

Report on the Forum on a National Approach to Clinical Trials

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Contents

Disclaimer	2
Contents	3
Executive Summary	4
Introduction	6
Opening Address: A National Approach to Clinical Trials	7
PIAA Perspective: Creating a Globally Competitive National Environment for Clinical Trials	8
Australian Health Ministers' Advisory Council Working Group Update: A streamlined national approach to ethical review for multi-centre clinical trials	11
TGA Perspective: A National Approach to Clinical Trials	13
NHMRC Update I: ANZ Clinical Trials Registry	15
NHMRC Update II: National Ethics Application Form (NEAF)	16
Updates from the States	17
New South Wales (NSW).....	17
Queensland	18
South Australia (SA)	19
Victoria.....	20
Western Australia (WA)	20
Workshops and Outcomes.....	22
Attachment 1 – Program	25
Attachment 2 – The Four Pillar Model.....	27
Attachment 3 – Workshop outcomes	31

Executive Summary

The Forum brought together a broad cross-section of stakeholders involved in conducting clinical trials, including those agencies already working on a national approach, industry, researchers, ethics committee representatives, a patient group advocate and industry/state development departments.

The aim of the Forum was to enhance the environment for clinical research in Australia, through supporting the development of a streamlined, national approach to clinical research.

The Pharmaceutical Industry Action Agenda (PIAA) Research and Development Taskforce (RDTF) presented the Forum with a “four pillar” model for analysing the global attractiveness of the clinical trial environment in Australia and identifying opportunities to improve it. The four pillars were quality, timeliness, value and capacity. The importance of maintaining the perceived quality of clinical research in Australia was discussed and stressed as clinical trials quality improves around the world and, in particular, in the fast growing markets in Asia, Europe and South America. Improvements in timeliness are crucial and efforts to streamline the ethical review process Australia are a very high priority. Value is a critical consideration for global decision makers and is more than just the direct the cost of the trial in Australia. Of great importance in considering value is the commercial environment for the resulting marketed drug and, to a lesser extent, government incentives for industry investment. Capacity includes both the absolute capacity to recruit patients and the relative capacity to produce data in niche areas, such as early phase clinical studies and hard-to-find study subjects.

Efforts to improve timeliness are largely focused on new initiatives to streamline ethical and scientific approval of multi-centre trials. An update was provided from an Australian Health Ministers' Advisory Council (AHMAC) Working Group on its project to allow recognition of ethics committee reviews across state and territory borders to introduce a single ethical review process at the national level. The Forum subsequently heard about the initiatives underway to produce single ethical review for multi-centre clinical trials in New South Wales (NSW) and Victoria. Both these initiatives are expected to be operational by the start of 2007. Many of the other states and territories are instituting similar initiatives or are monitoring progress in other states and on the national initiatives, with the intent of implementing complementary processes. These developments provide a valuable opportunity for Australia to dramatically improve the environment in Australia for multi-centre clinical trials through a far more streamlined process. This will have significant timeline advantages and also efficiency advantages for the start-up of trials.

The Therapeutic Goods Administration (TGA) discussed the suggestions put forward under the Review of Access to Unapproved Therapeutic Goods and other issues that could be considered for improving the clinical trial environment in Australia, pending a formal response from the TGA and the National Health and Medical Research Council (NHMRC). The NHMRC provided updates on the recent establishment of the Australian and New Zealand Clinical Trials Register and the current roll-out of the National Ethics Application Form (NEAF). NEAF will help to streamline ethics

submission via standardising the information requirements and allowing on-line submission to ethics committees.

Updates were also received from five states (Queensland, NSW, Victoria, South Australia and Western Australia) which signalled a preparedness to move ahead on a state by state basis to improve the environment for clinical trials, while maintaining willingness and commitment to achieve national solutions wherever possible.

In the afternoon, the Forum broke into four workshop groups to discuss other ways the environment for clinical trials in Australia could be improved. The workshops used the four pillar model presented by the PIAA RDTF to shape their discussions. The workshop groups focused on those issues the RDTF considered would make real improvements to the four pillars, and included issues not yet being progressed to any extent. The workshop groups ranked the issues and were asked to propose other issues they considered more important, if any.

The following issues emerged as the priority recommended actions to pursue under each of the four pillars:

Quality

- education and Good Clinical Practice accreditation of researchers, institutions and industry, formal accreditation of human research ethics committees and national standards for scientific and ethical review

Timeliness

- improving time to start-up through streamlining multi-centre clinical trial approval and the identification of potential subjects to improve recruitment

Value

- development of costing model to increase transparency of trial budget negotiation between institutions and sponsors and government incentives

Capacity

- increasing participation by potential subjects and expanding pool of investigators, study nurses, Clinical Research Associates etc

Participants clearly had a common goal and a strong commitment to achieving a national approach for clinical trials in Australia, recognising that the benefits to be gained from improvements in timeliness, quality, capacity and value are crucial for all stakeholders involved in clinical trials in Australia.

The PIAA RDTF took responsibility for ensuring that the momentum generated by the Forum is not lost and progress towards a national approach to clinical trials is maintained. The workshop outcomes will shape the Taskforce's work program for the next 1-2 years. The Chair of the PIAA RDTF was identified as the contact point for other stakeholders who want to become involved to work with each other cooperatively to achieve a positive outcome.

Introduction

The Pharmaceuticals Industry Action Agenda (PIAA) was launched by the Minister for Industry, Tourism and Resources in November 2002. It was a joint initiative between the Australian Government and the pharmaceutical industry. Government involvement included the Federal Minister for Industry, Tourism and Resources as well as the Federal Minister for Health and Ageing. The pharmaceutical industry encompasses the innovative, biopharmaceutical and generic manufacturers; research institutions; and development companies and related services.

The Forum on a national approach to clinical trials was sponsored by the Department of Industry, Tourism and Resources and organised with the assistance of the PIAA Research and Development Taskforce (RDTF).

The Forum brought together a broad cross-section of stakeholders involved in conducting clinical trials, including those agencies already working on a national approach (National Health and Medical Research Council (NHMRC), Therapeutic Goods Administration (TGA), state/territory health agencies), industry, researchers, ethics committee representatives, a patient group advocate and industry/state development departments.

The aim of the Forum was to enhance the environment for clinical research in Australia, and to maintain or enhance its global competitiveness, through supporting the development of a unified, national approach to clinical research by:

- Ensuring that all stakeholders know what work is underway on developing a national approach and the intended outcomes;
- Identifying and confirming what more can be achieved;
- Highlighting the key obstacles/issues that need to be addressed; and
- Developing strategies for overcoming these issues - especially coordination across all stakeholders to resolve the issues more quickly than might otherwise be the case.

Opening Address: A National Approach to Clinical Trials

Professor Jim Bishop
Chief Executive Officer, Cancer Institute NSW

Professor Jim Bishop opened the Forum with an overview of the Australian clinical trial environment and why we need to change to stay competitive globally.

Professor Bishop identified the obstacles to progress in Australia as a lack of focus and cohesion; uncompetitive ethics and scientific review; lack of infrastructure; too few trained trials staff; and a small market. He then described his vision for national clinical cancer trials in Australia:

- Clinical trials should be accessible to all cancer patients: a consumer and physician perspective;
- The quality and quantity of trials should be substantially expanded by international connections;
- A program should be built on existing strengths but developed more collectively; and
- Sustainable resources should be built based on common shared infrastructure.

This vision could be achieved by building on four basic concepts for national cancer trials:

- Developing a coordinating body to support national trials;
- Including national groups, state-based groups, Victorian Clinical Oncology Group, Cancer Trials Australia, Cancer Institute NSW, etc;
- Investing in shared infrastructure to run trials; and
- Funding international connections, meetings, communications, training.

Professor Bishop argued that these basic concepts could be adopted to build a national clinical trials model for Australia by:

- Encouraging disease specific groups to organise nationally;
- Providing “back of house” support;
- Providing training and career pathways in clinical trials; and
- Connecting government, academia, industry and charities to remove obstacles.

The role of academic groups in such a model would be to act as opinion leaders to set the scientific agenda; add science to clinical trials questions; provide international connections by personal contracts with colleagues; and work as advocates for Australia with overseas industry leaders.

The role of industry would focus on building a long-term collaboration with academia and government trials networks; using Australian expertise and science to win more research for Australia; keeping Australian trialists informed so they can be competitive and connected internationally; and providing feedback on obstacles for clinical research in Australia.

PIAA Perspective: Creating a Globally Competitive National Environment for Clinical Trials

Mitchell Kirkman

Novartis Pharmaceuticals Australia Pty Limited & Chair, PIAA Research and Development Taskforce

Mitch Kirkman, Chair of the PIAA R&D Taskforce, briefly described the Pharmaceuticals Industry Action Agenda, the role of the R&D Taskforce (RDTF) and its work on streamlining ethics approval processes in conducting health and medical research, including clinical trials.

The RDTF is working on strategies to ensure that Australia has a favourable clinical trials environment to attract both national and international investment and has identified four factors that influence investment decision making for clinical trials – quality, timeliness, value and capacity. These four factors were discussed as the Four Pillar model (see below and, for more details, see **Attachment 2**).

In working to further streamline ethics approval processes in conducting health and medical research, including clinical trials, the RDTF has engaged in and supported initiatives to streamline ethical approval, especially with state health departments, organised the PIAA Flagship Event Workshop “Developing a National Approach to Clinical Trials” at Parliament House Canberra in November 2005 and assisted with this Forum.

The Four Pillar Model – Creating a Competitive Clinical Trial Environment

Pillar 1 - Quality

Australia has had a good reputation for producing quality in clinical research and clinical trials. Our ability to quantify a quality difference is however very limited. For Australia to differentiate itself as being of superior quality, it will need to consider what more it can do to quantify such a difference. A number of possible initiatives to improve the clinical trial environment were proposed.

- education and accreditation of researchers and industry

It was proposed that all involved in clinical research to undertake a minimum International Conference for Harmonisation Good Clinical Practice (ICH GCP) and clinical research accreditation process and maintain ongoing accreditation. This could have many benefits – raising general quality standards in clinical research across Australia, in industry and investigator sponsored research and providing greater efficiency in study start-up through the ability drop GCP training for accredited study staff.

- accreditation of human research ethics committees
- national standards for scientific and ethical review

Both these issues are already under consideration as a part of the move towards streamlined multi-centre ethics approval at a state and national level and were covered in other presentations to the Forum.

Pillar 2 - Timeliness

Timeliness is critical to the success of clinical research projects to ensure the data is available in a timely fashion, and projects remain in budget and do not run out of funds for completion. It is an important source of competitive advantage globally provided quality is not compromised. Two factors in particular impact the timeliness of clinical research projects – time to start-up, especially for multi-centre projects, and being able to recruit all patients within the planned recruitment period.

- Time to start-up

This is impacted by the time for ethics approval, time for regulatory approval and time for resolution of research governance issues (such as clinical trial contracts and indemnity issues).

Time to start-up is currently being addressed by a number of national and state initiatives and was covered in other presentations to the Forum.

- Identification of potential subjects

Historically clinical trials were often run within major referral institutions. Changes in treatment patterns towards disease management in a general practice setting or new types of therapy for subjects can mean that traditional trials sites cannot produce the recruitment rates needed for Australia to be internationally competitive. The challenge for Australia is identify new ways to create suitable referral patterns to funnel patients to traditional trial centres at tertiary institutions.

Pillar 3 - Value

Cost is only one factor that determines the value global decision makers for placing global research and development projects into Australia. Other issues include the commercial environment for pharmaceuticals in the country (market growth rates, pharmaceutical reimbursement and prices) as well as Government incentives. The combination of improving global quality for clinical research (driven by the adoption of ICH GCP and new technologies such as electronic data capture) and rapid market growth can mean that Australia is no longer as competitive in attracting research

- Development of costing model

In costing studies in Australia, there is no good reference for the cost of investigations, study staff time and pathology costs. Development of a transparent Australian costing model for studies may ensure that Australian sponsors and study sites have a better understanding of the true cost of the work involved and whether this is globally competitive.

- Government incentives

A number of the countries are aggressively seeking to attract knowledge intensive industry into their countries through numerous incentives (tax concessions, etc). There is currently no follow-on to the P³ industry investment program, the R&D Tax Concession is linked to an intellectual property ownership test which limits its use, and ongoing discussion about reform of the pharmaceutical reimbursement system in Australia does not provide any competitive advantage for attracting clinical research to Australia.

Pillar 4 - Capacity

Australia's capacity for clinical research can be considered in terms of absolute capacity (numbers of available patients, sites, investigators, industry staff) and relative capacity (such as a focus on earlier phase, more complex trials or an ability to recruit patient groups that are difficult to recruit in other developed markets).

At present, in some areas, there is a dearth of experienced investigators, study staff and industry staff. For some patient populations, the number of clinical trials in Australia is currently using all accessible patient populations.

- expanding pool of investigators, study nurses, Clinical Research Associates (CRAs) and other industry staff

There is limited opportunity for undergraduate specialisation in clinical research and development of new trial sites has often not been a planned priority. Career paths for staff in clinical research can be variable, with no defined career path or pay scales that recognise their unique expertise. The rapid growth in research and often high turnover of industry staff has created a very limited supply of locally experienced staff. Increasing Australia's capacity will require careful planning and a concerted effort to ensure that adequate numbers of qualified staff are available at a reasonable price.

- increasing participation by potential subjects

With a relatively small population, Australia will need to improve its ability to access new patient populations or increase the participation rate of potential subjects to significantly expand its capacity for clinical research.

Australian Health Ministers' Advisory Council Working Group Update: A streamlined national approach to ethical review for multi-centre clinical trials

Ainsley Martlew, NSW Health (AHMAC Working Group Secretariat)

Ainsley Martlew from the Australian Health Ministers' Advisory Council (AHMAC) Working Group Secretariat presented a progress report on the work of the AHMAC Working Group on streamlining ethical and scientific review of multi-centre research.

Ms Martlew gave a brief description of the background leading up to the establishment of the AHMAC Working Group. She noted that there was a well-recognised need for reform and that the States and Territories had begun developing individual reform agendas. In February 2005, an Interjurisdictional Forum: *'Towards timely, efficient and effective review of multi-centre clinical trials'* was held, which was attended by most State and Territories, Commonwealth, NHMRC, TGA, AIHW, NZ HRC. The outcomes included the identification of nine principles characterising a "timely, efficient and effective system of ethical review of multi-centre clinical trials" (see below); and the need for national direction.

The potential impact of a national system for single ethical and scientific review would include:

- Human Research Ethics Committees – reduction in duplication of effort; increased quality of review; enhanced protection of research participants.
- Researchers and industry – reduction in duplication of effort; more timely recruitment of research participants.
- Governments – more timely, efficient, effective review; better use of limited resources; enhanced competitiveness in attracting quality research.

In June 2005, AHMAC decided to convene an interjurisdictional Working Group to develop a report for consideration by AHMAC on ways of achieving a nationally co-ordinated system for single ethical and scientific review. The report should be cognisant of the individual initiatives being undertaken by the various jurisdictions. The Working Group has agreed to the following Terms of Reference:

- To assess current arrangements for the review of multi-centre research, including the initiatives being undertaken to streamline the review process.
- To develop options for a nationally co-ordinated system for single ethical and scientific review.
- To report to AHMAC on ways forward for achieving this.

It has met twice, in September and December 2005, and discussed and agreed on the process for developing the report; agreed on the need for a consultancy to take the process forward; discussed the consultation scope; discussed the consultation process; and agreed on the timeframe for completion of the report to AHMAC.

Principles for Single, National, Ethical Review of Multi-centre Clinical Trials
(summarised)

1. Every trial is ethically and scientifically reviewed only once with a single submission point for applications.
2. All ethical/scientific review committees have demonstrated competency.
3. Time from submission to decision shall be no more than 60 days (stop clock may apply).
4. National policy & infrastructure.
5. Committees are responsible for ethical/scientific review and not research governance.
6. Substantial community input into the development of the system.
7. Clear accountability, responsibility and transparency of system
8. Proper resources must be ongoing for system set-up and maintenance.
9. The system shall include mechanisms to ensure natural justice/fairness.

TGA Perspective: A National Approach to Clinical Trials

Dr Jonathon Rankin, Drug Safety and Evaluation Branch, Therapeutic Goods Administration

Dr Rankin identified what he saw as ideal elements of a national approach to clinical trials:

- Nationwide ethical and scientific review accepted by all
- Collaborative efforts to recruit sufficient subjects from all States and Territories
- Well-understood Human Research Ethics Committee (HREC) review application process
- Well-understood regulatory requirements
- Uniform and consistent standards of clinical conduct
- A well-described set of common requirements for appropriate clinical governance issues
- Well-designed trials appropriately powered to answer specific primary outcome variable(s)
- Cost-minimisation for trials while maintaining international standards of GCP
- Easily accessed information and guidance for those considering conducting a clinical trial in Australia
- A standard of clinical conduct and data gathering that is given credence both within Australia and internationally
- A research environment that maintains standards and subject safety, but does not make the conduct of a clinical trial an insurmountable objective for all but large pharmaceutical companies
- Timeliness of trial related administrative processes
- Appropriate protection of subject well-being and safety

He then described what we now have in place:

Ethics:

- HREC review largely institution-focused, with some scope for nationwide ethical endorsement
- Attempts at resolution of the multi-centre issue
- Work on standardised application
- Some standardisation of HRECs re: National Statement and guidelines
- HREC tasked with some governance issues
- Issues include ADR reporting, DSMBs, local protocol amendments

Regulator:

- CTN/CTX trial arrangements; CTN overwhelmingly used, CTX used on occasion for specific reasons
- Minimal regulator oversight; additional role to HREC monitoring

Standards:

- National Statement on Ethical Conduct in Research Involving Humans (under revision; CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice);

CPMP/ICH/377/95 Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; Australian Code of Good Manufacturing Practice for Medicinal Products; Access to Unapproved Therapeutic Goods – Clinical Trials in Australia, and several European Union guidelines adopted in Australia.

Clinical Governance:

- Mainly institution-focused with HREC involvement; responsibilities defined under GCP guideline and also locally by individual institutions
- Issues include DSMBs, Indemnity, Liability

Costs:

- Ethical review costs in some cases; regulatory fees
- Clinical governance – indemnity, data gathering, etc.
- Meeting GCP standards – ADR reporting, provision of medical care, etc.
- Issues: largely indemnity, multiple ethics review fees, GCP requirements.

Dr Rankin then identified what we need to change or improve

- Bansemer review of Access to Unapproved Therapeutic Goods reviewed Australian arrangements for access to unapproved therapeutic goods including clinical trials under CTN/CTX; Government response shortly.
- Key issues raised in relation to clinical trials:
 - Retention of CTN/CTX choice
 - Complaints of cost; one trial/one fee
 - E-notification
 - Adverse event monitoring/reporting/management
 - Role of ethics committees different from other regulatory jurisdictions
 - Timelines for regulatory review/ethical review in other jurisdictions
 - Multi-centre review issue
 - Workload of ethics committees
 - Clinical Trial Register
 - Difficulty in obtaining trial indemnity
 - Safety of subjects in CTN trials

and identified those issues being or needing to be addressed as a priority:

- Multi-centre review: AHMAC Working Party.
- Clinical Trial Register – NHMRC Grant for Sydney University Clinical Trial Centre.
- Timeliness of HREC review: fees, standardisation measures, reduction in duplication, reduction in responsibilities
- Regulator – costs, safety of subjects, GCP
- ADRs
- Indemnity.
- Clinical Governance Issues
- Costs in general
- Ways to attract international research to Australia
- Improved guidance for those conducting trials

NHMRC Update I: ANZ Clinical Trials Registry

Tracey Cross, Director, Collaborations and Researcher Support, NHMRC

What is the ANZ Clinical Trials Registry (ANZCTR)?

- The register is a **national on-line** register of **all types** of clinical trials being undertaken in Australia and New Zealand:
 - trials looking at preventive therapies, rehabilitation strategies and complementary therapies;
 - all trials involving Australian researchers or participants and covering all areas of health.
 - Australia is one of the leading nations in the world in developing this Registry.

Why is the ANZCTR important?

- There is a growing international trend to better publicise the existence of clinical trials so that a true picture of the evidence for a particular new treatment, drug, medical device or therapy is publicly available.
- From 1 July 2005 the International Committee of Medical Journal Editors (ICJME) – which includes among many others, the Medical Journal of Australia, the Lancet and The New England Journal – will not publish the results of any clinical trials not included on an authorised register.

Key points about the ANZCTR

Status at this point in time:

- All data submitted to the ANZCTR is made publicly available.
- Registration is voluntary, but if a registrant chooses to register a trial, certain fields are mandatory.
- Registration is free of charge.
- Responsibility for registration lies with the Sponsor.

Achievements to date:

- As of February 2006, the ANZCTR had 854 trials registered.
- The ICMJE has indicated on their website that the ANZCTR is an authorised registry.
- An advisory board consisting of NHMRC, HRC, TGA, researchers, industry and consumer representatives is currently being established to provide policy guidance during the development of the ANZCTR – this group will hold its first meeting in April 2006.

Future Plans for the Registry:

- The Registry is in development and will be reviewed in 3 years time.
- The registry currently uses the WHO minimum dataset - but this may change over time.
- The registry will link in to the international platform being developed by the WHO.

NHMRC Update II: National Ethics Application Form (NEAF)

Professor Colin Thomson, Consultant in Health Ethics, NHMRC

Professor Colin Thomson gave an interactive demonstration of the National Ethics Application Form, the pilot testing version of which can be found at www.neaf.gov.au, and made the following points about the form.

It is to be web accessed, hosted on a dedicated website free to users for three years:

- designed to meet requirements of the National Statement on Ethical Conduct in Research Involving Humans
- applicable to any research involving humans
- dynamic – expands/contracts in response to answers
- contains hover (help) text, guidance, links to guidelines, reference material
- includes an Invite User function – facilitating research group applications
- using Access standard, it will permit data to be exported from the NEAF proposal to an institution's database
- a tool, not repository

It is being developed by NHMRC with the support of ARC, AVCC.

Updates from the States

Representatives from state government departments presented recent initiatives within their jurisdictions focused on increasing clinical trial activity and investment. There were a number of consistent themes identified:

- Commitment within governments to encourage growth in the bio-pharmaceuticals sector. Whilst this partly has an economic focus, it is also grounded in the desire to improve research activity and application of that research to improve health outcomes.
- Recognition of current barriers and inefficiencies from duplication of effort by multiple Human Research Ethics Committees (HRECs). NSW, Victoria and Queensland are each developing models for centralised HREC review of multi-centre clinical trials and more efficient management of research governance at local sites.
- Establishment of research networks and support for research infrastructure to promote cooperation and synergy leading to efficiency and greater attractiveness to international investment.
- Whilst the states are partly competing with each other to be the “first” or “smart” state, there is a strong commitment to work together to develop a more efficient and effective model for clinical research nationally and thereby make Australia more competitive on an international basis.

New South Wales (NSW)

Professor Maree Gleeson, Director Medical Research, Ministry for Science and Medical Research

Professor Maree Gleeson presented the NSW initiatives on behalf of several government departments and Cancer Institute NSW.

These government departments and the Institute are supporting initiatives to attract research and development activity to NSW – State and Regional Development, Ministry of Science and Medical Research (MSMR), and Department of Health. NSW has developed a 10 year strategic plan with an economic focus but also to improve medical research performance and health outcomes through translation of research into policy and practice.

The focus is on development of research-enabling platforms and resources with State-wide coordination:

- Clinical trials infrastructure – formation of hubs, networks and infrastructure support
- Streamlining research ethics review – single review for multi-centre trials
- Good research governance through standardisation of practice, eg standard indemnity arrangements
- Data Linkage Unit – facilitate information exchange
- State-wide research informatics facilities - sound management and statistical interpretation of research data

- Building people capacity (CINSW & *BioFirst*)
- IT connectivity (*BioFirst*)
- IP Commercialisation Services (*BioLink*)
- Biotechnology & Pharmaceutical industry support (*BioBusiness*)

Queensland

Mario Pennisi, CEO, Queensland Clinical Trials Network Inc

Mr Mario Pennisi discussed the Queensland approach to promote investment in R&D and manufacturing in the State. There has been a significant focus across the Departments of State Development, Trade and Innovation, and Health, with the establishment of a pharmaceuticals and nutraceuticals sectoral development unit and an office of biotechnology.

The Queensland Clinical Trials Network Inc (QCTN) has been established by the Office of Biotechnology. QCTN is an association of clinical trial service providers across the pharmaceutical value chain:

- Pre-clinical
- Phase 1
- Later Phase sites
- Central Laboratories
- CROs
- Regulatory Affairs
- Data Management
- Bio-statistics
- Contract Manufacturing

QCTN seeks to provide a central point of contact for organisations wanting to conduct clinical research in the State and co-ordinates introducing those entities on behalf of the members. To provide an environment conducive to clinical research, it focuses on raising public awareness of the need and importance of clinical trials and facilitates education and training for sector professionals. It has also compiled and published the Queensland Directory of Clinical Trials and Related Services.

QCTN has been active in the US, Japan and New Zealand, and given presentations at a number of international forums to promote interest in Australia, and Queensland in particular.

Queensland Health has developed two standard clinical trial agreements – for commercial sponsors and Contract Research Organisations – which are now available from the Department website. Although these standard agreements have been issued as final, Mr Pennisi and Dr Jane Jacobs from the office of the Queensland Chief Health Officer invited any comment or feedback on the documents. The Health Department is actively pursuing mutual recognition of HREC decisions, which should be achieved within metropolitan hospitals by the end of 2006.

South Australia (SA)

Andrew Stanley, Director, Strategic Planning, Policy and Research, Department of Health

Mr Andrew Stanley from the South Australian Department of Health discussed SA's approach to promoting clinical research.

BioInnovation SA recently established Drug Development SA in partnership with key providers of pre-clinical and clinical services in SA. Drug Development SA and its networks will promote the collective capabilities of SA's providers as well as enable linkages between players in the biotechnology and pharmaceutical industries.

Drug Development SA's objectives are to:

- promote the capabilities and services offered by SA's preclinical and clinical trial organisations locally, nationally and internationally;
- assist biotechnology and pharmaceutical companies to engage appropriate preclinical and clinical trial partners and facilities in SA; and
- strengthen the interface between basic studies, clinical research and manufacturing.

There are a number of commercial organisations in SA undertaking preclinical and clinical trials, such as CMax, Trident Clinical Research, VivoPharm and the Centre for Pharmaceutical Research at the University of SA.

SA hosts a number of world-class research centres, including four teaching hospitals, which conduct a number of significant clinical studies:

- Royal Adelaide Hospital, including the Hanson Institute
- Flinders Medical Centre, Flinders Institute for Health and Medical Research and the Repatriation General Hospital
- Queen Elizabeth Hospital, including the Basil Hetzel Institute
- Women's and Children's Hospital, including the Child Health Research Institute

Issues faced by SA HRECs are similar to those identified by the other States, but three issues in particular were highlighted:

- tracking serious adverse events to ensure sufficient monitoring of the safety of trials;
- multi-site trials and concerns relating to maintaining site-specific responsibility and duty of care; and
- adequate resourcing and support for committee members and support staff given the increasing complexity of clinical trials.

SA is in the very early stages of considering a system of multi-centre ethical review and will be guided by initiatives at a national level, whilst recognising the importance of having strategies in place at a local level to assist those undertaking clinical trials and the timeliness of the trial itself. Like the other State models, SA is considering separating research governance issues and risk management from issues associated with ethical review. A workshop is scheduled for late March 2006 to begin discussions in this area.

Victoria

Dr Suzanne Hasthorpe, Senior Project Officer, Research and Biotechnology, Department of Human Services

Dr Suzanne Hasthorpe presented the Victorian model for centralised ethical review of multi-centre clinical trials being developed by the Department of Human Services.

The model recognises the need for:

- high quality scientific and ethical review
- an efficient and timely system
- research governance at the institutional level
- development in line with a national approach

and proposes:

- Standard review time (eg 60 calendar days)
- Multiple committees with the opportunity for weekly meetings resulting in fast progression
- Standard forms – Application Form, Clinical Trial Agreement, Indemnity and Insurance (sponsor, public and/or private)
- Research governance reviewed in parallel with ethical review
- Standardised processes

The Department has conducted extensive consultation with a wide range of stakeholders in developing its model, which will be applicable to all types of ethical review – including clinical trials, epidemiology, population health and social research. The model recognizes the need for education and training for research governance and researchers at the institutional level as well, as training leading to accreditation for central HREC members.

Western Australia (WA)

Keith Anthonisz, A/g General Manager, Innovation and Emerging Industries, Department of Industry and Resources

Mr Keith Anthonisz from the Department of Industry and Resources presented the initiatives in WA.

Approximately \$15 million worth of clinical trial activity occurs in the State per annum across a network of clinical units and therapeutic areas, principally in the metropolitan teaching hospitals. The success factors, like the other states, are:

- National/international recognised clinical expertise;
- Excellent hospital system access;
- Quality track record for excellence;
- Cost effectiveness;

- Timeliness; and
- Recruitment/access to patient.

However, one difference for WA is its unique health record system, which is being held up as a model for data capture.

Like the other states, WA suffers from administrative time constraints leading to delayed ethics approvals. Clinical trials has been recognised as a potential growth area in the WA Biotechnology Industry Strategy, which has identified the need for dedicated clinical trials infrastructure.

The Australia New Zealand Biotechnology Alliance (ANZBA) was formed by an MOU between the Governments of NSW, Queensland, SA, Tasmania, Victoria, WA, ACT and New Zealand (NZ). ANZBA hosted a Clinical Trials Forum in Perth November 2005, which focused on business linkages and coordination.

The WA Forum recognised that, whilst some competition between states, territories and with NZ is acceptable, our real competitors, which are attracting much larger shares of R&D investment, are India and Singapore. By working together, Australia and NZ can regain a larger share of the pie.

By streamlining ethics committees across trial sites with one approval system, like the models being developed in the eastern states, it will improve Australia's competitiveness and facilitate domestic (and NZ) clinical trial networks.

Workshops and Outcomes

In the afternoon, the Forum broke into four workshop groups to discuss other ways the environment for clinical trials in Australia could be improved. The workshops used a four pillar model (quality, timeliness, value and capacity) to shape their discussions. This model has been proposed by the PIAA RDTF as describing the most important factors influencing global investment decision making for clinical trials. The workshop groups focused on those issues the RDTF considered would make real improvements to the four pillars, and included issues not yet being progressed to any extent. The workshop groups ranked the issues and were asked to propose other issues they considered more important, if any.

Each group was asked to discuss one of the four pillars and to rank what needs to be done in priority order. The outcomes sought from the workshop groups were:

1. validation of the issues identified;
2. relative importance of each issue; and
3. achieving outcomes.

Suggested priority issues under each pillar resulting from the workshops:

Quality

- education and Good Clinical Practice accreditation of researchers, institutions and industry
- formal accreditation of human research ethics committees
- national standards for scientific and ethical review

Timeliness

- improving time to start-up through streamlining multi-centre clinical trial approval
- improving the identification of potential subjects to improve recruitment

Value

- development of costing model to increase transparency of trial budget negotiation between institutions and sponsors
- Government incentives

Capacity

- increasing participation by potential subjects
- expanding pool of investigators, study nurses, CRAs etc

Each workshop group then chose one priority issue under each heading that it felt would offer the greatest improvement in the clinical trial environment while still being achievable. The groups were also asked to identify and consider the stakeholders influencing or controlling that issue and the major obstacles to be overcome. The next key steps to achieving the required outcome were discussed and summarised. These are described at **Attachment 3**.

Four issues were identified as leading to a major improvement while also being achievable (although challenging to achieve):

- “Education & accreditation of both researchers and Human Resource Ethics Committees (HRECs)” – to maintain and improve the quality of the Australian research environment and support the development of a streamlined, national trial approval process
- “Improving the time to study start-up through a national streamlined trial approval process” – ie, the time from submitting an application for approval to trial commencement
- “Development of costing model” – to provide a common platform for companies, researchers and government in identifying the cost of conducting clinical trials
- “Increasing patient participation” – to increase the capacity for clinical trials in Australia

Of these four priority issues, “Time to study start-up” is already being progressed by State and Federal agencies through efforts to streamline multi-centre ethics approval and is strongly supported by the R&D Taskforce. The other three issues will be considered by the RDTF as areas of focus for the next 1-2 years with involvement of suitable stakeholders.

It was assumed that the PIAA Industry Development Taskforce is already pursuing Government incentives (eg, a successor to P³, R&D Tax Concession, etc) identified as critical to making Australia attractive for global investment. Government policy settings regarding reimbursement of new medicines were also noted to be of fundamental importance to perceptions of value and ROI for investment in R&D in Australia by global companies.

Summary and next steps

Participants clearly had a common goal and a strong commitment to achieving a national approach for clinical trials in Australia, recognising that the benefits to be gained from improvements in timeliness, quality, capacity and value are crucial for all stakeholders involved in clinical trials in Australia.

The states are addressing similar issues in relation to clinical trials, but adopting solutions which differ in many respects despite the common themes of “streamlined” ethics approval for multi-centre trials; institutional governance issues relating to trials being handled at the local level; and appropriate resourcing.

The challenge for the states is to identify how their respective frameworks can be aligned/streamlined at a national level. Commonwealth agencies are looking at ways to continue to improve on current national arrangements, as well as support and work with the states and other stakeholders to achieve national solutions in a timely manner.

The PIAA RDTF took responsibility for ensuring that the momentum generated by the Forum is not lost and progress towards a national approach to clinical trials is maintained. The workshop outcomes will shape the Taskforce’s work program for the next 1-2 years. The Chair of the PIAA RDTF was identified as the contact point for

other stakeholders who want to become involved to work with each other cooperatively to achieve a positive outcome.

The Forum outcomes will also contribute to the work of AHMAC Working Group and Australia New Zealand Biotechnology Alliance, which are also actively pursuing the establishment of a national framework for clinical trials.

Attachment 1 – Program

Forum on a national approach to clinical trials - Program

Opening session – chaired by Alison Hemmings, Manager, Pharmaceuticals Section, Department of Industry, Tourism & Resources (0930-0945)

Overview presentation – the Australian clinical trial environment and why we need to change to stay competitive globally – Professor Jim Bishop, Director, Cancer Institute NSW

Presentations

20 minutes each (0945-1105)

1. Pharmaceuticals Industry Action Agenda R&D Taskforce scene setter – Mitchell Kirkman, Manager, GCP, Training & Administration, Australasian Clinical Research, Novartis Pharmaceuticals Australia Pty Limited (Chair PIAA RDTF)
2. Progress report from the AHMAC WG – process, where at, timeframes, what issues – Ainsley Martlew, Senior Analyst (Research), Research and Ethics Branch, NSW Department of Health (Secretary, AHMAC WG)
3. Therapeutic Goods Administration (TGA) – Government response to the Bansemer report; audit/inspection; other initiatives – Dr Jon Rankin, Experimental Drugs Section, Drug Safety and Evaluation Branch
4. National Health & Medical Research Council (NHMRC) – National Ethics Application Form, Clinical Trials Register; other initiatives – Tracey Cross, Director, Collaborations and Researcher Support & Professor Colin Thomson, NHMRC Consultant in Ethics

Morning tea
(1105-1130)

5. Update from the States – chaired by Mitchell Kirkman
15 minutes each (1130-1300)

Presentation on State initiatives from the perspective of the four pillars of quality, speed, cost and capacity and the contribution each of these objectives makes to a national approach. This will be a combined industry/health perspective.

Speakers

New South Wales – Professor Maree Gleeson, Director Medical Research, Ministry for Science & Medical Research

Queensland – Mario Pennisi, CEO, Queensland Clinical Trials Network Inc

South Australia – Andrew Stanley, Director, Strategic Planning, Policy & Research, Department of Health

Victoria – Dr Suzanne Hasthorpe, Senior Project Officer, Biotechnology & Ethics, Department of Human Services

Western Australia – Keith Anthonisz, A/g General Manager, Innovation & Emerging Industries, Department of Industry & Resources

Lunch
(1300-1345)

Workshop discussions

(1345-1530)

Afternoon tea

(1530-1550)

Closing session – chaired by Michael Schwager, General Manager, Pharma & Biotech
Branch, Department of Industry, Tourism & Resources

(1550-1700)

Feedback from workshops

General discussion on the national initiatives and agreed way forward

Attachment 2 – The Four Pillar Model

Creating a Competitive Clinical Trial Environment

Pillar 1 - Quality

Australia has had a good reputation for producing quality in clinical research and clinical trials. Our ability to quantify a quality difference is however very limited. The global adoption of International Conference for Harmonisation Good Clinical Practice (ICH GCP) is raising the standard of research in all countries of the world. Likewise, the adoption of electronic data capture at study sites is drastically reducing the data query rate due to real time build in queries, again narrowing the difference in query rates and data quality around the world.

For Australia to differentiate itself as being of superior quality, it will need to consider what more it can do to quantify such a difference. A number of possible initiatives to improve the clinical trial environment were proposed.

- education and accreditation of researchers and industry

Historically, demonstration of GCP knowledge and clinical research expertise has occurred on a study by study basis, often with the sponsor providing training on each occasion to ensure they could demonstrate compliance with ICH GCP. In non-industry sponsored studies there may be little or no such training. The proposal here would be for all involved in clinical research to undertake a minimum GCP and clinical research accreditation process and maintain ongoing accreditation. This could have many benefits – raising general quality standards in clinical research across Australia, in industry and investigator sponsored research and providing greater efficiency in study start-up through the ability to drop GCP training for accredited study staff.

- accreditation of human research ethics committees
- national standards for scientific and ethical review

Both these issues are already under consideration as a part of the move towards streamlined multi-centre ethics approval at a state and national level. Australia has comprehensive guidelines to guide ethics committees provided by National Health & Medical Research Committee (NHMRC). However, the move towards “lead” Human Research Ethics Committees (HRECs) or “central” HRECs that will provide national approval of clinical trials provides a greater incentive towards more formal processes to ensure minimum standards are met and provide greater assurance to all parties that a HREC from another institution of state is suitably qualified to review multi-centre research.

Pillar 2 – Timeliness

Timeliness is critical to the success of clinical research projects to ensure the data is available in a timely fashion, whether for a marketing submission, journal publication,

and presentation at major international symposia or to ensure timely translation to clinical practice. Timeliness is also important to ensure that projects remain in budget and do not run out of funds for completion. As such timeliness is an important source of competitive advantage globally (with the proviso that quality is not compromised).

Two factors in particular impact the timeliness of clinical research projects. The first is time to start-up, especially for multi-centre projects. This particularly impacted by the time for ethics approval, time for regulatory approval and time for resolution of research governance issues (such as clinical trial contracts and indemnity issues).

The second factor is being able to recruit all patients within the planned recruitment period. The available recruitment period may be reduced if the start-up time runs longer than intended. The recruitment period may also need to be extended if the recruitment rate does not meet expectations, particularly in populations of potential trial subjects that are not easy to identify in traditional trial settings (such as major teaching hospitals).

- Time to start-up

Time to start-up is currently being addressed by a number of national and state initiatives – Australian Health Ministers' Advisory Council Working Group, various state government initiatives to form centralised ethics committee approval for multi-centre studies, a standardised clinical trial contract by Victoria and NSW, as well as the NHMRC national on-line ethics application form (NEAF).

- Identification of potential subjects

Historically clinical trials were often run within major referral institutions. They may rely on a long term cohort of patients under the care of the institution or a steady supply of referrals. This may not always provide an adequate number of subjects suitable for clinical research projects. Changes in treatment patterns towards disease management in a general practice setting or new types of therapy for subjects, who may not currently be regarded as patients, can mean that traditional trials sites cannot produce the recruitment rates needed for Australia to be internationally competitive.

The challenge for Australia is identify new ways to create suitable referral patterns to funnel patients to traditional trial centres at tertiary institutions, to find new settings that will allow trials to be conducted to the required standards but also have access to the patient populations needed and to consider other novel ways that suitable patients may be identified (such as flagging possible patients based on pathology results).

Pillar 3 - Value

Cost is only one factor that determines the value global decision makers for placing global R&D projects into Australia. Australia has been perceived to be globally competitive in regard to the cost of conducting clinical research, especially against the USA and Western Europe.

Other issues which affect this pillar include the commercial environment for pharmaceuticals in the country (market growth rates, pharmaceutical reimbursement and prices) as well as government incentives. Rapidly growing new markets for pharmaceuticals (such as China, India, Korea and Taiwan) can often provide a lower cost for research. The combination of improving global quality for clinical research (driven by the adoption of ICH Good Clinical Practice and new technologies such as electronic data capture) and rapid market growth can mean that Australia is no longer as competitive in attracting research. Other countries have offset lack of market growth through significant government incentives for pharmaceutical investment, for example Singapore and Ireland.

- Development of costing model

The costs for clinical research in Australia in some therapeutic areas and for some trials are now higher than the costs provided from the USA and Western Europe. There can also be great variability between study centres. Study centres have also suggested that the fees proposed for clinical trials are not adequate to cover the true centre costs. In costing studies in Australia, there is no good reference for the cost of investigations, study staff time and pathology costs. Development of a transparent Australian costing model for studies may ensure that Australian sponsors and study sites have a better understanding of the true cost of the work involved and whether this is globally competitive.

- Government incentives

A number of the countries are very aggressive in seeking to attract knowledge intensive industry into their countries through numerous incentives (tax concessions, etc). At present there is no follow-on to the P³ industry investment Program, the R&D Tax Concession is linked to an intellectual property ownership test which results in very limited use of the Concession, and ongoing discussion about reform of the pharmaceutical reimbursement system in Australia does not provide any competitive advantage for attracting clinical research to Australia.

Pillar 4 – Capacity

Australia's capacity for clinical research can be considered in regards absolute capacity (numbers of available patients, sites, investigators, industry staff) and relative capacity (such as a focus on earlier phase, more complex trials or an ability to recruit patient groups that are difficult to recruit in other developed markets).

The growth in clinical research in Australia since 1990 has been very significant. At present, in some areas there is a dearth of experienced investigators, study staff and industry staff (such as Clinical Research Associates (CRAs)). It is not infrequently the case that existing, experienced study centres and staff are at or beyond capacity.

For some patient populations, the number of clinical trials in Australia is currently using all accessible patient populations. This may reflect that the referral patterns do not bring patients to current study sites.

- expanding pool of investigators, study nurses, CRAs and other industry staff

At present there is limited opportunity for undergraduate specialisation in clinical research and development of new trial sites has often been serendipitous and not been a planned priority for industry, government or health departments. Career paths for staff involved in clinical research can be very variable, in particular study nurses and coordinators in hospitals have no defined career path or pay scales that recognise their unique expertise. The rapid growth in research and the often relatively high turnover of industry staff (especially with the heavy travel involved) has created a very limited supply of locally experienced staff. Increasing Australia's capacity to achieve the PIAA Vision will require careful planning and a concerted effort to ensure that adequate numbers of qualified staff would be available to hospitals and industry (at a reasonable price).

- increasing participation by potential subjects

With a relatively small (by global standards) total population, Australia will need to either improve its ability to access new patient populations or else increase the participation rate of potential subjects into clinical research in order to significantly expand its capacity for clinical research.

Attachment 3 – Workshop outcomes

Quality

The priority issue was identified as “Education & accreditation of both researchers and Human Resource Ethics Committees (HRECs)”. The necessary actions to achieve appropriate accreditation were agreed as:

- Document all current educational initiatives seek framework to integrate and identify gaps
- Could draw together with education initiatives under HREC accreditation project
- Identify gatekeepers that can require accreditation/education
- Identify the carrots and the sticks
- Look to overseas experience
- Investigate Government support programmes (DEST, DITR, State Governments)
- Seek to ensure a national standardised process for scientific and ethical review continues in parallel

Timeliness

The priority issue was identified as “Time to study start-up”. The necessary actions to decrease the time to start-up were agreed as:

- Buy-in from stakeholders through a national forum on research governance
- Prioritise education programs for stakeholders
- Develop a national set of standards for accreditation based on therapeutic areas
- Explore private HRECs

Value/cost

The priority issue was identified as “Development of costing model”. The necessary actions to develop such a model were agreed as:

- Cost modelling advisory committee
- Need national champion – suggest Department of Industry Tourism and Resources
- National standardisation of costing model
- Specified timeframe for development
- Recommendation to Council of Australian Governments
- Funding initiatives

Capacity

The priority issue was identified as “Increasing patient participation”. The necessary actions to increase participation by both sites and researchers, and patients were agreed as:

- Community educational campaigns
- Leveraging patient groups
- Review UK cancer research model – linking funds to percentage participation rates of patients
- NGOs traditionally not research focused
- Patient screening resources
- How can we increase referrals – e.g. GP/physician involvement (WIFM)
- Clarification of Privacy Laws – e.g. intra-organisational screening is allowed within laws

The following table ranks the issues chosen as most critical to pursue against the potential positive impact on the clinical trials environment of achieving the desired outcome and the likely ability to achieve the outcome.

Impact on clinical trial environment		
<i>Major improvement</i>	<ul style="list-style-type: none"> • Development of a costing model 	
		<ul style="list-style-type: none"> • Education & accreditation • Time to start-up • Increasing patient participation
Ability to achieve outcome	<i>Very difficult</i>	<i>Moderately challenging</i>