Australian Government Response to the Recommendations of the Review of Clinical Trials and Access to Unapproved Therapeutic Goods (Bansemer Report)

July 2006

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1. Executive Summary

Introduction

This document details the Australian Government response to the recommendations made by an independent, external review of the Australian arrangements for clinical trials and access to unapproved therapeutic goods. The comments received following the release of the final report for consultation have been taken into account in the formulation of this response.

The Australian Government is committed to the fostering of clinical research in Australia to world-class standards, as well as ensuring timely access to therapeutics that are of the best possible quality, safety and efficacy for the Australian population. In concert with these goals, the protection and promotion of public heath and safety is of primary consideration in providing a regulatory framework that delivers these outcomes. This requires particular care in the use and availability of "unapproved" (or experimental) therapies, as the available information about these products is less than that of those approved for marketing.

This review investigated several regulatory areas with multiple major stakeholders, in particular the Australian clinical trial arrangements, the feasibility of a clinical trials register, and the regulation of unapproved therapeutic goods in Australia in the context of a future Trans-Tasman Regulatory Authority incorporating the Therapeutic Goods Administration (TGA) and New Zealand's Medsafe into a Joint Regulatory Authority.

The recommendations of the review are summarised at Chapter 2. Chapter 3 provides abridged recommendations and the government response to each. Chapter 4 discusses the recommendations and implementation of the responses in more detail. The contributors to the consultation process throughout both the development and circulation of the final report are acknowledged in the Appendices to this response, at "Chapters" 5-8.

The Clinical Trial Arrangements for Australia

The government shall maintain the current requirements of the Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) systems in Australia, while enhancing clinical trial oversight and safety by establishing a Good Clinical Practice (GCP) inspection capability within the TGA, in line with international trends in comparable regulatory agencies. The government will also assist with the streamlining of multi-centre research by supporting initiatives through the Australian Health Ministers' Advisory Council (AHMAC).

The government recognises the considerable work already undertaken by the National Health and Medical Research Council (NHMRC) in attempting to establish a national Human Research Ethics Committee (HREC) ethical review application form, as well as standards and guidance for HRECs. These efforts will be complemented by the review of TGA guidance documents for HRECs and sponsors. Such review shall occur in the context of an agreed model for ethical review for Australia to be determined by an AHMAC working party.

The Joint Regulatory Authority for the regulation of therapeutic products between Australia and New Zealand, set for commencement in mid-2007, shall include the regulation of clinical trials to international standards of GCP. However, the methods of clinical trial regulation in each nation shall fundamentally remain as they are, with different review and monitoring

mechanisms for clinical trials achieving the same outcomes. Any proposed changes to the Australian regulatory requirements for clinical trials shall be the subject of consultation with stakeholders prior to any changes being implemented, including the development of guidance documents for any new requirements.

The government recognises the needs of stakeholders to access basic data concerning the type, distribution, and volume of clinical research undertaken in Australia. Steps shall be taken to have these data available on an annual basis, in general terms, without impacting on any commercial-in-confidence concerns.

Ethical and Scientific Assessment of the use of unapproved therapeutic goods

It is accepted that ethical and scientific review of clinical trial proposals in Australia is, at present, significantly institution-based, such that multi-centre research may experience delays in obtaining the necessary approvals to commence a multi-centre clinical trial. Approvals may also vary with respect to the conditions imposed by different HRECs. The government supports the efforts of the AHMAC working party convened to investigate options for a streamlined approach to multi-centre clinical trial documentation review. This investigation will, of necessity, examine the current clinical trial governance arrangements and how they link with approval of trial proposals.

Clinical Trial Monitoring and Inspection

The government recognises the significant task that the ongoing monitoring and inspection of clinical research according to international standards of GCP involves. As a result, a clinical trial inspection function shall be established within the TGA, to bring such capability in line with those standards already existing in the USA, European Union (EU), Canada and Japan. The NHMRC provides guidance to HRECs about such oversight requirements, and these will be enhanced by the revision of the TGA's guidance document for ethics committees.

Other Avenues of Access to unapproved therapeutic goods

The government recognises that individual and other special-case usage of unapproved therapeutic products is necessary in particular circumstances. The avenues of access in these cases, primarily the Special Access Scheme and Authorised Prescriber arrangements, are considered to be maintaining the correct balance between risk and benefit of such products in Australia and will be maintained.

A clinical trial register

It is accepted that a clinical trials register has significant benefits to the Australian population, both in general and within the research community. Indeed, such trial registration, and thus publication of minimum information, is now an international requirement for journal publication of clinical research, and hence widespread recognition by international peers. While the government recognises that Australian industry must be able to protect commercial-in-confidence information to a degree, it is supportive of the notion of a clinical trial register and has provided funding through the NHMRC for 5 years for a pilot program. This register has a scope of trials well beyond just those trials regulated by the TGA and requiring an exemption from legislation for the therapeutic goods involved to be lawfully supplied. This initiative will be reviewed by the NHMRC on a regular basis.

The Trans-Tasman Regulatory Agency

The government acknowledges that the Trans-Tasman Mutual Recognition Agreement was intended to encompass therapeutic goods in the fullness of time. Both the Australian and New Zealand governments have undertaken considerable work over the past few years to engineer a Joint Regulatory Agency for the harmonised regulation of therapeutic products. The recommendations of the Bansemer review have taken account of the likely future regulatory framework for Australia, and both the consultation process in the production of the Bansemer report, as well as the final recommendations, have encompassed New Zealand comments and current regulatory practices.

Consultation

The government will continue to consult with all stakeholders as implementation of the Response to the Recommendations of the Bansemer Report proceeds, to ensure that any issues that arise during implementation can be picked up and addressed.

2. Summary of Review Recommendations

The following recommendations were made by the Review Team:

The Clinical Trial Notification and Exemption Schemes in Australia

R1. The Key elements of the CTX and CTN Schemes, and the regional ethics committee and SCOTT systems, should be retained by the Joint Agency, with a view to harmonising clinical trial arrangements as discussed in Chapter 11 of this report.

R2. The TGA should issue more guidance to ethics committees about what kind of clinical trial submissions should undergo assessment via the Joint Agency or a Scientific Assessment Panel, with the Agency to issue clear definitional statements in an effort to aid all stakeholders in determining the correct route of assessment for clinical trial proposals.

R3. Acknowledgment of lodging a clinical trial exemption from the Joint Agency should be available on-line and the Agency and sponsors should be encouraged to develop and use such systems.

R4. The timeframe for upgrading of the TGA/Joint Agency's IT and database capacity and for including the clinical trial database should be re-examined.

R5. The Joint Agency should produce general performance information about clinical trials and make it readily available, and should report regularly and in some detail on clinical trial activity in Australia/NZ and maintain a database with an appropriate quality system to ensure that analysis and reporting can be done.

R6. The Joint Agency should produce at least an annual report on the clinical trial activity being conducted in Australia and New Zealand, regulated by the Joint Agency. This should be in summary form (so as not to breach confidentiality of information) but should be comprehensive enough to provide informative data on the nature and extent of clinical trial activity.

R7. There should be an examination of the likely costs of the proposed clinical trial model in Chapter 7, in order to ensure that costs are not a barrier to clinical research.

R8. Serious consideration should be given to abolishing fees for clinical research and loading the costs onto other fees and charges. If fees are maintained, more appropriate fees for large multi-centre trials should be introduced.

R9. Phase I trials are recognised by the Review to often involve products of higher risk, and significant technical data describing their pharmacology and toxicology profiles. Dealing with the need for scientific assessment of such clinical trial proposals should occur in line with the proposed clinical trial model in Chapter 7.

R10. Efforts should be made to ensure the time frame for scientific review should be comparable to other overseas agencies – 21 calendar days for Phase I trials and 30 calendar days for all other trials.

R11. The Joint Agency should update the data requirements for scientific review of clinical trial documentation to be more appropriate and consistent with those set out in the European Directive.

R12. TGA should produce guidelines for data requirements for clinical trial evaluation by HRECs.

R13. To recognise the importance of clinical trials, to ensure no interference with the evaluation of marketing applications, and better to recognise the clinical trial activity of all products including prescription medicines, OTC and complementary medicines and medical devices, the Joint Agency should establish a separate Office of Clinical Trials separate from the current branches (particularly the Drug Safety and Evaluation (DSEB) Branch). The Office should have responsibility for all clinical trials.

R14. The Office of Clinical Trials should be pro-active as well as responsive to requests for advice and guidance, and should be more openly cooperative with other groups (eg industry, investigators, consumers, AHEC, NHMRC) to inform stakeholders and promote clinical trials in Australia.

R15. The role of the Joint Agency should be clarified to ensure that its role is to:

- ∉ Advise the HRECs and the NHMRC of regulatory requirements for clinical trials.
- ∉ Assist HRECs in determining how specific trials should be evaluated if requested.
- ∉ Review adverse drug reactions that are both serious and unexpected.
- ∉ Conduct a trial inspection program.

Monitoring and Inspection of Clinical Trials

R16. The Joint Agency should take a more involved role in monitoring clinical trial activity by requiring that sponsors of trials:

- ∉ Submit to the Agency an annual update of the status of each study that is in progress or has been completed in the past year, including the number of patients enrolled in each study and a summary of the clinical status of the product overseas, including in those countries where trials are being conducted and any regulatory actions which may have been taken (e.g. clinical hold or suspensions of trials, marketing approvals or rejections).

R17. The TGA, with a view to the development of the Joint Agency, should develop better capacity for the review of clinical trial adverse events, and should either adopt this role from ethics committees, or provide assistance and guidance in undertaking this task.

R18. The TGA, with a view to establishment of the Joint Agency, should develop an inspection program based on compliance with internationally accepted/agreed GCP requirements.

Ethics Committees and Scientific Assessment

R19. There should be greater clarity as to the role of the scientific assessment and the ethical review of clinical trial submissions. The Review team believes that an opportunity exists to architect a system, in collaboration with the TGA, NHMRC, Australian States and Territories and New Zealand, that could provide a standardised review process for each of these aspects and apply equally across the two countries, and believes the proposed clinical trial model outlined properly balances public health and safety concerns with the encouragement and fostering of research.

R20. The Review Team recognises the value of the CTN system as an attractive proposition in terms of minimal *regulatory* requirements for the conduct of clinical research in Australia and believes the proposed clinical trial model retains the best elements of this system.

R21. More guidance should be provided to HRECs to assist them in determining how best to undertake scientific review of a given clinical trial submission, ie. when to seek additional opinion and from whom. Some trials in the proposed model are to be mandated for specific review, but more detailed guidance should be provided for all other trials.

R22. There should be better information provided to HRECs at the time of review about the overseas status of regulatory review of products being trialled.

R23. The establishment of a limited number of Nationally Accredited Human Research Ethics Committees (NAHRECs), that could potentially provide ethical review for an entire multi-site trial, is recommended.

R24. The establishment and "accrediting" in some way of a small number of specialty-based (eg oncology, general practice) HRECs/SAPs, that could be approached for scientific review, both for trials required to have this review, and if the HREC reviewing the submission thought it necessary, should be undertaken.

R25. Individual "approving authorities" appear currently on the CTN forms in order to confer the right to inspect clinical trial sites on TGA officers. If the legislation could be amended to confer this right automatically to TGA/Joint Agency officers for trials in which the TGA has a regulatory role (ie. unapproved therapeutic goods), it would obviate the need for so many endorsements to be collected by the sponsor.

R26. Making submission to a NAHREC should be available as an option where any trial is to be undertaken at two or more sites.

R27. Providing for mutual recognition of the decisions of NAHRECs by all other HRECs if they wish.

R28. The provision of resources for the establishment of NAHRECs and specialty-based HRECs (including fees for review and Australian Government contributions through NHMRC).

R29. The AHECs role in verifying that HRECs operate to its standards should be strengthened to approach more of an "accreditation".

Australia's Special Access and Authorised Prescriber Schemes

R30. The SAS and Authorised Prescriber Schemes should be retained unchanged in Australia.

R31. TGA should be encouraged to be more proactive in promoting the current guidelines.

A Clinical Trials Register

R32. There should be a mandatory, comprehensive Register including all clinical trials conducted with medicinal products in Australia and New Zealand, with the Register established by legislation.

R33. The Register should be maintained and kept up to date by the TGA/Joint Agency, with the cost of the establishment and maintenance of the Register being met by Government through an ongoing grant to the TGA/Joint Agency.

R34. The purpose of the Register should be to allow widespread knowledge of trials that are ongoing, as well as completed, in order to provide a resource whereby the outcomes of these trials may be known through subsequent contact of the sponsor or investigator(s) concerned. The Register should be in the public domain.

R35. The minimum information to be included in the Register should be the disease being treated, contact details to enable the public to enquire about the trial, and the start and completion dates of the trial. The Register should have a user-friendly search capacity.

R36. It should be made clear that responsibility for the currency of information and contact details remains with the sponsor of the trial and the principal investigator, and not with the TGA. The legislation should make clear the level of information that TGA may disclose to people enquiring about trials on the register.

Infrastructure funding for Cooperative groups

R37. The Review recommends that the issue of increased infrastructure funding for cooperative groups be referred to the NH&MRC for further consideration.

R38. The Review recommends that governments should examine the issue of insurance and indemnification for industry-independent research for the public good as part of their overall strategies for indemnification for the provision of health services generally.

A Trans Tasman Joint Regulatory Agency

R39. Clinical trials should be regulated under a single system within the joint agency.

R40. The scope of clinical trials regulation should cover the range of therapeutic products regulated by the agency, which shall include complementary medicines and medical devices.

R41. The clinical trial system should allow for notifications of trials to the agency and evaluation of scientific data by the agency, based on risk-based classification rules. These rules should be developed by the agency in consultation with industry, consumers, and ethics committees, and clearly annunciated by the agency, possibly in legislation. The clinical trial model proposed outlines what the Review team believes this classification system should be.

R42. The clinical trial system should mandate both ethical and scientific review for some clinical trial proposals, while permitting HREC review for others, with scientific review at the discretion of the HREC concerned. Specific types of trial and trials using particular therapies shall be required to undergo scientific assessment either via TGA or an accredited "Scientific Assessment Panel".

R43. With reference to scientific assessment of some clinical trial documentation, ethics committees should have a range of review avenues including the TGA, Scientific Assessment Panels, and expertise within its own institution, as discussed in Chapter 7 of this report.

R44. Clinical trials should be regulated by the Joint Agency in line with internationally agreed standards. To this end, the new agency should adopt internationally agreed GCP guidelines for medicines and for medical devices.

R45. A transition period should be set to allow continued operation of current arrangements in both jurisdictions, while the joint agency promulgates guidance documents for ethics committees and proposed SAPs, in consultation with the AHEC and HRC.

R46. A comprehensive monitoring program, including review of adverse events and the inspection of clinical trial sites should be implemented immediately by the agency to maintain public confidence.

R47. The key elements of the Australian systems of Special Access and Authorised Prescriber access to unapproved medicinal products should be adopted by the joint agency. These schemes will cover the entire scope of the regulatory program, including medical devices and complementary medicines.

R48. Detailed guidelines should be formulated by the joint agency, giving details of how data should be submitted and evaluated under the proposed clinical trial model, the forms to be used and the obligations and requirements of the sponsors and investigators involved in the trials.

R49. The recommendations in relation to a clinical trials register should be implemented in the context of a Joint Agency.

3. Synopsis of Submissions and Government Response to the Report Recommendations

Submissions

Those who made submissions in the consultation period for the final report are listed at Appendix 1. There were 20 written submissions, including 13 from the pharmaceutical industry, 2 from State or Federal government stakeholders, 3 from researchers or research organisations, primarily cancer-related and one from an institution/HREC. Four of these submissions came from New Zealand stakeholders. One was unrelated to this particular review report.

Government response

The following table summarises the government's response to the recommendations contained in the Bansemer Report. The table includes a note of the organisation responsible for implementation of the recommendation, as accepted (or otherwise amended) by government:

Rec #	**Recommendation**	***Organisation Responsible***	***Response***
The Clinical Trial Notification and Exemption Schemes in Australia			
1	The key elements of the CTX and CTN Schemes and the regional ethics committee and SCOTT systems, should be retained by the Joint Agency with a view to harmonising clinical trial arrangements as discussed in Chapter 11 of this report.	TGA	Accepted.
2	The TGA should issue more guidance to HRECs about what kind of clinical trial submissions should undergo assessment via the Joint Agency or a Scientific Assessment Panel, with the Agency to issue clear definitional statements in an effort to aid all stakeholders in determining the correct route of assessment for clinical trial proposals.	TGA in consultation with NHMRC	Accepted. The TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation" (June 2001) will be reviewed and updated in consultation with the NHMRC and stakeholders. See also Rec. 42.
3	Acknowledgment of lodging a clinical trial exemption from the Joint Agency should be available on-line and the Agency and sponsors should be encouraged to develop and use such systems.	TGA	Accepted. The TGA shall explore options for providing this facility.

4	The timeframe for upgrading of the TGA/Joint Agency's IT and database capacity and for including the clinical trial database should be re-examined.	TGA	Accepted, in the context of a CTN database to extract useful general information, noting that a trial database has been commenced by Sydney University on a grant from the NHMRC.
5	The Joint Agency should produce general performance information about clinical trials and make it readily available, and should report regularly and in some detail on clinical trial activity in Australia/NZ and maintain a database with an appropriate quality system to ensure that analysis and reporting can be done.	TGA	Accepted, noting that the database shall provide data with respect to CTNs only, not the scope of that commenced by Sydney University Clinical Trial Centre, which includes many other trials, such as those with registered medicines (post-market) and others not associated with medicines (e.g. comparison of surgical techniques).
6	The Joint Agency should produce at least an annual report on the clinical trial activity being conducted in Australia and New Zealand, regulated by the Joint Agency. This should be in summary form (so as not to breach confidentiality of information) but should be comprehensive enough to provide informative data on the nature and extent of clinical trial activity.	TGA	Accepted. See Recs. 4 and 5.
7	There should be an examination of the likely costs of the proposed clinical trial model in Chapter 7, in order to ensure that costs are not a barrier to clinical research.	TGA	Accepted. The cost impact of any changes to regulation must be considered prior to implementation.
8	Serious consideration should be given to abolishing fees for clinical research and loading the costs onto other fees and charges. If fees are maintained, more appropriate fees for large multi-centre trials should be introduced.	TGA	Not accepted. This recommendation was not generally supported by stakeholders, particularly the pharmaceutical industry. However, if approval for multi-centre trials is streamlined, this will lower costs.

9	Phase I trials are recognised by the Review to often involve products of higher risk, and significant technical data describing their pharmacology and toxicology profiles. Dealing with the need for scientific assessment of such clinical trial proposals should occur in line with the proposed clinical trial model in Chapter 7.	TGA with input from NHMRC as appropriate	The assessment of risk is a complex issue, not simply based on the Phase of the clinical trial. This will be examined in the context of the development of new processes and guidance for Human Research Ethics Committees, and will be included in the revised TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation".
10	Efforts should be made to ensure the time frame for scientific review should be comparable to other overseas agencies – 21 calendar days for Phase I trials and 30 calendar days for all other trials.	TGA in consultation with NHMRC	Accepted in principle noting that there may be resource implications for both the TGA and Human Research Ethics Committees. The TGA will work towards ensuring uniform timeframes that meet international best practice.
11	The Joint Agency should update the data requirements for scientific review of clinical trial documentation to be more appropriate and consistent with those set out in the European Directive.	TGA	This is accepted, noting that such requirements are consistent at present. More promotion of guidelines may be needed.
12	TGA should produce guidelines for data requirements for clinical trial evaluation by HRECs.	TGA in consultation with NHMRC	Accepted. The TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation" (June 2001) will be reviewed and updated in consultation with the NHMRC and stakeholders.
13	To recognise the importance of clinical trials, to ensure no interference with the evaluation of marketing applications, and better to recognise the clinical trial activity of all products including prescription medicines, OTC and complementary medicines and medical devices, the Joint Agency should establish a separate Office of Clinical Trials separate from the current branches (particularly the Drug Safety and Evaluation (DSEB) Branch). The Office should have responsibility for all clinical trials.	TGA	This proposal was not generally supported by stakeholders, who viewed it as a possible reproduction of resource needs and likely to impact significantly on costs of research. This recommendation is noted, with the understanding that any such establishment would require further consultation given the resource requirements.

14	The Office of Clinical Trials should be pro-active as well as responsive to requests for advice and guidance, and should be more openly cooperative with other groups (eg industry, investigators, consumers, AHEC, NHMRC) to inform stakeholders and promote clinical trials in Australia.	TGA	Accepted in part. Initiatives for advice and guidance will be made, as detailed in other responses.
15	The role of the Joint Agency should be clarified to ensure that its role is to: - Advise the HRECs and the NHMRC of regulatory requirements for clinical trials. - Assist HRECs in determining how specific trials should be evaluated if requested. - Review adverse drug reactions that are both serious and unexpected. - Conduct a trial inspection program.	TGA in consultation with NHMRC	Accepted. The TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation" (June 2001) will be reviewed and updated in consultation with the NHMRC and stakeholders to address provision of information about regulatory requirements and evaluation of trial documentation. The TGA has a role in the review of adverse event reporting and this will be examined in the context of establishing any new processes for clinical trial oversight. The TGA will establish a trial inspection program, in accordance with the standards of comparable regulatory agencies and the EU directive on GCP inspection capability for member states. This shall likely be phased in over 12-24 months.

Monitoring and Inspection of Clinical Trials			
16	The Joint Agency should take a more involved role in monitoring clinical trial activity by requiring that sponsors of trials: - Submit to the Agency an annual update of the status of each study that is in progress or has been completed in the past year, including the number of patients enrolled in each study and a summary of the clinical status of the product overseas, including in those countries where trials are being conducted and any regulatory actions which may have been taken (eg clinical hold or suspensions of trials, marketing approvals or rejections).	TGA	Accepted.
17	The TGA, with a view to the development of the Joint Agency, should develop better capacity for the review of clinical trial adverse events, and should either adopt this role from ethics committees, or provide assistance and guidance in undertaking this task.	TGA with input from NHMRC	Accepted in part. The TGA has a role in the review of adverse events and will provide guidance to HRECs through the revised TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation".
18	The TGA, with a view to establishment of the Joint Agency, should develop an inspection program based on compliance with internationally accepted/agreed GCP requirements.	TGA	Accepted, see Rec.15 also.

Ethics Committees and Scientific Assessment			
19	There should be greater clarity as to the role of the scientific assessment and the ethical review of clinical trial submissions. The Review team believes that an opportunity exists to architect a system, in collaboration with the TGA, NHMRC, Australian States and Territories and New Zealand, that could provide a standardised review process for each of these aspects and apply equally across the two countries, and believes the proposed clinical trial model outlined properly balances public health and safety concerns with the encouragement and fostering of research.	NHMRC	Accepted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review is expected to assist by establishing a national model. Roles and responsibilities within any new model will need to be clarified and guidance provided as appropriate.
20	The Review Team recognises the value of the CTN system as an attractive proposition in terms of minimal *regulatory* requirements for the conduct of clinical research in Australia and believes the proposed clinical trial model retains the best elements of this system.	TGA with input from NHMRC	Accepted. The CTN will be retained.
21	More guidance should be provided to HRECs to assist them in determining how best to undertake scientific review of a given clinical trial submission, ie. when to seek additional opinion and from whom. Some trials in the proposed model are to be mandated for specific review, but more detailed guidance should be provided for all other trials.	NHMRC with input from TGA	Accepted that HRECs need more guidance. The TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation" (June 2001) will be reviewed and updated substantially in consultation with the NHMRC and stakeholders to ensure clear guidance about scientific review.
22	There should be better information provided to HRECs at the time of review about the overseas status of regulatory review of products being trialed.	TGA	Accepted. This issue will be included in the revised TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation".

23	The establishment of a limited number of Nationally Accredited Human Research Ethics Committees (NAHRECs), that could potentially provide ethical review for an entire multi-site trial, is recommended.	NHMRC	Noted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review are expected to assist by establishing a national model.
24	The establishment and "accrediting" in some way of a small number of specialty-based (eg oncology, general practice) HRECs/SAPs, that could be approached for scientific review, both for trials required to have this review, and if the HREC reviewing the submission thought it necessary, should be undertaken.	NHMRC	Noted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review are expected to assist by establishing a national model. The issue of accreditation cannot be addressed until a national model is known.
25	Individual "approving authorities" appear currently on the CTN forms in order to confer the right to inspect clinical trial sites on TGA officers. If the legislation could be amended to confer this right automatically to TGA/Joint Agency officers for trials in which the TGA has a regulatory role (ie. unapproved therapeutic goods), it would obviate the need for so many endorsements to be collected by the sponsor.	TGA	Accepted. This recommendation shall be investigated to establish if such a proposal is legally possible.
26	Making submission to a NAHREC should be available as an option where any trial is to be undertaken at two or more sites.	NHMRC	Noted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review are expected to assist by establishing a national model.
27	Providing for mutual recognition of the decisions of NAHRECs by all other HRECs if they wish.	NHMRC	Noted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review are expected to assist by establishing a national model.

28	The provision of resources for the establishment of NAHRECs and specialty-based HRECs (including fees for review and Australian Government contributions through NHMRC).	NHMRC	Noted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review are expected to assist by establishing a national model. Costs cannot be examined until a model has been identified.
29	The AHECs role in verifying that HRECs operate to its standards should be strengthened to approach more of an "accreditation".	NHMRC	Noted. Initiatives underway through the Australian Health Ministers' Advisory Council (AHMAC) to formulate a national approach to multi-centre ethical review are expected to assist by establishing a national model. The role of AHEC will be considered and clarified when AHMAC has agreed on a national model.
Australia's Special Access and Authorised Prescriber Schemes			
30	The SAS and Authorised Prescriber Schemes should be retained unchanged in Australia.	TGA	Accepted.
31	TGA should be encouraged to be more proactive in promoting the current guidelines.	TGA	Accepted. The TGA will review guidance documents and the publications web page in the context of the new Joint Regulatory Agency.

A Clinical Trials Register			
32	There should be a mandatory, comprehensive Register including all clinical trials conducted with medicinal products in Australia and New Zealand, with the Register established by legislation.	TGA in consultation with NHMRC	Noted. The NHMRC has provided funding for five years to establish a clinical trials register. The register is still under development, however the requirements of the International Committee of Medical Journal Editors and other international initiatives have been taken into account in its establishment. Additionally, the Health Research Council of New Zealand wrote to the NHMRC on 26 Sept 05 indicating its desire to be a formal participant in the register.
33	The Register should be maintained and kept up to date by the TGA/Joint Agency, with the cost of the establishment and maintenance of the Register being met by Government through an ongoing grant to the TGA/Joint Agency.	TGA in consultation with NHMRC	Noted. Future governance arrangements for the register will be decided following a review in year 3 of the 5 year funding.
34	The purpose of the Register should be to allow widespread knowledge of trials that are ongoing, as well as completed, in order to provide a resource whereby the outcomes of these trials may be known through subsequent contact of the sponsor or investigator(s) concerned. The Register should be in the public domain.	TGA in consultation with NHMRC	Noted. Details of appropriate levels of public disclosure are being investigated. Neither the NHMRC nor the TGA have control of the register in its present form, but both may offer advice in the context of a governance board.
35	The minimum information to be included in the Register should be the disease being treated, contact details to enable the public to enquire about the trial, and the start and completion dates of the trial. The Register should have a user-friendly search capacity.	TGA in consultation with NHMRC	Noted. Details about the content of the register and how the information is presented are still being worked through. See Rec. 34.

36	It should be made clear that responsibility for the currency of information and contact details remains with the sponsor of the trial and the principal investigator, and not with the TGA. The legislation should make clear the level of information that TGA may disclose to people enquiring about trials on the register.	TGA in consultation with NHMRC	Noted. Future governance and appropriate levels of public disclosure are being examined. See Rec. 34.
Infrastructure Funding for Co-operative Groups			
37	The Review recommends that the issue of increased infrastructure funding for cooperative groups be referred to the NH&MRC for further consideration.	NHMRC	Whilst the NHMRC is only one of many players supporting clinical trials in Australia, in 2005 the NHMRC funded a round of Enabling Grants which targeted clinical trials infrastructure support. Approximately $10 million was awarded to 8 cooperative groups over five years. Additionally, as part of the 2005 budget a new Government initiative of $5 million per year for the next three years was announced targeting cancer clinical trials infrastructure.
38	The Review recommends that governments should examine the issue of insurance and indemnification for industry-independent research for the public good as part of their overall strategies for indemnification for the provision of health services generally.	DoHA	Noted. This issue was cited by the consultant as outside of the Terms of Reference of the Review, and not commented on further.
A Trans Tasman Joint Regulatory Agency			
39	Clinical trials should be regulated under a single system within the joint agency.	TGA	Accepted. Clinical trial arrangements will be harmonised as far as possible in the context of a Joint Agency.

40	The scope of clinical trials regulation should cover the range of therapeutic products regulated by the agency, which shall include complementary medicines and medical devices that are currently not regulated at the level of TGA scrutiny in New Zealand.	TGA	Accepted. There has always been a policy of accepting "no decrease" in regulatory standards in either nation.
41	The clinical trial system should allow for notifications of trials to the agency and evaluation of scientific data by the agency, based on risk-based classification rules. These rules should be developed by the agency in consultation with industry, consumers, and ethics committees, and clearly enunciated by the agency, possibly in legislation. The clinical trial model proposed outlines what the Review team believes this classification system should be.	TGA	Accepted. Further consultation shall be necessary in determining a suitable risk-based regulatory framework.
42	The clinical trial system should mandate both ethical and scientific review for some clinical trial proposals, while permitting HREC review for others, with scientific review at the discretion of the HREC concerned. Specific types of trial and trials using particular therapies shall be required to undergo scientific assessment either via TGA or an accredited "Scientific Assessment Panel".	TGA in consultation with NHMRC	Not accepted. There is no support amongst Australian stakeholders for this recommendation. Both scientific review and ethical review are important aspects of assessment of clinical trial proposals. Roles and responsibilities will be clarified through the revised TGA guidance document "Human Research Ethics Committees and the Therapeutic Goods Legislation".
43	With reference to scientific assessment of some clinical trial documentation, ethics committees should have a range of review avenues including the TGA, Scientific Assessment Panels, and expertise within its own institution, as discussed in Chapter 7 of this report.	NHMRC with input from TGA	Accepted. HRECs currently have flexibility to draw on a range of experts to inform their deliberations. This flexibility is provided through the *National Statement on Ethical Conduct in Research Involving Humans*. Any additional scientific assessment avenues involving the TGA would have to be considered on a cost-recovery basis.

44	Clinical trials should be regulated by the Joint Agency in line with internationally agreed standards. To this end, the new agency should adopt internationally agreed GCP guidelines for medicines and for medical devices.	TGA	Accepted. This is already the case.
45	A transition period should be set to allow continued operation of current arrangements in both jurisdictions, while the joint agency promulgates guidance documents for ethics committees and proposed SAPs, in consultation with the AHEC and HRC.	TGA with input from NHMRC as appropriate	Accepted for existing trials. New trials commenced under the proposed Joint Agency will be expected to implement the regulations of that Agency.
46	A comprehensive monitoring program, including review of adverse events and the inspection of clinical trial sites should be implemented immediately by the agency to maintain public confidence.	TGA	Accepted. The TGA has a role in adverse event review at present, and its monitoring activities are complementary to those of HRECs. An inspection program shall be implemented to afford an increased degree of monitoring without impeding research.
47	The key elements of the Australian systems of Special Access and Authorised Prescriber access to unapproved medicinal products should be adopted by the joint agency. These schemes will cover the entire scope of the regulatory program, including medical devices and complementary medicines.	TGA	Accepted.
48	Detailed guidelines should be formulated by the joint agency, giving details of how data should be submitted and evaluated under the proposed clinical trial model, the forms to be used and the obligations and requirements of the sponsors and investigators involved in the trials.	TGA	Accepted in the context of coming to an agreement about a clinical trial model for the Joint Agency. Appropriate documentation will be created.
49	The recommendations in relation to a clinical trials register should be implemented in the context of a Joint Agency.	TGA in consultation with NHMRC	Noted. The NHMRC has provided five-year funding for establishment of a clinical trials register, commencing in 2005. Both the TGA and New Zealand are participating in the development of the register.

4. The Recommendations of the Bansemer Report

Historical context

Under the *Therapeutic Goods Act 1989* and its associated Regulations, therapeutic goods for human use that are imported, manufactured in Australia, supplied by a corporation, supplied interstate or to the Commonwealth, or exported from Australia must be included in the Australian Register of Therapeutic Goods (ARTG) unless specifically exempted from that requirement. The ARTG is the key point of control for the supply of therapeutic products in Australia.

Products must undergo a risk-based evaluation and be included on the Australian Register of Therapeutic Goods before they can be supplied in Australia. However, the legislation also has provisions that allow limited supply of products not included on the ARTG (so-called "unapproved" therapeutic goods). The main avenues of access to such goods are:

- The Special Access Scheme (SAS);
- Clinical Trials (CTN and CTX) schemes;
- Authorised Prescribers; and
- Importation for personal use.

These mechanisms of access are well established and their operation is supported by a range of "*Access to Unapproved Therapeutic Goods"* documents published on the TGA website. It is chiefly these avenues of access that were examined by the Bansemer review, in terms of their smooth function, public health and safety, allowing appropriate access to unapproved therapies in specific circumstances, ongoing adherence to more rigorous international standards, and the context of a Trans Tasman Regulatory Agency forming in the near future. While the issue of a clinical trials register was also examined and provoked much debate and discussion, such a register reflects a desire for access to information about use of unapproved therapeutic goods, rather than use of the goods themselves.

A key point noted by the Review was that the legislation obliges the TGA to balance the broader community interest that therapeutic products available in Australia have acceptable quality, safety and efficacy/performance with the need for timely access for individual patients in need of potentially life saving and enhancing treatments.

It is also important to appreciate that unapproved therapeutic goods have undergone little or no evaluation of quality, safety or efficacy by the Therapeutic Goods Administration. Accordingly, use of all such goods carries with it some risks that have not been defined in the Australian context. As such, use of these products is considered to be experimental and should be guided by the principles and practices outlined in the NHMRC's *National Statement on Ethical Conduct in Research Involving Humans* (1999). It is in relation to this issue, that ethics committees (Human Research Ethics Committees or HRECs) have an important role to play because of their developed expertise in assessing risks and precautions in research involving humans. Such ethics committee involvement is mandatory for all CTN and CTX trials in Australia, as well as the bestowing of authorised prescriber status by the TGA on medical practitioners, to supply unapproved therapeutic goods for specific medical conditions.

Clinical Trials In Australia

Clinical trials in Australia that make use of unapproved therapeutic goods are regulated currently by the Therapeutic Goods Administration (TGA) under two schemes – the Clinical Trial Notification (CTN) Scheme and the Clinical Trial Exemption (CTX) Scheme.

Under the CTN Scheme, all material relating to the trial, including the trial protocol, scientific information about the product and information for participants is submitted directly to an institution for review. Approval for the conduct of the trial is given by the institution on the advice of its HREC after review of the scientific and ethical validity of the trial. The trial can commence once the TGA has been notified of these approvals by the sponsor of the trial. Under the Therapeutic Goods legislation, the HREC is responsible for monitoring the conduct of the trial at its institution. It may withdraw its approval for the continued conduct of the trial if it considers the rights, wellbeing and safety of participants are unduly at risk, in which case the trial must stop. The TGA receives reports of serious and unexpected adverse events from the sponsor of the trial and has the power to stop clinical trials where it considers there is a risk to public health and safety.

Under the CTX Scheme, applications to conduct clinical trials are submitted to the TGA for evaluation and comment. The TGA reviews summary scientific data about the safety of the product and decides whether or not to object to its proposed usage. Clinical trials cannot proceed until any TGA objections have been overcome. If no objection is raised by the TGA, the sponsor may conduct any number of clinical trials of the product under that particular CTX approval without further assessment by the TGA, provided such use falls within usage guidelines approved by the TGA. However, approval to conduct individual trials under the CTX must be given by the institution, which is responsible for review and approval of the trial protocol and the ethical approval for the study. Each trial conducted under the CTX must be notified to the TGA within 28 days of its commencement. The monitoring roles of the HREC and TGA are the same as for the CTN scheme.

Clinical trial activity regulated by the TGA is currently averaging approximately 750 trials of therapeutic products per annum (medicines ~700: medical devices ~50). Pharmaceutical, biotechnology or medical device companies sponsor approximately 65% of trials, with the remainder sponsored mostly by research groups, individual doctors, universities and hospitals. Importantly, almost all trials are being conducted under the CTN Scheme.

To understand the current levels of trial activity in the context of the operation of the CTN and CTX schemes, it is important to appreciate that the regulatory and ethical frameworks under which clinical trials have been conducted in Australia have evolved considerably over the past 30 years.

The Review noted there is an overview of the history of these frameworks contained within the TGA's document *Access to Unapproved Therapeutic Goods – Consolidated Information*, available on the publications page of the TGA website. Chapter 3 of that document describes the repeated changes to the administration and legislation underpinning clinical trial regulation that have led to reduced involvement of the regulatory agency in the approval of trial protocols and review of scientific data over the past 20 years. This has coincided with greater responsibilities for ethics committees and institutions in the clinical trial approval process.

The current dual system of CTN and CTX arose with the introduction of the CTN Scheme in 1991. At the time of its introduction, the CTN was a significant departure from previous clinical trial approval procedures. Questions were raised about whether the CTN Scheme would afford adequate protection for trial participants and whether ethics committees would be able to cope with additional responsibilities and pressures placed on them. The last major review of the operation and effectiveness of the CTN, undertaken in 1993, concluded the CTN Scheme should be retained as an alternative to the CTX Scheme, while acknowledging that it was still too soon to draw any firm conclusions. At the time it was also noted that, although the CTN Scheme was most suited to the conduct of later phase studies, the CTN option should be available for earlier phase studies providing there was adequate preclinical review, particularly with respect to safety. Further, the 1993 review was firmly of the opinion that it was appropriate for ethics committees to be responsible for monitoring research projects for which they had given ethical approval.

More recently, a 1998 review was conducted to examine whether the current regulatory arrangements for the TGA's various notification schemes (CTN Scheme and the Category A arrangements for SAS) could be relied on to provide the balance between access to important unapproved treatments and safeguards to protect the public interest required by the legislation. The 1998 review led to several important amendments of the Therapeutic Goods legislation including authority for the TGA to request information, including protocols, relating to the use of therapeutic goods in clinical trials and the inspection of clinical trials. The legislative changes also made it mandatory for sponsors to conduct trials in accordance with internationally agreed good clinical practice (GCP) guidelines and for investigators to adhere to protocols approved by the HREC. The legislative changes also provided the power for the TGA to inspect clinical trial sites to verify adherence to good clinical practice standards if required.

Standards of ethical review of clinical trial documentation in Australia are maintained primarily by the guidance of the NHMRC and its Principal Committees, such as the Australian Health Ethics Committee (AHEC). Sponsors and investigators of clinical trials in Australia are required, as part of the authority to supply unapproved therapeutic goods, to adhere to international standards of Good Clinical Practice (GCP), outlined in the Note for Guidance document CPMP/ICH/135/95, formally adopted in Australia by the TGA. Inspection of trial sites initiates an extra measure of assurance by verifying such compliance in a number of trials annually, promoting Good Clinical Practice principles and verifying data credibility.

It is also worth nothing that recently a report into access of extemporaneously compounded products was conducted by Dr. Brian Wall on behalf of the TGA. This represents another major avenue of access to unapproved therapeutic goods. Dr. Wall's report is available on the TGA website at:

http://www.tga.gov.au/meds/extempcomp.htm (current as at 18.10.05)

At the same time as the final Bansemer Report was released by the TGA and NHMRC for consultation, the Australian Health Minister's Advisory Council (AHMAC) was approached jointly by the NHMRC and NSW Health, to suggest a way forward for the streamlining of ethical and scientific review of multi-centre research in Australia. AHMAC subsequently established a working party to investigate and report on proposals for improving current procedures. AHMAC's intention is to recommend a single, national system and a report is expected in the first half of 2006. Any therapeutic goods legislation changes or proposed

amendments to TGA or NHMRC practices would need to take these recommendations into account.

International initiatives

In addition to the issues raised above, impetus for a detailed review of clinical trial arrangements in Australia has come from two important international initiatives. Firstly, over the past 10 years there has been sustained progress toward the global harmonisation of regulatory requirements for medicines (through the International Conference for Harmonisation on Technical Requirements for Registration of Pharmaceuticals for Human Use, known as ICH) and medical devices (through the Global Harmonisation Taskforce for Medical Devices, known as GHTF).

With the move to the acceptance of common data packages for marketing submissions across the various jurisdictions, there has been recognition that the basis of these data packages, i.e. the clinical trials used to generate these data, should also be harmonised with respect to design, conduct, recording and reporting of clinical trials. Adherence with GCP principles provides assurance that the rights, safety and well-being of trial participants are protected and that clinical trial data are credible. Inspection of clinical trials by regulators is seen as an integral part of achieving this assurance. At present, although the acceptance of the possibility that an inspection may be carried out by the TGA is required of sponsors and investigators by legislation in the case of CTX and via undertakings given on the CTN form in the case of CTN in Australia, very few actual inspections of clinical trials are carried out by the TGA.

At the time of the initiation of the Bansemer Review, the United States of America, the United Kingdom, Canada and Sweden, countries that are considered to have regulatory systems for medicinal products comparable to that in Australia, had all implemented regulatory programs for inspecting clinical trials.

In addition, the European Union (EU) Directive 2001/20/EC *Directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use* has been passed and guidance issued. One of the key requirements of the Directive is that Member States must set up inspection systems enforced by legislation to ensure compliance of clinical trials with GCP principles. The date required for EU members to have this capability in place has now passed, such that clinical trial inspections are considered an integral part of the drug development process in the EU, whether conducted by Member States or the central European Medicines Evaluation Agency (EMEA)

It is, therefore, seen as important for Australia to develop and implement a GCP inspection program so it does not fall behind its peers in this important international development. This has implication also for the way that data gathered from clinical trials conducted in Australia may be viewed by other regulatory agencies when submitted as part of a marketing application.

The proposed Trans Tasman Joint Regulatory Agency

The second important international consideration is that in June 2000 the Australian and New Zealand Governments reached in-principle agreement to establish a single Trans-Tasman

therapeutic products agency to regulate medicines and therapeutic products as a means of implementing the Trans-Tasman Mutual Recognition Agreement (TTRMA) signed in 1998.

Formal agreement for the initiative was reached in 2003 and it is the intention of both governments that from 1 July 2006 the joint agency will replace the Australian TGA and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).

In recognition of existing differences in the regulatory and ethical frameworks for clinical trials and access to unapproved therapeutic goods by other means in Australia and New Zealand, the Review was asked to examine the current regulatory provisions for clinical trials and access to unapproved therapeutic goods in both Australia and New Zealand. The Review team was asked to suggest arrangements for the regulation of these activities under a joint Australia / New Zealand therapeutic goods regulatory agency, with a view to harmonisation where possible.

One of the foundations of the agreement to proceed with a Joint Agency is the understanding that the joint regulatory framework will not result in a lowering of regulatory standards in either jurisdiction. Furthermore, there is an explicit expectation within the terms of the Treaty that the Joint Agency will regulate therapeutic products in keeping with international best practice. Unfortunately, 'international best practice' is not readily defined and can be interpreted according to one's frame of reference. Returning to the earlier concept of needing to achieve balance between timely access to treatments and the need for availability of products of acceptable quality, safety and efficacy, it can be appreciated that 'international best practice' could be defined anywhere from ensuring protection of patient safety through to early access to treatments and research. It is intended that the Joint Agency shall regulate to similar standards in comparable regulatory agencies around the world. This includes with respect to avenues of access to unapproved therapeutic goods.

Other developments

In April 2003, the TGA initiated the recall of more than 1600 complementary medicines from the Australian marketplace. It was the largest recall of medicines in Australia and heightened interest in complementary medicines. The recall was a result of the failure of one medicine manufacturer to maintain appropriate manufacturing and quality control standards.

Following the recall, consumer groups, health professionals, researchers and practitioners raised concerns regarding the level of trust that can be placed in complementary medicines. These concerns included doubts about the reliance consumers may have in the information available about complementary medicines and confidence in their effectiveness and the education and training of practitioners supplying complementary medicines.

These concerns were also seen to extend to the regulation of the supply of unapproved complementary medicines.

In May 2003, to reassure the public and maintain confidence in Australia's reputation as a supplier of high quality and safe medicines, the Australian Government established the Expert Committee on Complementary Medicines in the Health System (the Expert Committee). This committee reported to the Parliamentary Secretary to the Minister for Health and Ageing in September 2003.

This Review acknowledged the report and recommendations of the Expert Committee, and did not revisit the broad issues already studied by that Committee. However, the

recommendations of this Review's report apply to the regulation of unapproved complementary medicines as equally as to other unapproved therapeutic products.

Implementation

Clinical Trials

It is clear from the report that the CTN/CTX system is recommended for retention in Australia. What remains to be defined is how it shall be refined to enhance its practicality, strengthen the standard of the research carried out under its auspices, and shorten timelines associated with it. For example, the results of the AHMAC working party's deliberations on a model for review of multi-centre research shall impact on timelines for ethical review, and may, depending on what is recommended, require minor legislative changes to the Therapeutic Goods legislation. Introduction of clinical trial inspections for a small number of trials per annum shall not delay research in any way, but will require the regulator to put in place a framework by which such inspections can operate.

It is also clear that, for historical reasons, New Zealand intends to preserve the separate systems of ethical and scientific review of clinical trial documentation, i.e. geographic ethical reviews and the SCOTT committee for scientific review. Both countries regulate trials in keeping with international GCP standards, but fulfil these requirements differently. The Joint Regulatory Agency, with further stakeholder consultation prior to implementation, shall develop a risk-based classification model for the ethical and scientific review of clinical trial documentation such that scrutiny of trials in each nation is of a similar degree, albeit being achieved via different means. The draft Medicines Rule currently proposed for the Australia Nez Zealand Therapeutic Products Authority includes provision for CTN and CTX-like schemes that will allow both countries to regulate clinical trials in keeping with international GCP standards. Mandating regulatory review of Phase I trials is not in keeping with a risk-based model and is not supported by government. The government recognises that Australian stakeholders prefer an inclusive review approach of ethical and scientific concerns, whereas New Zealand has a separate, geographical ethics review and central scientific review.

Clinical Trials Register

All stakeholder groups recognised in principle the benefits that such a clinical trial register could bring. These are well described in the Bansemer report and will not be elaborated upon here. A pilot register has been funded by a grant from the NHMRC, to be conducted by the clinical trials unit at the University of Sydney. An advisory board including NHMRC, TGA, and New Zealand representatives is to be established to advise on such issues as scope of trials encompassed by the register, as well as the level of detail about research that is make up a register entry, and other general operational advice. This pilot initiative shall be reviewed at appropriate intervals and a decision made at a future date with respect to continued funding.

Clinical Trials Inspection

It is clear from international trends in all comparable regulatory arenas that clinical trials conducted in Australia must be subject to the possibility of inspection by the regulator for compliance with GCP standards. This is necessary for two key reasons. Firstly, to support the credibility of such research as part of marketing dossiers submitted by the pharmaceutical industry to regulatory agencies worldwide. Such research may only be look upon as lending

any weight to a scientific dossier if it has been conducted to these standards *and subject to verification.* While the CTN system provides a minimum of red tape for the conduct of research in Australia, it only comprises a reassurance by the trial sponsor that GCP is being followed. Knowledge of GCP standards will clearly vary from sponsor to sponsor, so an increased regulatory role will go further to ensure uniform standards of clinical research. Secondly, it is the primary role of any regulator to protect and promote the health of the public. Devoting more resources to ensuring clinical research meets agreed international standards of conduct and patient safety provides an additional and key safeguard to protecting the rights, health and well-being of clinical trial subjects.

A pilot GCP inspection programme shall be established as part of the Joint Regulatory Agency, with much in-house expertise already having been developed. The program shall initially be voluntary for a one-year period from 1 July 2006, similar to the establishment scenario conducted by Health Canada for that country's GCP inspection programme. Thereafter, the inspection unit shall aim to review approximately 2% of clinical trials per annum (i.e. around 15-20 trials), encompassing both inspections where concerns have been raised, and other, "random" inspections to promote and verify GCP awareness among sponsors and investigators. The programme shall be funded from general TGA revenue.

Special Access Scheme and Authorised Prescribers

The Special Access Scheme and Authorised Prescriber Schemes were found to be fulfilling their intended function in the Australian context and were recommended for continuance without substantial alteration. Consultation in New Zealand did not reveal any objection to these systems, and the Joint regulator shall therefore implement similar systems in New Zealand as well.

Guidance documents and statistics

These publication shall be reviewed, upgraded, and published by the relevant agency as detailed in the response table in Chapter 3.

5. Appendix 1: Terms of Reference and Consultation Strategy of the Review

Terms of Reference

The terms of reference for the review are described below. They included a complete examination of methods of access to unapproved therapeutic goods in Australia, with any comments taking light of the fact that the TGA shall be part of a Trans Tasman Regulatory Agency at a future date.[1]

The review involved consideration of the following:

- existing legislative and regulatory controls for clinical trials, and existing mechanisms relating to access to unapproved therapeutic goods, e.g., special access scheme, authorised prescriber scheme, etc.;
- international practices in comparable countries, e.g., the European Union, Canada, United States;
- the cost of regulation, and the existing fees and charges model for clinical trial notifications/applications in Australia;
- national and international standards relating to consumer protection, and the protection of participants in clinical trials;
- issues relating to public safety and timely access to therapies;
- the ongoing development of a proposal for the establishment of a Trans Tasman regulatory agency, which will result in a single therapeutic goods market between Australia and New Zealand.

The review team consulted widely and provided a number of opportunities for stakeholder comment throughout the review process. Stakeholders included consumers, industry, health professionals, researchers, and human research ethics committees.

The review was to examine and advise on:

- the current regulatory systems for clinical trials in Australia and New Zealand;
- the current regulatory systems for access to unapproved therapeutic goods in Australia and New Zealand;
- international practices in comparable countries, and their relevance and applicability to Australia and New Zealand with regard to the volume, scope and safety of clinical research conducted in Australia and New Zealand;
- any necessary improvements to the current system so as to maximise protection of patient safety and to maintain public confidence;
- the need and practicability of a clinical trial register system for Australia, and
- barriers to the further development of clinical research in Australia.

Oversight for the review was provided by a Steering Committee consisting of relevant Australian and New Zealand representatives, and chaired by the Chief Medical Officer of the Department of Health and Ageing. The committee is described more fully below.

The review was to be completed by the end of December 2003.

1. where this includes medicines and medical devices

Steering Committee

The Steering Committee met on a regular basis to provide advice and oversight of the review process. The members of the committee were:

Chair

Professor Richard Smallwood
Chief Medical Officer
Department of Health & Ageing

Members

Mr Terry Slater
National Manager
Therapeutic Goods Administration

Professor Alan Pettigrew
Chief Executive Officer
National Health & Medical Research Council

Dr Leonie Hunt
Director, Drug Safety Evaluation Branch
Therapeutic Goods Administration

Dr Jon Rankin
Head, Experimental Drugs Section
Drug Safety Evaluation Branch
Therapeutic Goods Administration

Dr Stewart Jessamine
Senior Advisor
Medsafe
New Zealand Ministry of Health

Dr Bruce Scoggins
Chief Executive Officer
New Zealand Health Research Council

Dr Richard Robson
Chair
Standing Committee on Therapeutic Trials (SCOTT)

Contact Officers

(until 30 June 2003)
Ms Jocelyn Kula
Project Officer
Clinical Trials Review

(from June 2003)
Dr Jon Rankin
Head, Experimental Drugs Section
Drug Safety Evaluation Branch

Consultation Strategy

On 24th April 2003, Professor Richard Smallwood, the then Chief Medical Officer of the Commonwealth, wrote to a wide range of specific stakeholders in both Australia and New Zealand in the following terms:

Call for Expressions of Interest

Review of the Australian Arrangements for Clinical Trials and Access to Unapproved Therapeutic Goods

The Therapeutic Goods Administration (TGA) and the National Health and Medical Research Council (NHMRC) have initiated a review of the Australian arrangements for clinical trials and access to unapproved therapeutic goods. This review is timely in light of recent changes to clinical trial arrangements in comparable countries, e.g., the European Union, Canada, etc., and to confirm that the regulation and oversight of clinical research ensures the protection of trial participants and the public interest. In addition, the Commonwealth Department of Health and Ageing needs to be sure that the present arrangements are suitable as it moves towards the establishment of a joint Australia / New Zealand therapeutic goods regulatory agency.

This review will examine the current regulatory provisions for clinical trials and access to unapproved therapeutic goods in Australia and New Zealand; and assess international practices in comparable countries (in terms of volume, scope and safety of clinical research conducted) for their relevance and applicability to Australia and New Zealand.

The primary objectives of the review are to:

- identify any necessary improvements to the current arrangements, thereby maximising protection of patient and trial participant safety, and maintaining public confidence;
- assess the need for, and practicability of, a clinical trial register system; and
- identify any barriers to the further development of clinical research.

A copy of the Terms of Reference for the review is enclosed for your information.
The review, which is to be conducted by a consultant, Mr Alan Bansemer, will involve consultation with interested individuals and organisations. Oversight will be provided by a Steering Committee that I chair, and that includes representatives from the TGA, NHMRC, MedSafe (the New Zealand Medicines and Medical Devices Safety Authority) and the Health Research Council of New Zealand, as well as experts in the field of clinical trials.

You are invited to provide input on one or more matters covered by the Terms of Reference, for consideration by the consultant.
In this regard, an indication of your interest, or any other enquiries, should be directed to the Review project officer, Ms Jocelyn Kula, by 25 May 2003, using the following contact information:

Ms Jocelyn Kula
Project Officer
Clinical Trials Review
Therapeutic Goods Administration (MDP 122)
P.O. Box 100
Woden ACT 2606
Tel: (02) 6232 8665
Email: jocelyn.kula@health.gov.au
I look forward to your participation in this important review.

On 18th June 2003, that first letter was followed up by a further notification and formal call for submissions to those potentially interested stakeholders who had registered their interest in response to the first letter, expressed by Ms Jocelyn Kula in the following terms:

Call for Submissions

> **Review of the Australian Arrangements for Clinical Trials and Access to Unapproved Therapeutic Goods**
>
> Thank you for your response to the Therapeutic Goods Administration's (TGA) and the National Health and Medical Research Council's (NHMRC) notice regarding a Review of the Australian arrangements for clinical trials and access to unapproved therapeutic goods.
>
> The purpose of this letter is to inform you of the next steps in the Review.
> At its most recent meeting, the Clinical Trials Review Steering Committee decided that the deadline for submissions to the Review shall be **10 July 2003**.
>
> All submissions should be directed to the following address:
> Ms Jocelyn Kula
> TGA-NHMRC Clinical Trials Review
> c/o Therapeutic Goods Administration
> MDP 122
> PO Box 100
> Woden
> ACT 2606
>
> In addition, please be advised that in response to the high level of stakeholder interest, the overall time line for completion of the Review has now been extended to 30 September 2003.
>
> Using the preliminary comments that many of you have submitted as a guide, Mr Alan Bansemer (the consultant carrying out the Review) and his associates have begun meeting with stakeholders, and further interviews will be arranged once all submissions have been received. A series of focus groups will also be organised in Sydney, Melbourne, Christchurch and Auckland for the end of July/ early August.
>
> We look forward to receiving any additional information you may wish to provide to this important Review.
>
> Should you wish to discuss this correspondence further, please do not hesitate to contact me by email at jocelyn.kula@health.gov.au or by telephone on (02) 6232 8665.

A list of those who provided written submissions to the review process is provided at Appendix 2. During its consultative phase, the Review also met for numerous small discussions with stakeholders who had expressed a wish to meet with the Review Team and to present oral submissions. A list of such persons is presented at Appendix 3.

Facilitated Workshops were conducted on Tuesday 11 November 2003 (in Sydney) and on Thursday 13 November 2003 (in Melbourne) to examine significant issues that had come to light from the submissions received and from the interviews conducted. Similarly, two

workshops were conducted in New Zealand with similar stakeholder groups. Participants at the Workshops included the Review Team, TGA officials (Australian workshops), Medsafe and SCOTT committee representatives (New Zealand workshops) and a wide range of persons invited from among those who had made submissions or who had participated in the interview program.

The completed report was presented to the TGA and NHMRC by Mr. Alan Bansemer in late 2004. A three-month consultation period was provided for stakeholder feedback on the completed document, ending on 8th July 2005. A list of those persons or organisations that provided written comments is located at Appendix 1.

6. Appendix 2: Summary of submitters to the consultation process on the final report

Amgen Australia
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03 9818 5123 (Fax)

AusBiotech
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03 9208 4204

Australian Medical Devices Industry Action Agenda
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02 6213 6480 (Ph)

Australian Self-Medication Industry
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Pharmaceutical Industry Action Agenda Implementation Group
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NHMRC response
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Researched Medicines Industry
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G.P.O. Box 1670N
Melbourne VIC 3001

Medicines Australia
Level 1, 16 Napier Close
Deakin ACT 2600

7. Appendix 3: Written Submissions received in response to written calls for submissions, public advertisements and focus groups in Australia and New Zealand

Organisation	Date
Akzo Nobel / Organon Australia Pty Ltd	10 July 2003
AusBiotech	24 November 2003
Austin and Repatriation Medical Centre Human Research Ethics Committee	Undated
Australian Consumers' Association	June 2003
Australian Hepatitis Council	14 July 2003
Australian Nuclear Science and Technology Organisation	14 July 2003
Australian Nuclear Science and Technology Organisation	24 July 2003
Baker Heart Research Institute (Dr Reid)	5 June 2003
Baker Heart Research Institute (Prof Jennings)	10 June 2003
Cancer Council of Australia	8 July 2003
Cancer Voices NSW	23 July 2003
Christine Hirst and Associates	22 July 2003
Clinical Oncological Society of Australia	27 May 2003
Clinical Trials Centre, St Vincent's Hospital.	May 2003
Clinical Trials Victoria	30 June 2003
Consumers' Health Forum of Australia	3 September 2003
Datapharm Australia	9 July 2003
Department of Health, Western Australia	16 June 2003
Genesis Research and Development Corporation Ltd, New Zealand	23 May 2003
GlaxoSmithKline	May 2003
GlaxoSmithKline	28 November 2003
Jean Hailes Foundation	30 July 2003
Kendle International	15 May 2003
Lowenthal, Professor RM, Director of Medical Oncology, Royal Hobart Hospital	19 May 2003
Medical Industry Association of Australia	26 May 2003
Medical Industry Association of New Zealand	21 May 2003
Medicines Australia	10 July 2003
Merck Sharp and Dohme	4 July 2003
Merck Sharp and Dohme	2 September 2003
Monash University, Department of Epidemiology and Preventive Medicine	2 June 2003
Monash University, Faculty of Medicine	27 May 2003
National Association of People Living with HIV/AIDS (NAPWA)	July 2003

NHMRC Clinical Trials Centre	28 July 2003
NHMRC Clinical Trials Centre	17 November 2003
Novo Nordisk	22 May 2003
NSW Department of State and Regional Development	22 May 2003
NSW Health	14 July 2003
Office of the NHMRC, Health Ethics Section	23 May 2003
Office of Devices, Blood and Tissues, TGA	17 October 2003
Peter MacCallum Cancer Centre	30 June 2003
Pharmaceutical Benefits Branch, Department of Health and Ageing	21 July 2003
Pharmaceutical Industry Action Agenda	11 July 2003
Quintiles Pty Ltd	11 July 2003
Royal Children's Hospital Melbourne, Ethics and Training Office	9 July 2003
Royal Australasian College of Surgeons	28 May 2003
Servier Laboratories (Australia) Pty Ltd	22 May 2003
Society of Hospital Pharmacists of Australia	14 July 2003
Svec, Dr Jennifer & Cleal, Dr Andrea	22 July 2003
Sydney Centre for Reproductive Health Research	23 July 2003
UNSW - Pro-Vice-Chancellor (Research)	3 June 2003
Wesley Radiation Oncology Pty Ltd	11 July 2003

8. Appendix 4: Verbal Submissions received

Interviewee	Date
Associate Professor Joe Tjandra, Chair of the Australian Gastrointestinal Trials Committee, [Colorectal Surgical Oncology Department, University of Melbourne)	1 July 2003
Associate Professor Mark Rosenthal (CEO), - Centre for Developmental Cancer Therapeutics (now Cancer Trials Australia), Royal Melbourne Hospital, Grattan Street, Parkville.	2 July 2003
Dr Anne ALTMANN, Clinical Research Manager, International Centre for Therapeutic Research (Australia and New Zealand, Servier Laboratories, 8 Cato Street, Hawthorn, Victoria.	31 July 2003
Dr Christopher Reid, Head, Cardiovascular Disease Prevention Unit and Director ANBP2.	1 July 2003
Dr David Christie, Radiation Oncologist, Chair of the Australian Radiation Oncology Reference Group, Wesley Hospital, Level 3, Pacific Private Clinic, 123 Nerang Street, Southport.	11 Aug 2003
Dr David Herd, Director of Regulatory Affairs, GlaxoSmithKline, 1061 Mountain Highway, Boronia, Victoria.	3 July 2003
Dr Grant Cameron, Director of Palliative Care, Royal Brisbane Hospital and Prince Charles Hospital and Chairman of the Health Research Ethics Committee, Prince Charles Hospital, Old Queensland Institute Building, Herston Road, Herston, Qld.	11 Aug 2003
Dr Greg Pearce, Medical Advisor, Alphapharm Pty Ltd, Chase Building 2, Wentworth Park Road, Glebe, NSW.	13 Aug 2003
Dr Helen McARDLE, Chair, Southern Tasmania Health and Medical Human Research Ethics Committee, 9th Floor, A block, Royal Hobart Hospital, 28 Campbell Street, Hobart Street, Hobart.	22 July 2003
Dr Jacqueline Waterkeyn PhD, Regulatory Affairs and QA Manager, Clinical Trials Victoria, c/o Baker Heart Research Institute, PO Box 6083, St Kilda Rd Central, Melbourne.	30 July 2003
Dr Jean-Luc PICKER, Director, International Centre for Therapeutic Research (Australia and New Zealand, Servier Laboratories, 8 Cato Street, Hawthorn, Victoria.	31 July 2003
Dr John Miller, Medical Director, Novo Nordisk Pharmaceuticals Pty Ltd, Level 3, 21 Solent Circuit, Baulkham Hills, NSW.	15 Aug 2003
Dr L Damien Cramer, Head of Clinical R&D Operations,[GlaxoSmithKline, 1061 Mountain Highway, Boronia, Victoria.	3 July 2003
Dr Linda Swan, Medical Director, Merck Sharp & Dohme (Aust) Pty Ltd, 54-68 Ferndell Street, South Granville, NSW.	15 Aug 2003
Dr Mark Nelson, Department of Epidemiology and Preventive Medicine, Monash University.	30 July 2003

Dr Megan SARSON-LAWRENCE, Project Officer, Centre for Developmental Cancer Therapeutics, 6th Floor, Charles Connibere Building, Royal Melbourne Hospital, Grattan Street, Parkville.	30 July 2003
Mr Aran Maree, Clinical Research Manager, Merck Sharp & Dohme (Aust) Pty Ltd, 54-68 Ferndell Street, South Granville, NSW.	15 Aug 2003
Mr Brian Vale, Chief Executive Officer, Medical Industry Association of Australia, Level 2, 82 Christie Street, St Leonards, NSW.	15 Aug 2003
Mr Carlo Maccarrone, Head of Clinical Research, GlaxoSmithKline, 1061 Mountain Highway, Boronia, Victoria.	3 July 2003
Mr Geoff Young, Principal Advisor, Regulatory Affairs, Quintiles Pty Ltd, Levels 17/18 Northpoint 100 Miller Street, North Sydney, NSW.	12 Aug 2003
Mr Lyle Borlase (Manager, Research; Department of Economic Development, Tasmania)	25 Jun 2003
Mr Martyn Goddard, Senior Policy Officer, Health, Australian Consumers' Association, 57 Carrington Road, Marrickville, NSW.	13 Aug 2003
Mr Peter Carnavan, ANET Policy Officer, National Association of People Living with HIV/AIDS, Level 1, 222 King Street, Newtown, NSW.	13 Aug 2003
Mr Rodney Eccleston, Executive Director of Research, St Vincent's Hospital, 406 Victoria Street, Darlinghurst, NSW.	14 Aug 2003
Mr Warren Back, Regulatory Affairs Manager, Merck Sharp & Dohme (Aust) Pty Ltd, 54-68 Ferndell Street, South Granville, NSW.	15 Aug 2003
Ms Brigitte Kendall, Clinical Research Manager, Organon (Aust) Pty Ltd, Unit B, 31-33 Sirius Road, Lane Cove, NSW.	12 Aug 2003
Ms Carmel Edwards, Senior Analyst (Research Ethics), Health Ethics Branch, NSW Health Dept, 73 Miller Street, North Sydney, NSW.	14 Aug 2003
Ms Carole Alt (Manager), - Centre for Developmental Cancer Therapeutics (now Cancer Trials Australia), Royal Melbourne Hospital, Grattan Street, Parkville.	2 July 2003
Ms Deborah Frew, Manager, Health Ethics Branch, NSW Health Department, 73 Miller Street, North Sydney, NSW.	14 Aug 2003
Ms Felicity Cassidy-Powell, Clinical Operations Manager, Novo Nordisk Pharmaceuticals Pty Ltd, Level 3, 21 Solent Circuit, Baulkham Hills, NSW.	15 Aug 2003
Ms Helen Allars, Managing Director, Datapharm Australia, PO Box 220, Five Dock, NSW, 2046, 56-56A Thompson Street, Drummoyne, NSW.	12 Aug 2003
Ms Jacki Waterkeyn, Manager, Regional Affairs and Quality Management, Clinical Trials Victoria, Baker Medical Research Institute.	1 July 2003
Ms Jo Watson, Executive Director, National Association of People Living with HIV/AIDS, Level 1, 222 King Street, Newtown, NSW.	13 Aug 2003
Ms Judith Griffin, Senior Manager Public Policy, Merck Sharp & Dohme (Aust) Pty Ltd, 54-68 Ferndell Street, South Granville, NSW.	15 Aug 2003
Ms Linda Nielsen, Executive Director, Product Development, Quintiles Pty Ltd, Level 18 Northpoint, 100 Miller Street, North Sydney, NSW.	12 Aug 2003
Ms Lisa Nelson, Manager, Centre for Clinical Studies, Alfred	1 July 2003

Hospital, Commercial Road, Prahran.	
Ms Lyn Tozer, Medical Services Manager, Datapharm Australia, PO Box 220, Five Dock, NSW, 2046, 56-56A Thompson Street, Drummoyne, NSW.	12 Aug 2003
Ms Maggie Oh, Scientific Affairs Manager, Orphan Australia 48 Kangan Drive, Berwick, Victoria.	30 July 2003
Ms Margaret Dodds (Team Leader - Clinical Trials) - Centre for Developmental Cancer Therapeutics (now Cancer Trials Australia), Royal Melbourne Hospital, Grattan Street, Parkville.	2 July 2003
Ms Marie Malica, Cancer Council of NSW, 153 Darling Street, Woolloomooloo, NSW.	14 August 2003
Ms Marie Malica, Project Manager, Cancer Trials NSW, Cancer Council of NSW, Health Development Division, 153 Dowling Street, Woolloomooloo, NSW.	12 Aug 2003
Ms Megan Lawrance, Clinical Research Associate, Organon (Aust) Pty Ltd, Unit B, 31-33 Sirius Road, Lane Cove, NSW.	12 Aug 2003
Ms Michelle Tilley, Manager, Customer Relations Management, Novo Nordisk Pharmaceuticals Pty Ltd, Level 3, 21 Solent Circuit, Baulkham Hills, NSW.	15 Aug 2003
Ms Penny Adams, Manager, Regulatory & Scientific Affairs, Medical Industry Association of Australia, Level 2, 82 Christie Street, St Leonards, NSW, 2065, PO Box 299, St Leonards, NSW.	15 Aug 2003
Ms Sally Crossing, Co-chair, Cancer Voices NSW, PO Box 138, Gladesville, NSW, 2111 and Chair, Breast Cancer Action, Greenwich, NSW.	14 Aug 2003
Ms Suzanne Elliot, Operation Manager Q-Pharm Pty Ltd, Level F, 300C Herston Road, Herston, Qld.	11 Aug 2003
Professor Alan Coates, Chief Executive Officer, Cancer Council of Australia, Level 5, Medical Foundation Building, 92-94 Parramatta Road, Camperdown, NSW.	12 Aug 2003
Professor Andrew Penman, President, Cancer Council of NSW, 153 Darling Street, Woolloomooloo, NSW.	14 Aug 2003
Professor Garry Jennings, Chair, Centre for Clinical Studies Board of Management, Melbourne.	1 July 2003
Professor Gordon Clunie, Executive Director for Surgical Affairs, Royal Australasian College of Surgeons. College of Surgeons' Gardens, Spring Street, Melbourne.	2 July 2003
Professor Haydn H WALTERS, Clinical Chief of Medicine, Royal Hobart Hospital; Senior Adviser, Medical Services, State Government of Tasmania; Head of Medicine, University of Tasmania; Director, Clinical Research Centre, 43 Collins Street, Hobart.	15 July 2003
Professor Henry Krum, Director, NHMRC CCRE in Therapeutics, Departments of Epidemiology & Preventive Medicine and Medicine, Monash University, Alfred Hospital, Commercial Road, Melbourne.	1 July 2003
Professor John Zalcberg (Director, Haematology & Medical Oncology, Peter MacCallum Cancer Institute, Melbourne)	20 May 2003
Professor John ZALCBERG, Director, Haematology & Medical	31 July 2003

Oncology, Peter MacCallum Cancer Institute, Melbourne.	
Professor Ken KIRKBY, Professor of Psychiatry, University of Tasmania, 28 Campbell St, Hobart.	21 July 2003
Professor Ray M Lowenthal, Director of Medical Oncology, Room 325, University of Tasmania Clinical School, Royal Hobart Hospital, Hobart, and National President of the Cancer Council of Australia.	14 July 2003
Professor Terry DWYER, Director, Menzies Centre for Population Health Research, University of Tasmania; Liverpool Street, Hobart.	16 July 2003
Professor Tony Rebuck, Chief executive Officer, Clinical Trials Victoria.	1 July 2003