australia, however it is anticipated that all jurisdictions will contribute to future NAS reports.
[4] Metric 4b (With Clock) results with Standard Errors: 86.6±4.4 days (2014-15), 77.7±2.2 days (2016-17)
[5] Metric 4a (Without Clock) results with Standard Errors: 38.2±3.6 days (2014-15), 31.2±1.2 days (2016-17);
[6] Metric 5a (from ethics approval date): 201.3±5.9 days (2014-15) to 146±2.9 days (2016-17); Metric 5b (from SSA validation date): 32.7±1.7 days (2014-15) to 23.0±1.1 days (2016-17)

- There were mixed results in the *proportion* of clinical trials approved within the benchmark of 60 days over the reporting period. For example, the proportion of clinical trials approved within 60 days declined from 40 per cent (2014-15) to 30 per cent (2016-17), when measuring the time taken for processing of an ethics (HREC) and SSA/Site/assessment application by the administering body (Metric 3). However, the majority of trials continued to complete the approval process within 120 days (Metric 3). In addition, there was an increase over the three years in the number of ethics applications that were processed within 60 days by an administrating institute (Metric 4b[5]).

The report findings indicate a substantial clinical trial sector in Australia, and strong improvements in ethics approval processing times by administering bodies. The findings also highlight priorities for further improvements.

For example, Metrics 4 provides a comparison of ethics approval time by the administering body only (Metric 4b – With Clock) and total time, including time to respond to queries by the applicant (Metric 4a – Without Clock). With clock, the proportion of ethics approval in 60 days is between 89 and 94 per cent, compared to 45 to 49 per cent 'Without Clock'. This is an area where strategies are needed to address performance improvement of respondents, although it may be largely due to lack of resources for investigators and trial coordinators in the public health sector. Industry's contribution to this time measure should be open for discussion with the sector.

Metrics 5 also provides an important comparison of timeliness of the SSA/Site assessment process 'Without Clock', using two different start points. Most jurisdictions have a policy to commence the SSA/site assessment concurrently with the ethics process, but the metrics suggest this is not occurring frequently. The apparent lag in 'commencement' of an SSA/site assessment may be due to at least four factors: (1) research governance officers are delaying acceptance of an SSA/site assessment application until ethics approval is competed; (2) investigators may be unable to submit a timely application due to clinical loads and lack of resources; (3) industry delays may occur in providing key documents and protracted negotiations on trial budget; and (4) investigator-initiated and collaborative groups may have limited funding and resources to prepare timely submissions.

The Explanatory Notes (see page 25) details NAS data sources and methodology (including limitations), and should be read in conjunction with report findings.

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. As opportunities arise, the CTPRG is also working to expand reporting to include private health sector data. Opportunities to partner with the industry sector to harness commercial sector data sources will also continue to be pursued.

Introduction

Background

Health and Medical Research (HMR) is the backbone of health system delivery and continuous improvement, and clinical trials are a key part of the Australian HMR sector and often seen as the gold standard in HMR evidence. They benefit patients, advance medical knowledge and for every dollar invested in clinician-driven clinical trials it is estimated that $5.80 is returned in health benefit[7].

Australia has traditionally been perceived as an attractive place to undertake safe and high quality trials. Particular strengths have been identified as Australia's Clinical Trials Notification (CTN) and National Mutual Acceptance (NMA) schemes; experienced researchers; site study coordinators; feasibility assessments; accurate patient recruitment estimates; established referral networks; and national patient databases.[8] However, international competition is increasing, and delays in gaining approval and in recruiting patients are challenging Australia's competitiveness. In response, all jurisdictions are collaborating to improve the Australian clinical trials environment with a view to achieve better health outcomes and increasing international investment in Australia. The Australian clinical trial policy landscape is complex, and no single government or agency holds all the levers for change, a key role has been supporting greater sector collaboration. Much of this work is being achieved through collaboration between Commonwealth and jurisdictional agencies, as health system managers of public hospitals in Australia, where the majority of clinical trials occur.

COAG Health Council Revitalised Clinical Trials Agenda

In April 2016 the COAG Health Council noted that while jurisdictions have worked to improve the environment for clinical trials, issues of fragmentation and inefficiencies remain, that impact on Australia's attractiveness as a preferred location for trials. Health Ministers agreed to develop approaches to organise public health services to better support and streamline clinical trial processes in Australia. In response, the Clinical Trials Project Reference Group (CTPRG) developed a set of Principles and Priority Action Areas to underpin redesign of jurisdictional clinical trial systems.

Jurisdictions and the Commonwealth are also collaborating on key measures to address Priority Action Areas. This includes further strengthening Australia's clinical trial sector using stimulus from the Australian Government's *Encouraging More Clinical Trials in Australia* initiative, under which $7 million is available nationally to assist State and Territory governments achieve system redesign in accordance with the revitalised COAG Health Council clinical trials agenda. Among other things, this agenda seeks to establish central points of contact to improve system navigation for sponsors and participants, streamline trial processes, time to trial start-up, and improve workforce capability.

[7] http://www.clinicaltrialsalliance.org.au/wp-content/uploads/2018/08/Economic-evaluation-of-investigator-initiated-clinical-trials-conducted-by-networks.pdf

[8] Analysis of Recently Conducted Clinical Trials (2015) http://www.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials

Clinical Trials Project Reference Group (CTPRG)

The Clinical Trials Project Reference Group (CTPRG), formerly the Clinical Trials Jurisdictional Working Group (CTJWG), was established in July 2014 operating under the COAG Health Council governance structure and involves senior officials from Commonwealth, state and territory health departments. Its purpose is to identify and implement actions and system redesign that will enable a streamlined and consistent national approach to clinical trials within Australia with the intention of enhancing health outcomes and building Australia's ability to attract national and international clinical trials.

Ensuring efficient government investment in these reform efforts is critical, given the sustainability challenges facing Australia's health system. Since its inception, the CTPRG has identified the absence of, and critical need for, national data 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.

To both support and measure the effectiveness of activities designed to improve the environment for clinical trials in Australia, the CTPRG agreed to a Framework for National Aggregate Statistics (NAS), and annual collection of NAS data. It builds on the NMA, and represents an agreed framework for collection of national aggregate statistics on clinical trials that will be progressively implemented by all jurisdictions and facilitate a quality improvement approach to the sector (see below for further details). The Framework will also inform strategic and targeted promotion of Australia as a preferred global location for clinical trials, and inform strategic and operational objectives to improve approval timelines.

The NAS Framework was approved by the Hospitals Principal Committee (HPC), the Australian Health Ministers Advisory Council (AHMAC) and the Council of Australian Governments (COAG) Health Council in 2015. This data is intended to complement other current sources of national data on clinical trial activity in Australia, including the Australian New Zealand Clinical Trial Registry (ANZCTR) and TGA's eCTN scheme.

Development of a National Clinical Trials Governance Framework is another key element of the COAG Health Council revitalised clinical trials agenda and the CTPRG Implementation Plan. The Department of Health has engaged the Australian Commission on Safety and Quality in Health Care (ACSQHC) to undertake this work on behalf of all jurisdictions. The outcome will be a Clinical Trials Governance Framework, an important first step towards nationally consistent accreditation of health services undertaking clinical trials in Australia, which will ultimately be included in the National Safety and Quality Health Service Standards. The Governance Framework will also include measures of performance for each Standard, with likely linkages with NAS.

An overview of other CTPRG priority activities is available at:
http://www.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials.

NMA scheme

The NMA scheme supports the acceptance of a single scientific and ethical review for multi-centre research conducted in publicly-funded health services. As at January 2019, all states and territories, with the exception of the Northern Territory and Tasmania, are a part of the NMA scheme. NMA involves linking cross-jurisdictional applications so each jurisdiction hosting a trial site has a record of ethical review in another jurisdiction. NMA also established the collation and

reporting against objectives for metrics on cross-jurisdictional clinical trials in Australia and this in-part provided the framework for the reporting of cross-jurisdictional clinical trials within NAS.

Clinical trial approval processes in Australia

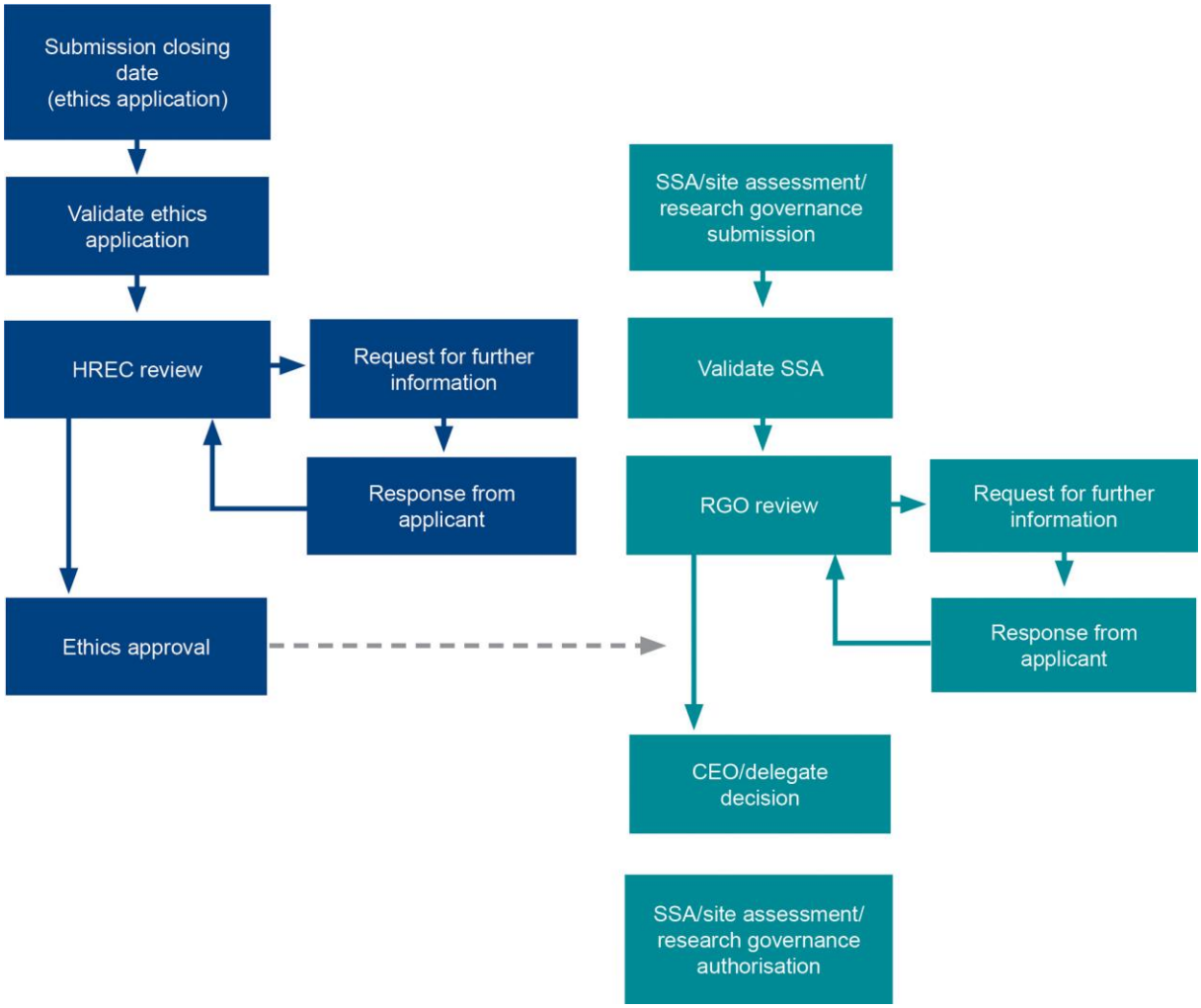
The approval requirements for clinical trial conduct in Australia align with international best practice and the strong regulatory framework determined by the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP). They are underpinned by a framework of guidelines that all research in Australia must comply with, including the *National Statement on Ethical Conduct in Human Research (updated 2018)*and *Australian Code for the Responsible Conduct of Research*, maintained by the NHMRC, and guidance specific to clinical trials of medicines and medical devices[9]. These guidelines are implemented through the following clinical trial principles:

- (*mandatory for all human research*) **approval by a Human Research Ethics Committee (HREC)** according to the National Statement on Ethical Conduct in Human Research (the National Statement);
- (*mandatory for all human research*) **Site-Specific Assessments (SSA)** are undertaken at each trial site by local governance offices, to confirm the capability of the site to conduct the trial;
- (*if the trial uses an unapproved therapeutic good or identifies an adverse event during implementation*) require **notification to the Therapeutic Goods Administration (TGA)**; and
- (*required for all human research according to the National Statement*) **registered** on a publically available WHO primary clinical trials registry such as Australian New Zealand Clinical Trials Registry (ANZCTR).

Diagram 1 illustrates the process framework in the NAS Framework (HREC review and SSA/site assessment), which occur with separate administration but in a parallel timeframe. The approval process begins with the submission of an ethics application to the reviewing HREC, and in most cases, parallel submission of the SSA/site assessment. As part of each process, there is allowance for the reviewing administrator to request further information from the applicant (lead investigator/trial coordinator/sponsor/Contract Research Organisation (CRO)). The end point of the approval process is the authorisation of SSA/site assessment at the trial site and this can then trigger the initiation of a trial at that site. As noted above, there are also requirements to register clinical trials, and where applicable, notify TGA of trial conduct prior to commencement.

[9] Clinical trials of medicines and medical devices must comply with *Note for guidance on good clinical practice* (CMP/ICH/135/95), and clinical trials of medical devices with *ISO 14155:2011 Medical devices*.

***Diagram 1**: Clinical trial regulatory processes: Ethics and SSA/site assessment*



NAS Framework

The NAS Framework, as endorsed by all Health Ministers in 2015, comprises the eight metrics agreed by all jurisdictions as essential to evaluate the success of clinical trials improvement initiatives, and to promote Australia as a preferred global destination. These include metrics to measure the clinical trial activity (number, phase and sponsor type), timelines for trial start-up as measured by the timelines for two mandatory approval processes for clinical trials to be conducted in Australia (ethics and SSA/site assessment), and associated recruitment and investment levels.

NAS Metrics

National Clinical Trial Activity

Metric 1: Number of new trials per trial phase (by trial type 'medicine' only)

Metric 1a: Number of new clinical trials per sponsor type

Regulatory Timelines - total

Metric 2: Overall study start-up timeline (regulatory timeline) – Without Clock

Metric 3: Ethics and SSA/site assessment approval timeline – With Clock

Regulatory Timelines - components

Metric 4: Ethics approval timeline (4a) Without Clock (4b) With Clock

Metric 5: SSA/site authorisation timeline - Without Clock - (5a) from HREC approval date (5b) from validation date

Recruitment/Investment

Metric 6: Trial Recruitment Actual/Planned

Metric 7: Site Recruitment: Actual/Planned

Metric 8: Total inbound (internal and external) investment annually (FY) Actual/Planned

Scope

The current scope of the NAS Framework – and this NAS report – are all clinical trials conducted in public health organisations in Australia. This also includes trials managed by universities that involve clinical treatment within public health organisations[10]. Some trials reported in NAS may include trial sites at some private health organisations and universities that accept ethical review but these are not reported in the SSA/Site assessment data due to lack of information capture. 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's information management platform.

Within the public health system, the NAS captures all trial types, including trials that are funded by commercial organisations such as pharmaceutical or device companies and non-commercial, including Investigator Initiated, Collaborative Group, Institution and other clinical trials. NAS also captures both multi and single-site studies.

In 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

[10] As researchers will either have both clinical and university appointments or are required to seek ethics review through the public health institution.

clinical trials in public health organisations. The CTPRG is also working 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.

Benchmarks

The CTPRG is working to establish agreed national benchmarks for the NAS Framework. Until these are finalised, the NAS metrics in this report are compared against commonly used domestic or international benchmarks, where available.

The benchmark often used by industry for time to recruit the first patient into a trial (which NAS Metric 2 provides a proxy for) is 12 weeks (84 days). The NMA has a benchmark of 60 days for ethics approval 'With Clock' (Metric 4b). Benchmarks for the time to process ethics applications in Europe and England is 60 days; 30 days in United States and Canada; and 145 days in China. In South Korea, there is a 30 working-day benchmark for clinical trial protocol approval, and in New Zealand ethical review (including a decision) must be undertaken within 35 calendar days[11]. The degree to which these benchmarks are met outside of Australia is not within the scope of the current NAS Framework or reports.

[11] *Clinical Trials Governance Framework – Literature Review* (unpublished), ACSQHC, June 2018

Metrics Report

Metric 1: Number of new trials per trial phase

For the annual period 1 July 2016 – 30 June 2017 there were 807 new clinical trials reported from six (6) jurisdictions that submitted data. Previous NAS reporting periods had totals of 839 (2014-15) and 861 (2015-16) new trials.

Of these new trials, trial phase was reported for 375 (of a potential 807) trials in 2016-17, and a similar proportion in 2015-16 and 2014-15 (Figure 1)[12]. The low response is largely the result of some jurisdictions that do not report or have incomplete reporting of 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 and Definitions for a fuller explanation of trial phase.

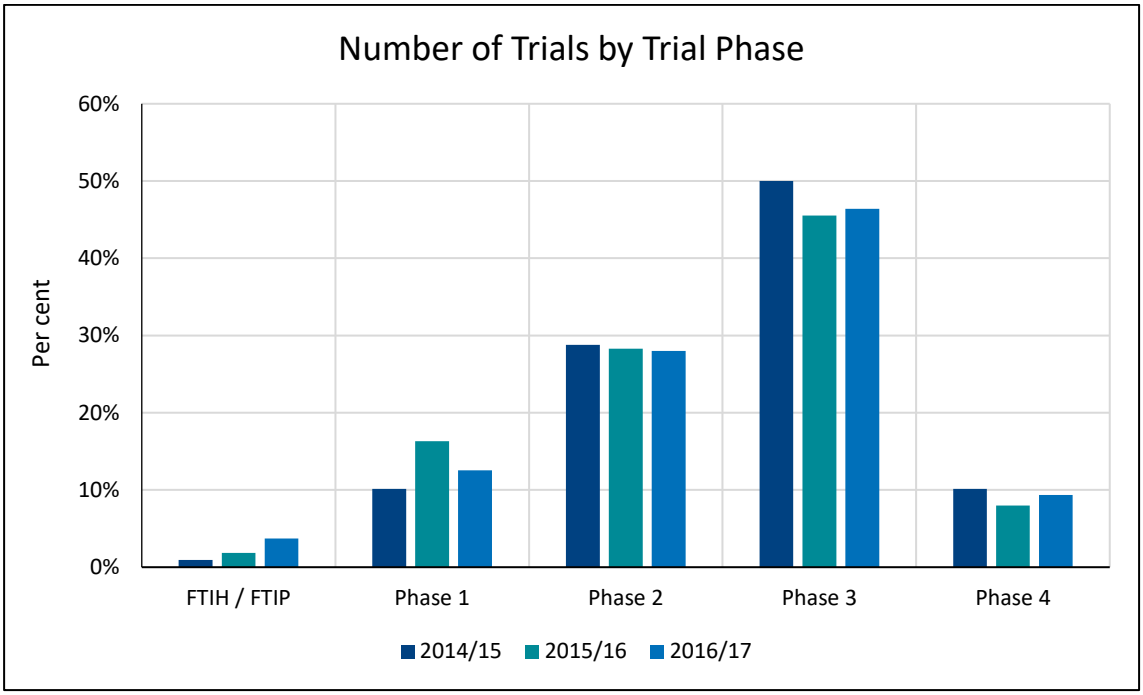
As shown below, Phase 3 trials were the majority, followed by Phase 2 trials. Phase 1 represented 10-18 per cent, and Phase 4 were 9-10 per cent of trials undertaken across these reporting periods. This suggests that the majority of trials in public hospitals were Phase 2 and 3. A notable increase in first time in human/patient occurred from 2015-16 and was maintained.

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

	2014-15		2015-16		2016-17	
Trial phase	**No.**	**Per cent**	**No.**	**Per cent**	**No.**	**Per cent**
FTIH / FTIP	3	1	10	4	14	4
Phase 1	32	10	43	18	47	13
Phase 2	91	29	62	25	105	28
Phase 3	158	50	107	43	174	46
Phase 4	32	10	25	10	35	9
Total	316	100	247	100	375	100

[#]*Note: Jurisdictions represented are: Australian Capital Territory, 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).*

[12] Trial phase reported for trial type 'medicine' only.



[#]Note: Jurisdictions represented are: Australian Capital Territory, Northern Territory, Queensland, South Australia and Victoria.

The clinical investigations pathway for medical technology/devices differs from the clinical trial pathway for medicines. While Phases I, 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 endpoints.

There is no data recorded for device trial Stages but overall there were 84 device trials reported in 2015-16 (12 per cent of total trials).

The majority of clinical trials were multi-site trials occurring across jurisdictions and within a jurisdiction, the data was 70 per cent in 2014-15, 69 per cent in 2015-16 and 66 per cent in 2016-17.

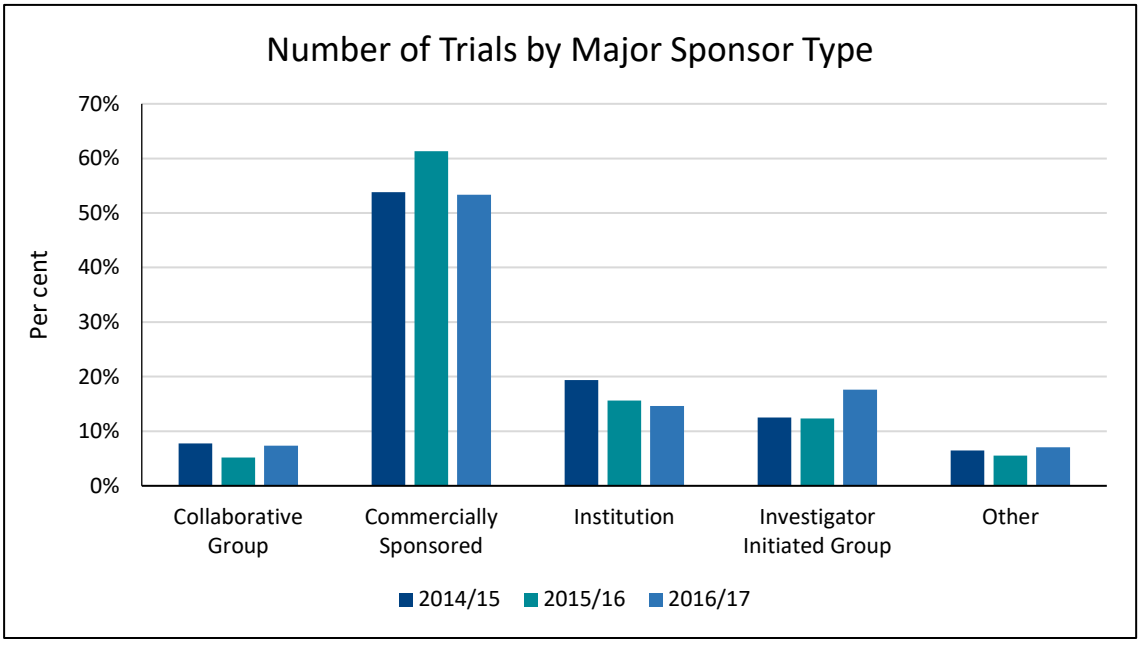
1a Number of new trials per sponsor type

Commercially sponsored clinical trials were predominant in Australia and reported data indicated there were 54 per cent (2014-15), 61 per cent (2015-16) and 53 per cent (2016-17) sponsored by industry. Investigator centred trials, including collaborative groups, investigators and institutions represent between 33 and 40 per cent of trials.

Figure 2 *Number of Clinical Trials by sponsor type*

	2014-15		2015-16		2016-17	
Sponsor Type	No.	Per cent	No.	Per cent	No.	Per cent
Collaborative Group	59	8	39	5	54	7
Commercially Sponsored	408	54	463	61	393	53
Institution	147	19	118	16	108	15
Investigator Initiated Group	95	13	93	12	130	18
Other	49	6	42	6	52	7
Total	758	100	755	100	737	100

[#]*Note: Jurisdictions represented are: Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia and Victoria. The 'Sponsor Type' field is not reported for some individual trials. The number of trials represents a high proportion of the overall number of clinical trials for each year.*



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.

Sponsors have emphasised that clinical trial site selection globally depends on timelines, for both the regulatory approval, site authorisation, study start up and first patient recruited. 'Time to first patient recruited' is the most widely accepted international indicator for efficiency of trial start-up. While 'time to first patient recruited' is the long-term goal for inclusion in NAS, and mechanisms to collect this are being considered and actively progressed, data is not currently available to measure this in Australia. As an interim, **Metric 2** provides a proxy for study start up timeline by measuring the timeline for the two mandatory approval/regulatory processes for clinical trials in Australia: from ethics application submission closing date to date of first SSA/site authorisation, noting that these processes should be completed concurrently but some jurisdictions may be an exception.

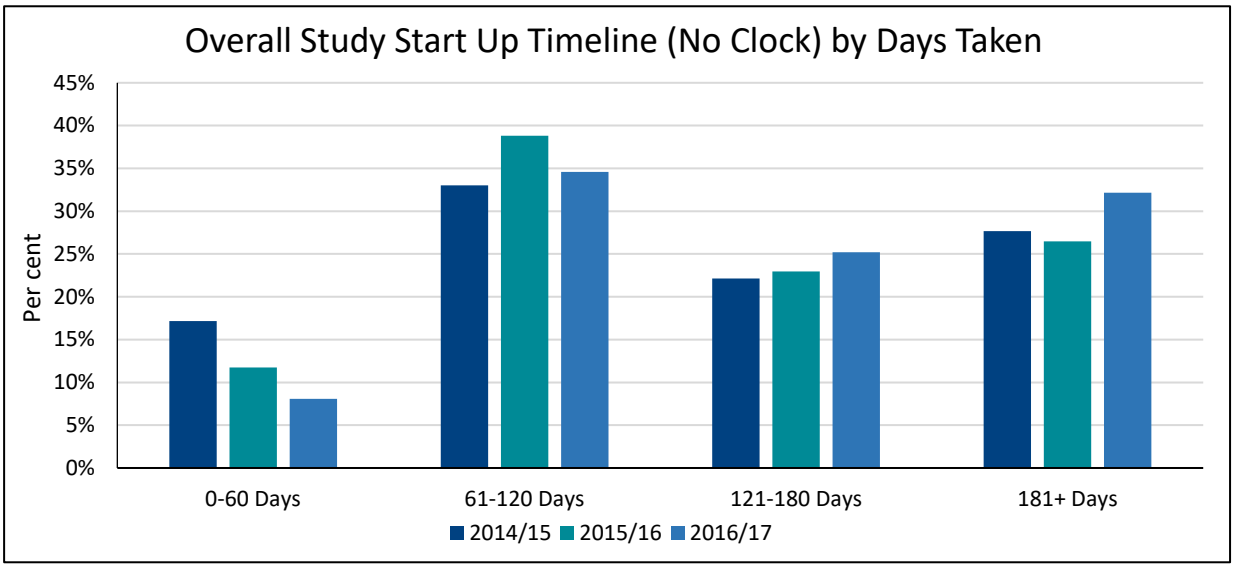
Over these reporting periods, there were over 500 clinical trials reported for this measure. The period commences at ethics submission and the date for the first SSA/Site assessment authorisation is the end-point. This measure gives a real indication to sponsors of the time from submission of ethics 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 (84 days). The proportion of clinical trials achieving the international metric (84 days) has declined from 31 per cent in 2014-15 to 27 per cent in 2015-16 and 21 per cent in 2016-17[13] , 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.

Between 8 and 17 per cent of clinical trials completed the regulatory process in 60 days or less, and a total of and 31.5 (2014-15), 42 (2015-16) and 51 (2016-17) per cent of trial applications were 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. The per cent of trials being processed within the various time intervals is shown over a three-year period. Reduction in this metric time relating to SSA/site assessment is likely to be achievable with improved adherence to jurisdiction's policy at health services. However, industry do stress that consistency and predictable timelines is primarily important for their planning and the metrics over three years are within a tight range.

[13] As the NAS metric proxy is likely to be an under-estimate of the time to first patient recruited (as it excludes the time from approval to patient recruitment), these proportions are likely to be over-estimates.

Figure 3 *Overall estimated trial study start-up*



#Note: Jurisdictions represented are: Australian Capital Territory, New South Wales, Queensland, South Australia and Victoria.

Estimated study start-up mean and standard error has been calculated across four time intervals ranging from 0-60 days up to 180+ days. The trial number in each time interval is shown in brackets.

The longer ethics and SSA/Site assessment timeline trend above is also reflected in the average time for both ethics approval and the first SSA authorised. Data aggregated for each year indicates that the average time for ethics review and authorisation of the first SSA ranges from 157.2 ±5.9 days (2014-15), 150.2 ±4.7 days (2015-16) to 160.2 ±4.3 days (2016-17) (see below).

Table 1: *Overall mean estimated trial study start-up*

Year	Time (days; mean±SE)				
	0-60	**61-120**	**121-180**	**181+**	**Total**
2014/15	31.5 ± 2.3 (n=93)	91.2 ± 1.2 (n=179)	144.9 ± 1.5 (n=120)	323.7 ± 13.0 (n=150)	157.2 ± 5.9 (n=542)
2015/16	42.0 ± 1.9 (n=63)	91.3 ± 1.2 (n=208)	144.9 ± 1.5 (n=123)	289.1 ± 10.2 (n=142)	150.2 ± 4.7 (n=536)
2016/17	39.4 ± 2.2 (n=43)	92.0 ± 1.3 (n=184)	148.1 ± 1.4 (n=134)	273.4 ± 7.1 (n=171)	160.2 ± 4.3 (n=532)

#Note: Some clinical trials did not meet the criteria for this metric as they were either approved but an SSA was not yet authorised, or no SSAs were processed in NT.

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

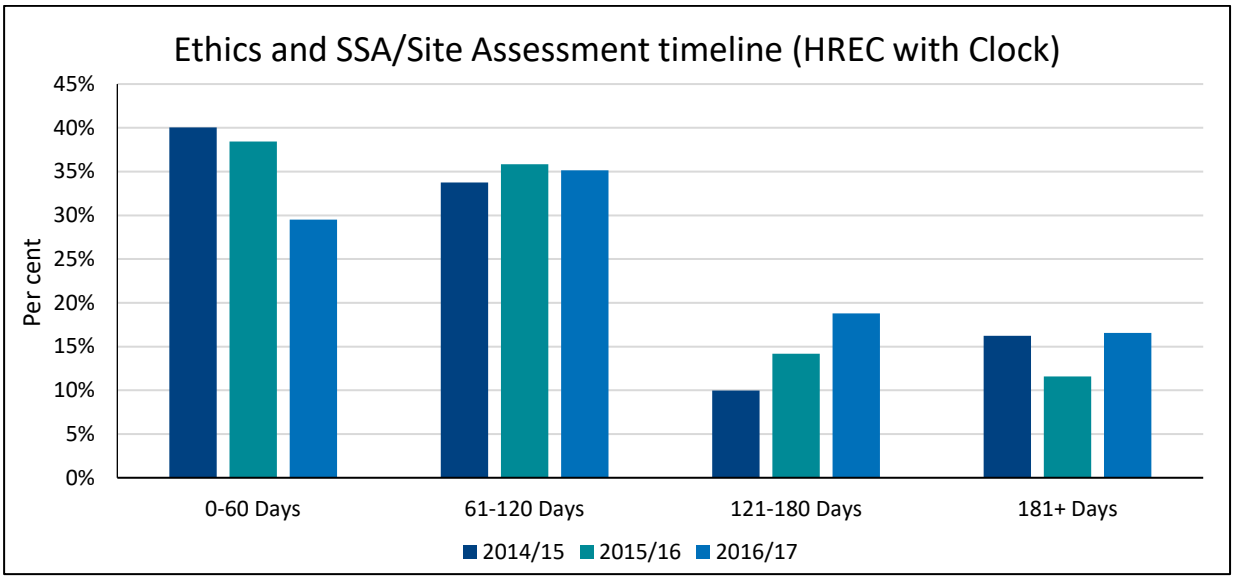
This reflects overall study start up but it has an administrative clock which distinguishes the responsibility for time between the administering organisation and the investigator/trial coordinator/sponsor/CRO. The start of the process is the submission closing date and the completion is the date of 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 deducted when the responsibility for the ethics application is with the investigator/trial coordinator, sponsor/CRO. Therefore this is a measure of administration time.

The majority of trials complete the process for ethics review and site assessment within 60 or 120 days. There is a trend to increased time in the 2015/16 and 2016/17 years, with the proportion of clinical trials completing the two processes within 60 days declining from 40 per cent in 2014-15, 38 per cent in 2015-16 to 30 per cent in 2016-17.

This measure reflects the administrative time only and Metric 2 (above) also showed movement to increased times for study start-up.

Figure 4 *Ethics and SSA/Site Assessment timeline (With Clock)*



[#]Note: Jurisdictions represented are: Australian Capital Territory New South Wales, Queensland, South Australia and Victoria. Some clinical trials did not meet the criteria for this metric as they were either approved but an SSA was not yet authorised or some jurisdictions do not process an SSA.

The mean and standard error for each time period is shown below. Within 0-60 days the mean time ranged from 32.8 ±1.2 to 39.2 ±1.1 days. Overall, the total trials in each year had a time-range between 101.9 ±4.2 and 114.7 ±3.8 days for the administrative process for ethics and first site assessment.

The time difference between Metric 2 and 3 is due to the investigator/trial coordinator/ sponsor/CRO being responsible for providing an ethics response back to administrators. With no clock the timelines range between 157.2 ±5.9 days (2014-15), 150.2 ±4.7 days (2015-16) to 160.2 ±4.3 days (2016-17). Approximately an additional 50 days is due to delays in responding to administrators.

Table 2: *Ethics and SSA/Site Assessment mean timeline (With Clock)*

Year	Time (days; mean±SE)				
	0-60	61-120	121-180	181+	Total
2014/15	32.8 ± 1.2 (n=217)	88.2 ± 1.3 (n=183)	149.9 ± 2.2 (n=54)	340.9 ± 17.5 (n=88)	113.2 ± 5.4 (n=542)
2015/16	37.3 ± 1.0 (n=206)	85.3 ± 1.2 (n=192)	146.2 ± 2.1 (n=76)	313.5 ± 17.2 (n=62)	101.9 ± 4.2 (n=536)
2016/17	39.2 ± 1.1 (n=157)	86.9 ± 1.3 (n=187)	147.7 ± 1.8 (n=100)	270.9 ± 8.8 (n=88)	114.7 ± 3.8 (n=532)

Administration of the ethics/HREC and authorisation of the first SSA/site assessment were completed within 60 days for 38 per cent of trial applications and within 120 days for 74 per cent in 2015-16. In 2016-17 there were 30 per cent under 60 days and 65per cent were processed in less than 120 days.

Metric 4: Ethics approval timeline

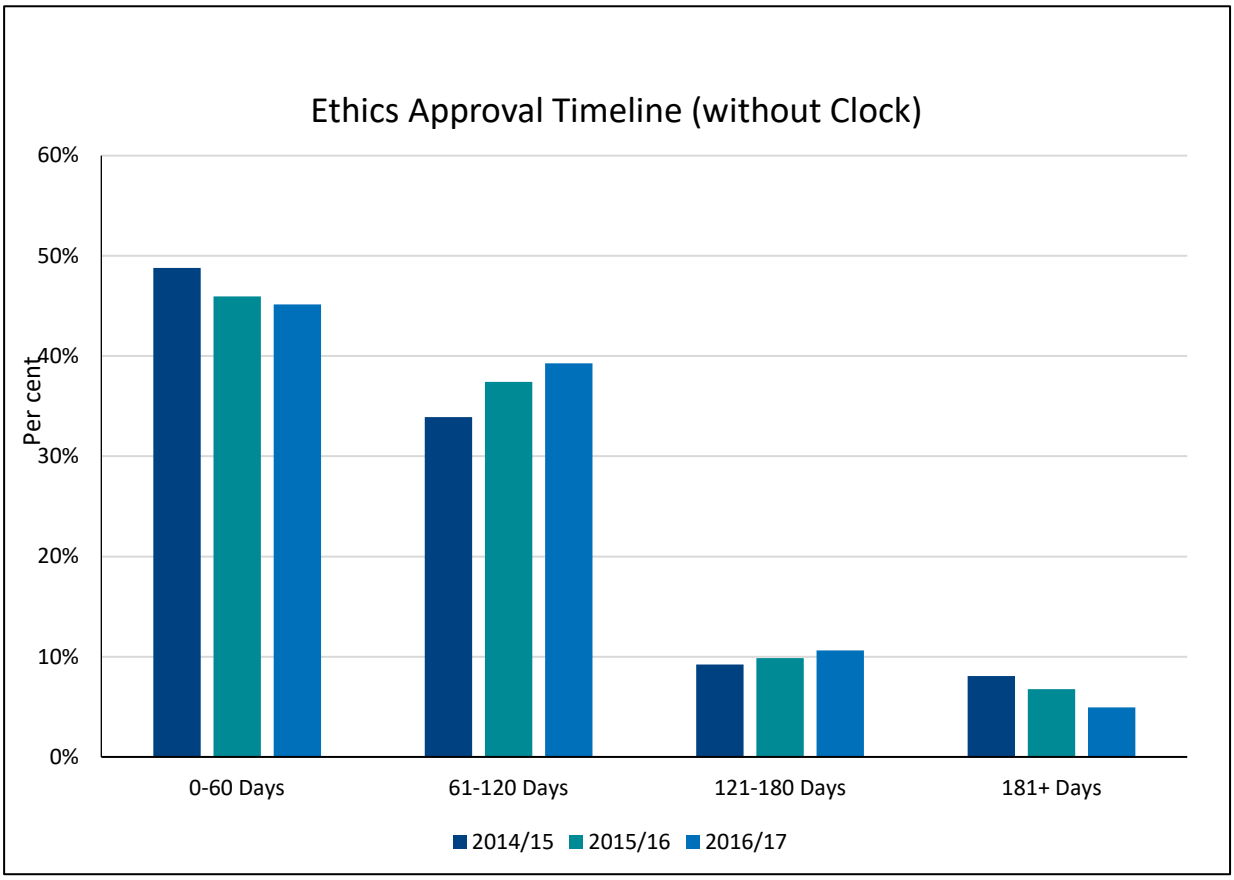
4a HREC approval timeline - 'Without Clock'

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 ethics review where there is a request for information from investigator/trial coordinator/ sponsor/CROs.

There is a trend of less trial applications being reviewed within 60 days and a rise in the 61-120 day time interval, indicating that the ethics times to approval were taking longer in 2015/16 and 2016/17. With no clock operating this may be due to ethics administration or to longer response times for information requested from investigator/trial coordinator/sponsor/CROs.

Without operation of an administrative clock ethics review was completed within a 60 day period in 49 per cent (2014-15), 46 per cent (2015/16) and 45 per cent (2016/17) of trial applications. Sixty days is a commonly used benchmark for the ethics process in Australia and the United Kingdom.

Figure 5 *Ethics timeline (Without Clock)*



[#]Note: Jurisdictions represented are: Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia and Victoria.

The mean and standard error for each time period is shown below. Within 0-60 days the mean time ranged from 35.4 ±1.0 to 38.5 ±0.8 days. Overall, the total trials in each year had a time-range between 77.7 ±2.2 and 86.6 ±4.4 days for the ethics review process.

Table 3 *Ethics mean timeline (Without Clock)*

Year	Time (days; mean±SE)				
	0-60	**61-120**	**121-180**	**181+**	**Total**
2014/15	35.4 ± 1.0 (n=302)	85.4 ± 1.1 (n=210)	148.7 ± 2.3 (n=57)	330.0 ± 37.3 (n=50)	86.6 ± 4.4 (n=619)
2015/16	38.5 ± 0.8 (n=312)	85.4 ± 1.1 (n=254)	142.4 ± 2.1 (n=67)	273.8 ± 13.6 (n=46)	82.2 ± 2.6 (n=679)
2016/17	38.5 ± 0.8 (n=293)	83.5 ± 1.0 (n=255)	143.6 ± 2.0 (n=69)	248.9 ± 12.6 (n=32)	77.7 ± 2.2 (n=649)

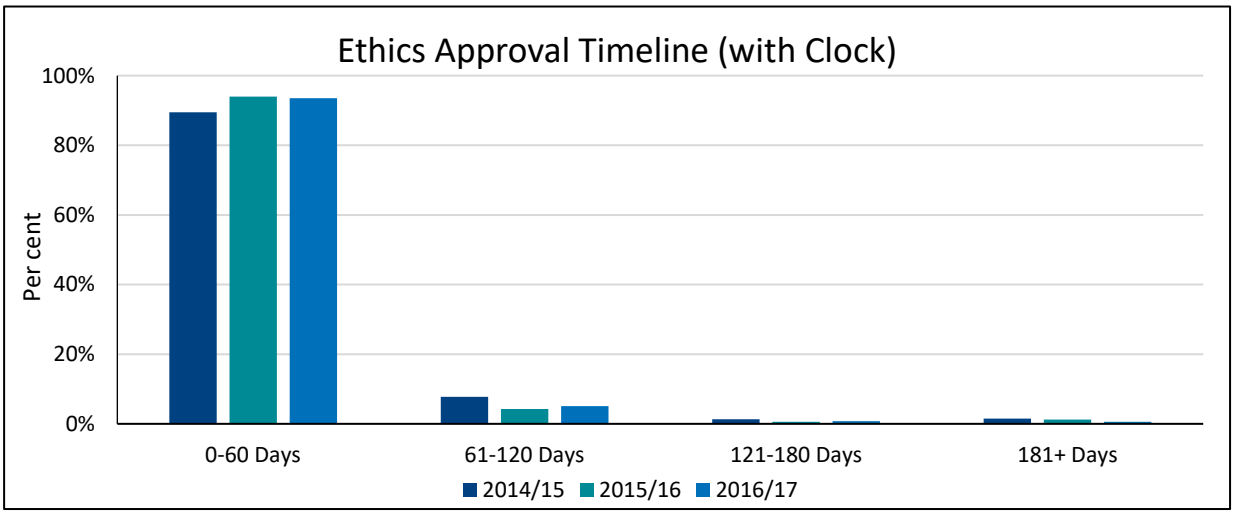
4b HREC approval timeline 'With Clock'

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

'With Clock' allows measurement of 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. This measures the administrating organisations' timeliness for the ethics process.

Between 89 (2014/15) and 94 per cent (2015/16 and 2016/17) of ethics applications were reviewed and approved within a 60 day benchmark, with operation of an administrative clock. This is a very high level of performance when complexity of clinical trials is considered.

Figure 6 *Ethics timeline (With Clock)*



#*Note: Jurisdictions represented are: Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia and Victoria. Of the applications meeting the criteria, some clinical trials were eliminated because a 'with clock' function was not available and administrative time could not be calculated.*

The mean time for ethics review in the 0 to 60 days timeframe was between 24.5 (2014/15) and 25.7 (2016/17) days and indicates timely ethics review and administration. The total trial applications, over all time intervals, had a mean of 38.2 ±3.6 days (2014/15) and 31 ±1.4 days (2015/16) for the ethics review process. A small number of trial applications had considerably longer review times and these outliers were likely due to specific circumstances and un-associated with the general review process.

Table 4 *Ethics mean timeline (With Clock)*

Year	Time (days; mean±SE)				
	0-60	61-120	121-180	181+	Total
2014/15	24.5 ± 0.5 (n=554)	82.1 ± 2.4 (n=48)	152.9 ± 6.6 (n=8)	546.0 ± 176.0 (n=9)	38.2 ± 3.6 (n=619)
2015/16	24.8 ± 0.5 (n=638)	76.7 ± 2.6 (n=29)	157.0 ± 6.4 (n=4)	301.6 ± 30.6 (n=8)	31.0 ± 1.4 (n=679)
2016/17	25.7 ± 0.5 (n=607)	82.9 ± 3.1 (n=33)	137.8 ± 1.2 (n=5)	300.5 ± 39.5 (n=4)	31.2 ± 1.2 (n=649)

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

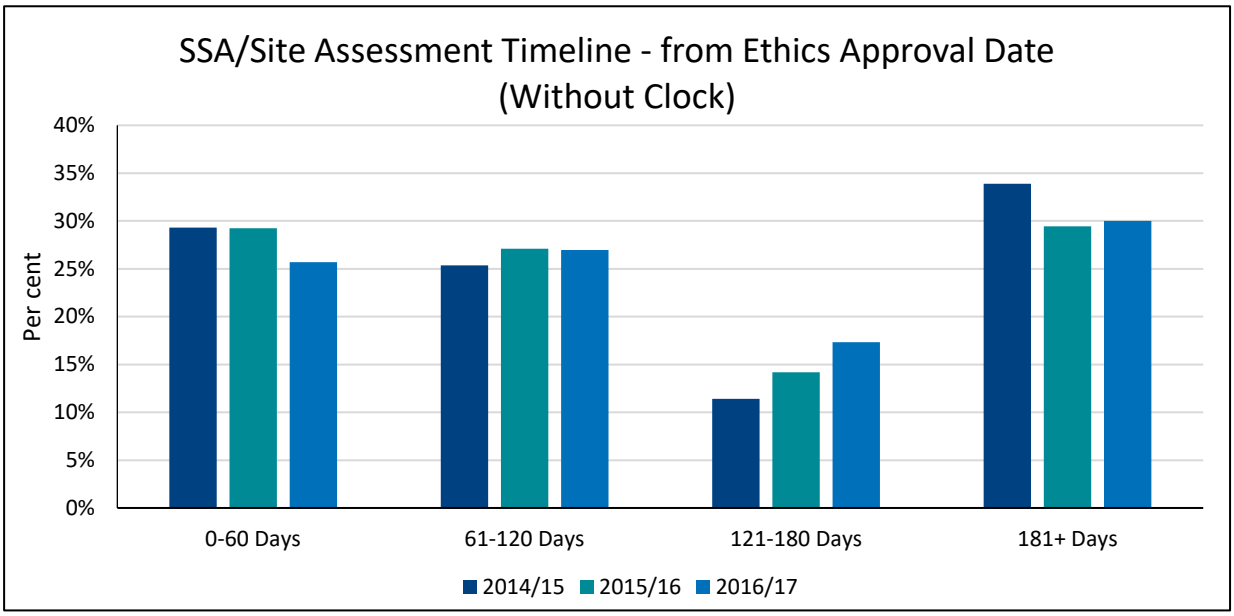
Improvement in SSA/Site assessment is necessary to position Australian clinical trials to be globally competitive. The timeline for the SSA site authorisation process can be measured from different start points. For instance from ethics/HREC approval date (Metrics 5a) or from SSA validation date (Metric 5b) (see Explanatory Notes). It is important to note that Metric 5 measures time for approval of *all* trial sites, compared to Metric 2 and 3 that measure time to approval of the *first* site only.

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.

Metric 5a indicates that approximately 30 per cent of SSAs were authorised within 60 days of ethics approval. The proportion has declined slightly from 29 per cent in 2014-15 and 29 per cent in 2015-16 to 26 per cent in 2016-17. This suggests that the investigator/trial coordinator may be delayed in preparing the SSA documentation, either due to lack of resources and time or the research governance officer delays the process until ethics approval is completed. A proportion of very long times (180^{+}days) may occur when additional trial sites are added later or due to other complexities associated with trials.

Figure 7 *SSA/Site Assessment timeline – from Ethics Approval Date (Without Clock)*



Note: Jurisdictions represented are: Australian Capital Territory, New South Wales, Queensland, South Australia and Victoria. The ethics application must be approved before an SSA/site assessment can be authorised/completed.

Although the proportion of SSA's authorised within 60 days decreased over the reporting period, the average (mean) number of days decreased, from 201.3±5.9 days in 2014-15 to 146.9±2.9 days in 2016-17 (see below).

Note that in Metric 2 (without clock) the overall study start-up times were shorter as this calculation uses the first authorised SSA only (n=532 to 542). In Metric 5a when all SSA/Site Assessment times are measured authorisations take longer and have a broad distribution across the time intervals. SSAs/site assessments in the case of multi-centre trials may be slower and could be an area of focus for performance improvement at trial sites.

As table 5 below indicates, this is largely due to the decrease in the average time of SSA authorisations with approval times over 181 days.

Table 5 *SSA/Site Assessment mean timeline – from Ethics Approval Date (Without Clock)*

Year	Time (days; mean±SE)				
	0-60	**61-120**	**0-60**	**181+**	**0-60**
2014/15	29.2 ± 0.8 (n=512)	86.8 ± 0.8 (n=443)	147.7 ± 1.2 (n=199)	453.8 ± 11.3 (n=592)	201.3 ± 5.9 (n=1746)
2015/16	29.8 ± 0.8 (n=505)	88.0 ± 0.8 (n=468)	149.2 ± 1.0 (n=245)	387.0 ± 9.2 (n=508)	167.7 ± 4.5 (n=1726)
2016/17	31.4 ± 0.9 (n=421)	89.4 ± 0.9 (n=442)	149.8 ± 1.0 (n=284)	295.6 ± 4.1 (n=492)	146.9 ± 2.9 (n=1639)

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

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

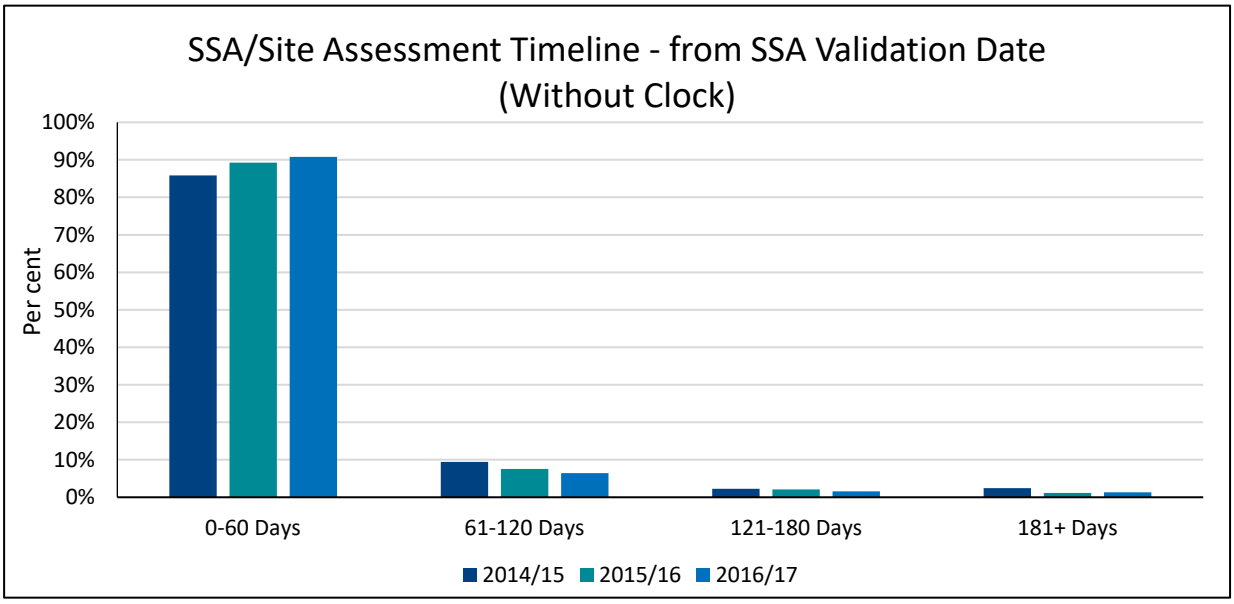
There is no deduction of time intervals (clock stop and re-start) for the SSA/site assessment process. There is inconsistent use of the stop and re-start clock function across jurisdictions and sites and therefore the clock was not used in the SSA process measure for this report.

The action to validate an SSA/site assessment application has no formal 'start' date and an SSA/site assessment application may be submitted and require further additional documentation before review and sign-off by the authorising organisation.

Measuring the time to process an SSA/Site assessment application from validation indicates that in most cases (over 86 per cent) the process is completed within 60 days. This is a measure of administrative time only. When compared to Metric 5a (above) this suggests that submission of applications is significantly delayed after the ethics approval date and/or the processes were not being administered concurrently. The ethics application must be approved before an SSA can be authorised/completed.

Using a measure from SSA validation date **(Metric 5b**) shows the majority were processed by the research governance officer within 60 days, from 86 per cent in 2014-15 to 89 per cent in 2015-16 and 91 per cent in 2016-17.

Figure 8: SSA/Site Assessment timeline – from SSA Validation Date (Without Clock)



Note: Jurisdictions represented are: Australian Capital Territory, New South Wales, Queensland, South Australia and Victoria.

The time taken to authorise an SSA/Site assessment once validated is less than 60 days in the majority of cases with a mean time between 14.2 ±0.4 days (2014/15) and 12.7±0.4 days (2016/17). Over all time intervals, SSAs/site assessments were processed within a mean of 32.7±1.7 days (2014/15) and 23.0±1.1 days (2016/17).

These times indicate that the site assessment process is short but as Metric 5a shows, large variation and time delays occur during and after ethics approval rather than these two processes being concurrent.

Table 6 *SSA/Site Assessment mean timeline – from SSA Validation Date (Without Clock)*

Year	Time (days; mean±SE)				
	0-60	**61-120**	**121-180**	**181+**	**Total**
2014/15	14.2 ± 0.4 (n=1568)	83.8 ± 1.3 (n=172)	145.4 ± 2.4 (n=41)	378.8 ± 35.3 (n=45)	32.7 ± 1.7 (n=1826)
2015/16	13.0 ± 0.4 (n=1549)	82.9 ± 1.4 (n=131)	143.1 ± 2.9 (n=36)	254.0 ± 21.4 (n=20)	23.8 ± 1.0 (n=1736)
2016/17	12.7 ± 0.4 (n=1474)	83.6 ± 1.5 (n=104)	146.9 ± 3.6 (n=25)	298.6 ± 20.2 (n=21)	23.0 ± 1.1 (n=1624)

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.

Explanatory Notes

A1. Glossary

Glossary terms	Definitions
Administrative clock	A number of NAS metrics include the concept of an 'administrative clock', which allows distinction of responsibility for time between the administering organisation and the investigator/trial coordinator/sponsor/CRO (see also 'With Clock'/'Without Clock' below).
Authorisation date (SSA)	Authorisation decision date for a SSA/site application given by the site organisation's CEO/delegate and recorded in the jurisdiction's electronic information platform, such as Ethics Review Manager (ERM).
Clinical trial governance	Clinical trial 'governance' is the term used for institutional review or site-specific assessment (SSA). From a broader perspective, ethics-approval form parts of the overall governance framework that ensures the compliance, accountability and transparency of research activity at a site.
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	A 'collaborative group' is an academic and/or non-commercial collaborative research group responsible for sponsoring, initiating, managing, developing and coordinating a research 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.

Glossary terms	Definitions
Metrics	Any type of measurement used to gauge some quantifiable component of an entity's performance.
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 I clinical trials involve the first administration of the medicine to humans, usually to small numbers of healthy volunteers. Phase I 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 (eg. tablet, liquid or injection) and help determine the appropriate doses for later studies. Phase I clinical trials are usually undertaken in centres appropriately equipped for the specialised monitoring and the high degree of surveillance needed.
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 2 clinical trials indicate the medicine has potential benefit that outweighs the hazards.
Phase 4	Phase 4 clinical trials are those clinical trials undertaken in Australia after the medicine has been approved (either in, or external to Australia) for the treatment of a particular disease. Phase 4 clinical trials may relate to a product that is registered in another country at the time the trial is being conducted in Australia. Phase 4 trials may be a follow-on study from a previous trial and the rationale is that the data from the trial is being used to support a post marketing study. Phase 4 clinical trials are also undertaken to further investigate the use of the medicine in the normal clinical setting of the disease, as this may differ quite markedly from the conditions under which the other clinical trials were conducted. This includes post marketing surveillance studies.
Public Health Organisation/ Institutions	A statutory health corporation or affiliated health organisation in respect of its recognised establishments and recognised services.

Glossary terms	Definitions
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	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'. In line with the Good Clinical Practice guidelines, the sponsor type relates to the risk-owner, not the provision of funding.
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	Metrics provided 'With Clock' (such as Metric 3) are a measure of the time taken for processing of the application by the administering body only. 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 Clock	Metrics provided 'Without clock' are a measure of the total timeline – including both the time taken to process the application by the administering body, and the time to respond to queries by the investigator/trial coordinator/sponsor/CRO.

A2. NAS Metric definitions

National clinical trial activity

Metric 1 provides the total number of new clinical trials, by trial phase. In addition, **Metric 1a** provides the number of new clinical trials by major sponsor type (see Glossary above).

Regulatory Timelines – total

Sponsors have emphasised that clinical trial site selection globally depends on timelines, for both the regulatory approval, site authorisation, study start up and first patient recruited. Time to first patient recruited is the most widely accepted international indicator for efficiency of trial start-up.

While 'time to first patient recruited' is the long-term goal for inclusion in NAS, data is not currently available to measure this in Australia. As an interim – **Metric 2** provides a proxy for study start up timeline by measuring the timeline for the two mandatory approval/regulatory processes for all clinical trials in Australia: from ethics application submission closing date to date of first SSA/site authorisation, noting that these processes are sometimes completed in parallel (see Diagram 1). SSA/site assessment occurs at each trial site where authorisation to conduct the trial must be provided.

It is important to note that as the NAS metric proxy is likely to be an under-estimate of the time to first patient recruited (as it excludes the time from approval to patient recruitment), these proportions are likely to be over-estimates.

Timelines for compliance with a regulatory body such as the Therapeutic Goods Administration are currently not included in the NAS metrics, as it has not been feasible to use the date of Clinical Trial Notification or Clinical Trial Exemption (CTN or CTX) notification as an end point. Mechanisms to collect data on first patient recruited are being considered and actively progressed.

Metric 3 also measures the timeline for the entire regulatory process (ethics + SSA/site assessment), however differs from Metric 2 as it introduces the use of an administrative clock.

Regulator Timelines – components

Metric 4 and **Metric 5** each analyse timelines for one of the two components of the regulatory process – ethics and SSA/site assessment (see Diagram 1).

Metric 4 measures the time taken for ethics/HREC approval alone, both 'Without Clock' (Metric 4a), and 'With Clock' (Metric 4b). This includes submission closing date, validation, HREC review, request for further information, responses from applicants, and final ethics approval. 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.

Metric 5 measures the time take for SSA/site assessment alone. This includes submission, validation, Research Governance Officer (RGO) review, request for further information, responses from applicants, CEO/delegation decision, and SSA/site assessment/research governance authorisation. The metric measures the total timeline (ie. 'Without Clock' only), as there is no prescribed submission date for SSA processes, and therefore no defined start point. 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[14]/CRO. In addition, research governance officers do not uniformly stop and re-set the clock in processing SSA applications.

Given the lack of a prescribed submission date/formal start date, the following two process steps are used as proxy starting points for NAS analysis:

- Metric 5a. The ethics/HREC approval (date) 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 5b. SSA validation date is the first date that may appear in electronic information systems 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.

Recruitment/Investment

The CTPRG identified capacity to track changes in trial recruitment and investment as important metrics in measuring improvements in Australia's competitiveness as a preferred destination for clinical trials, and therefore included the following three metrics in the NAS Framework:

- Metric 6: Trial Recruitment Actual/Planned
- Metric 7: Site Recruitment: Actual/Planned
- Metric 8: Total investment annually (FY) Actual/Planned

These metrics have not been provided to date through annual NAS reporting, due to the lack of reliable and accessible data at jurisdiction level. However, CTPRG members have committed to provision of these metrics through the $7 million *Encouraging More Clinical Trials in Australia* Budget Measure (see above), which in turn will be enabled for a number of jurisdictions through recent upgrades to electronic information platforms.

A3. NAS Reporting

As identified above, annual NAS reporting is a key deliverable of the CTPRG. Development of annual reports, data definitions, data collection templates and analysis has been led by Victoria, in collaboration with contributing jurisdictions, and as agreed by CTPRG.

In May 2016, AHMAC endorsed the *First National Activity Report on Commercially Sponsored Clinical Trials in Australian Public Health Organisations* (NAS 1 Report). It provided data on total clinical trial activity, and timelines for ethics and SSA/site assessment (NAS Metrics 1 – 5) for all commercially sponsored clinical trials in public health organisations, in six jurisdictions[15] for the year 2014-15. The NAS 1 Report represented the first attempt to measure national clinical trial

[14] A sponsor may be an institution, investigator or a commercial industry company which has overall responsibility for the trial
[15] Australian Capital Territory, New South Wales, Northern Territory, Queensland, South Australia and Victoria.

activity, an important step in understanding Australia's performance in the clinical trials sector, and reflected the committed cooperation of all jurisdictions. As the NAS 1 Report reflected a new process and data collection methodology, it was not intended for publication. In the current NAS 3 Report, the 2014-15 result reflect all clinical trials (including non-commercial).

The *Second National Aggregate Statistics Report on Clinical Trials in Australia (NAS 2 Report) was* approved for publication by AHMAC, and published in June 2017. It included data from five jurisdictions[16] for the year 2015-16. Like the NAS 1 Report, the NAS 2 Report included data for clinical trials conducted in public health organisations, but was expanded to include trials from *all* sponsor types (not just commercially sponsored trials). In addition to the metrics provided in the NAS 1 Report (data on total clinical trial activity, and timelines for ethics and SSA/site assessment (NAS Metrics 1 – 5)), the NAS 2 Report also disaggregated trials by sponsor type (NAS Metric 1a).

It is important to note that the published NAS 2 Report represents interim 2015-16 data, and therefore may differ slightly from the final (revised) 2015-16 data presented in this current NAS 3 Report. Interim NAS data is produced immediately after a reporting period (FY), and therefore may miss timelines for the small number of trials that commenced, but did not complete, the approval process in the reporting period. Final NAS data is collated up to a year later, in order to also capture all timelines for those trials. To minimise potential confusion from two data sets being circulated for the same reporting period, only final data will be reported publically from NAS 3 onwards.

This current report, the *Third National Aggregate Statistics Report on Clinical Trials in Australia* (NAS 3 Report) was approved for publication by AHMAC in 2019. It includes data for all clinical trials in public health organisations from 6 jurisdictions[11], and represents final 2016-17 data. Like the NAS 2 Report, it provides data on total clinical trial activity (including number and sponsor type), and timelines for ethics and SSA/site assessment. In addition, this report includes, where available, time-series analysis between NAS 1, NAS 2 and NAS 3 Reports. Time-series analysis was not included in NAS 1 or NAS 2 Reports.

A4. NAS Data Collection Methodology

Data Sources

NAS is currently sourced from jurisdictional public health information platforms – both electronic and manual. Based on an initial scan of available sources, these systems were identified and agreed by CTPRG as the most current and reliable source of data for NAS. They were also the only systems that provided a (national) unique identifier for an ethics/HREC application to ensure that duplication of applications in reports is eliminated, and more importantly, links the HREC and SSA applications for a trial to measure the overall study start-up timelines.

[16] New South Wales, Northern Territory, Queensland, South Australia and Victoria

There are four different platforms used by jurisdictions and institutions in Australia to manage the 'research governance' of each individual research project. In general, these platforms enable (to varying degrees) the three mandatory processes for human research governance of clinical trials and other health research involving humans:

- ethics application, submission, review, and response/approval by a HREC;
- SSA application, submission, review, and response by an authorising site; and
- post approval monitoring and reporting.

The platforms are predominantly used (and therefore data input is provided) by researchers/sponsors and reviewing/approving entities (such as HRECs and RGOs/sites). It is important to note that these platforms do not contain participant data, or trial results.

Each jurisdiction sourced NAS data for this report from their own platform, the majority of which were electronic and allowed measurement of the metrics with 'administrative clock', which as noted elsewhere, provides capacity to measure timelines and also time intervals when applications are or are not the responsibility of administering organisations.

Data aggregation process

Data contained in this report is based on a template developed by the NMA and expanded for state-only records for the CTPRG and in accordance with agreed data definitions, sourced from jurisdictional information platforms as noted above. The NMA framework operating between six participating jurisdictions has provided the infrastructure for NAS data collection and analysis and has been established since 2013. 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 records in this report is an important step and has relied on cooperative relations between jurisdictions.

Limitations

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

- 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; and
- incomplete records (and therefore missing metrics) for some clinical trials included in this report. Results therefore reflect the proportion of the trials reporting that *particular data element/NAS metric*. These limitations particularly apply for analysis of metrics with low response rates – for example, only 47 per cent of all trials reported a trial phase in 2016-17.

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