Report of the Review of Access to Unapproved Therapeutic Goods

22 February 2005

Banscott Health Consulting Pty Ltd

Table of Contents

1. Table of Contents 2

2. Glossary of Terms 7

3. **Executive Summary** 10

- Introduction 10
- Structure of the Report 10
- Summary of Conclusions 11
- Recommendations of the Review 15

4. **Chapter 1: Introduction** 21

- Establishment and modus operandi of the Review 21
- Call for expressions of Interest 23
- Call for Submissions 24
- Context of the Review 25
- Overview of Access to therapeutic products in Australia 25
- The Clinical Trials Environment in Australia 26
- International Initiatives 27
- The proposed Trans Tasman Joint Regulatory Agency 28
- Other developments of importance arising during the conduct of the Review 29

5. **Chapter 2: Scope of the Review's Deliberations** 30

- Overview of Submissions 30
- Issues covered 30
- Workshops on significant issues 31

6. **Chapter 3: The Current Situation in Australia and New Zealand** 33

- Australia: Clinical Trials 33
- Legislation 33
- Clinical Trials 33
- Clinical Trial Notification Scheme 34
- Clinical Trial Exemption Scheme 35
- Sponsor of the Trial 35
- Trials involving Gene Therapy and Related Therapies 36
- Clinical Trials in Australia 37
    - Table 1: Clinical Trials 1990 to 2000 37
    - Table 2: CTX and CTN Sites 1990 to 2000 38
    - Table 3: Single Site and Multi-Site trials 39
    - Table 4: Trials by State 1991 to 1998 39
    - Table 5: Types of Trials 1991 to 1998 40

- Table 6: Nature of Trials 1991 to 1998 40
- Table 7: Comparison with CT in Europe 41
- Table 8: Where Clinical trials are routinely conducted 41

- Australia: Special Access 42
- The Legislation 42
- The Special Access Scheme 42
- Category A 42
- Category B 43
- Conditions of the Approval 44
- Reporting Adverse Reactions 44
- Authorised Prescriber 44
- Personal Importation 46
- New Zealand: Clinical Trials 47
- Legislation 47
- Procedure for clinical trial approval 47
- Good Clinical Practice 48
- Ethics Committees 48
- Follow up by Medsafe 48
- New Zealand: Special Access 48
- Supply of Unapproved Medicines 48
- Similarities and Differences 49
- Clinical Trials 49
- Supply of Unapproved Medicinal Products 50

7. **Chapter 4: Comparison with current Avenues of Access to Unapproved Therapeutic Goods in the United Kingdom (UK), the United States of America (USA), and Canada** 51

- **United Kingdom** 51
- Clinical trials 51
- The Clinical Trials Directive of the EU 51
- Costs and Fees 52
- Ethics Committee Review 52
- Good Clinical Practice (GCP) 53
- Manufacturing and Import requirements 53
- Pharmacovigilance 54
- Access to Unapproved Products 54
- **United States of America** 56
- Clinical trials 56
- Legislation 56
- Types of IND 56
- Procedure for clinical trial approval 57
- The Investigational New Drug Application 57
- Ethical Review of Clinical Trials 58
- Data to be submitted in an IND application 58
- Costs of FDA evaluation work in Clinical Trials 59
- Follow-up Procedures - Pharmacovigilance 59
- Clinical Trial Inspections 59
- Clinical Trial Registers 60

- Access to Unapproved Products - Other Avenues 61
- **Canada** 61
- Clinical trials 61
- Legislation 61
- Procedure for application 61
- Ethics Review 62
- Follow up by Health Canada 62
- GCP inspection 62
- Good Manufacturing Practice 62
- Access to Unapproved products 63
- Similarities and Differences between Agencies 63
- Role of the Regulatory Agency 63
- Scope of Trials Regulated 64
- Ethical Standards 64
- Clinical Trial Audits 64
- Fees 64
- Timelines 65

8. **Chapter 5: Clinical Trial Notification/Exemption** 66

- Submissions to the Review 66
- Table 1: Clinical Trials (Medicines) 1990-2000 67
- Table 2: CTN protocols (NSW) notified to TGA, expected start date 2000 67
- Consideration of the Issues 70
- CTN/CTX 70
- HREC Review 71
- CTX Issues 73
- Benchmarking 74
- Notification and Application Options 74
- Sponsorship 75
- Reporting and Database capability 75
- Fees 75
- Options for Change to the Clinical Trial System in Australia 76
- Possible changes to CTX 77
- Role of the Regulator 79
- Review Recommendations 79

9. **Chapter 6: Monitoring and Audit** 82

- Submissions to the Review 83
- Consideration of the Issues 86
- Review Recommendations 88

10. **Chapter 7: Ethics Committees and Scientific Assessment** 89

- The Role of Human Research Ethics Committees in Australia and New Zealand 89

- Issues raised regarding the role of ethics committees in Submissions to the Review 91
- Submissions received raising issues related to Human Research Ethics Committees 91
- Table 1: Summary, by area health service, of different requirements for gaining ethics approval for a multicentre study. 95
- The Australian Health Ethics Committee 99
- The Issue of Scientific Assessment 100
- Consideration of the Issues 103
- Scientific Review 105
- Multi-centre trials 106
- Legal basis of HRECs 107
- Role of AHEC 108
- Recommendations 109

11. **Chapter 8: Special Access Scheme (SAS) and the Authorised Prescriber Scheme** 111

- Consideration of the Issues 113
- Recommendations 116

12. **Chapter 9: Clinical Trials Register** 117

- Consideration of the Issues 122
- Recommendations of the Review 123

13. **Chapter 10: Infrastructure Funding for Cooperative Groups** 125

- Infrastructure Funding 125
- Insurance and Indemnity 128
- Consideration of the Issues 130
- Recommendations of the Review 130

14. **Chapter 11: Trans Tasman Joint Agency** 132

- Clinical trials and the Trans Tasman Agency 133
- Other Mechanisms of Supply for Unapproved Products 135
- Human Research Ethics Committees 135
- Consideration of the Issues 136
- A proposal for a Trans Tasman Clinical Trial Model 139
- Avenues for Trial Scrutiny 139
- Operational aspects of the Model 140
- Monitoring 141
- Comparison between the old and the new 141
- Recommendations 142

15. **Appendices** 143

- Appendix 1: Written Submissions made to the Review 143
- Appendix 2: Oral Submissions made to the Review 145
- Appendix 3: Workshops on Significant Issues 149
- Appendix 4: Extracts from the NHMRC "National Statement on Ethical Conduct in Research Involving Humans" 158
- Appendix 5: Relevant Australian and New Zealand Legislation 168
- Appendix 6: Reference List 178

Glossary

AHHRPP	US Association for the Accreditation of Human Research Protection Programs
ACA	Australian Consumers' Association
ACRP	US Association of Clinical Research Professionals
ADRAC	Adverse Drug Reactions Advisory Committee, an advisory committee to TGA
AHEC	Australian Health Ethics Committee
ARTG	Australian Register of Therapeutic Goods
BMP	Bioresearch Monitoring Program of the US FDA
CHREC	Coordinating Human Research Ethics Committee (proposed)
CRO	Contract Research Organisation
CTA	Clinical Trials Australia – formerly The Centre for Developmental Cancer Therapeutics Inc.
CTC	Clinical Trial Certificate
CSM	Committee on Safety of Medicines
CTN	Clinical Trial Notification Scheme
CTX	Clinical Trial Exemption Scheme
DSMB	Data and Safety Monitoring Board
EU	European Union
EU Directive	The European Directive number 2001/20/EC – "Directive of 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."
FDA	Food and Drug Administration (USA), the equivalent of the Australian TGA
GCP	Good Clinical Practice
GMAC	Genetic Manipulation Advisory Committee

GTRAP	Gene and Related Therapies Research Advisory Panel
HRC	Health Research Council (New Zealand)
HREC	Human Research Ethics Committee
IBC	Institutional Biosafety Committee
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation Good Clinical Practice Guidelines
IEC	Institutional ethics committee, equivalent to HREC
IMP	Investigational medicinal product
IND	Investigational New Drug Application (USA), the application to do a clinical trial in the USA
INDA	Investigational New Drug Amendment (USA)
IRB	Institutional Review Board (USA), the US equivalent of an Australian HREC
Medicines Act	Medicines Act 1981 (New Zealand)
Medicinal Product	A term which includes medicines (prescription, over the counter and complementary) and medical devices
Medsafe	Medicines and Medical Devices Safety Authority (New Zealand), the NZ equivalent to the Australian TGA
MHRA	Medicines and Healthcare Products Regulatory Agency (UK), the equivalent of the Australian TGA. This agency was formed by the merger of the previous Medicines Control Agency (MCA) and the Medical Devices Agency (MDA)
NAHREC	Nationally Accredited Human Research Ethics Committee (proposed)
NAPWA	National Association of People Living with AIDS
NCQA	The United States' National Committee for Quality Assurance
NHMRC	National Health and Medical Research Council (Australia)
NHS	The National Health Service of the United Kingdom

National Statement	*National Statement on Ethical Conduct in Research Involving Humans* (1999)
OGTR	Office of Gene Technology Regulator, an office within TGA
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBS	Pharmaceutical Benefits Scheme (Australia)
Phase I	Clinical Trial in which a medicinal product is used for the first time in humans
Phase II	Clinical Trial in which a medicinal product is used for the first time in patients with the condition it is intended to treat – to assess safety and efficacy and determine pharmacokinetics
Phase III	Clinical Trial in which a medicinal product is assessed for safety and efficacy
Phase IV	Clinical Trial in which a medicinal product is used within it conditions of marketing approval
RACGP	Royal Australian College of General Practitioners
SAE	Serious Adverse Event
SAP	Scientific Assessment Panel
SAS	Special Access Scheme
SCOTT	Standing Committee on Therapeutic Trials (New Zealand)
SSAS	Shared Scientific Assessment Scheme (NSW)
Therapeutic Good	The term used within Australian legislation to define all products covered by the therapeutic goods legislation. The term "medicinal product" in used with the same meaning within the report.
TGA	Therapeutic Goods Administration (Australia)
Therapeutic Goods Act	Therapeutic Goods Act 1989 (Australia)
TTMRA	Trans Tasman Mutual Recognition Agreement
UKECA	United Kingdom Ethics Committee Authority
VCOG	Victorian Cooperative Oncology Group

Executive Summary

Introduction

The Review of Access to Unapproved Therapeutic Goods here presents its Final Report. The review has evaluated existing regulatory controls for such goods in Australia, New Zealand, Canada, the United States and United Kingdom. Extensive consultation has been undertaken through direct invitations for comment to an extended list of stakeholders, as well as advertisements in the national press. Consultants have undertaken extensive personal visits to many institutions and stakeholders, as well as holding four focus groups in New Zealand and Australia to gather the views of industry, academia, consumers and other interest groups.

Taking into consideration international standards for consumer protection and quality measures for clinical research, coupled with the cost-recovery regulatory model in Australia, as well as the proposed establishment of a Trans Tasman Joint Regulatory Agency for the regulation of therapeutic products in Australia and New Zealand, the Review has reached several conclusions with respect to the best way forward for the regulation of unapproved therapeutic goods.

With timely access to safe and efficacious new therapies for the public while ensuring public safety a primary motivation for the Review team, several recommendations are made that are considered to improve the delivery of these goals. The Review was also asked to specifically comment about the need and practicality of a clinical trial register for Australia, as well as identify any barriers to clinical research in Australia and suggest any methods by which these barriers might be reduced or removed.

Structure of the Report

The review document consists of eleven main chapters. Chapters one and two provide a more detailed description of how the review process was conducted and the scope of issues that the review considered. Chapter three describes current regulatory controls in Australia and New Zealand for unapproved therapeutic goods, with Chapter four providing a synopsis of the regulatory framework for other comparable agencies around the world, specifically those of the United States of America, Canada and the United Kingdom.

Chapters five and six discuss the CTN and CTX schemes of Australia and provide some historical data, giving a picture of the range of research and number of studies carried out in Australia over recent years. Chapter six specifically explores monitoring issues associated with clinical research that form part of international Good Clinical Practice (GCP) standards, and discusses inspection of clinical trials by regulatory agencies as a means of promoting GCP standards, validating credibility of data collection, and most importantly of all, ensuring public safety via verification of standard practices such as informed consent.

Chapter seven explores issues surrounding the ethical and scientific assessment of clinical trial documentation, as well as clinical trial monitoring responsibilities of ethics committees. Current issues such as approval of multi-centre research proposals are commented upon in detail.

Chapter eight discusses the chief other methods of access to unapproved therapeutic goods in Australia and New Zealand, apart from use in clinical trials. Chapter nine explores opinion regarding a clinical trial register and makes specific recommendations regarding the establishment of such a register, its scope, content, cost and maintenance. Chapter ten raises issues around infrastructure funding to assist research, and discusses insurance and indemnity issues surrounding clinical trials, identified as one key barrier to the fostering of research.

Chapter 11 discusses the regulation of unapproved therapeutic goods in the context of a likely Trans Tasman Joint Regulatory Agency for therapeutic products coming into being on July 1, 2005. Discussion of clinical trial practices, as well as other regulation of unapproved goods in both countries is undertaken, with the review proposing how unapproved products might be regulated in such an Agency. A specific model for the harmonization of clinical trial approval and monitoring processes is put forward.

Summary of Conclusions

Regulation of Clinical Trials by other Agencies

The review found that the primary scientific assessment of unapproved goods to be used in clinical trials within the domains of the regulatory agencies of the UK, USA and Canada, is undertaken by the regulatory agencies, unlike Australia.

Regulation of trials in Australia and New Zealand was found to be carried out to comparable standards with respect to ethical and scientific review, based on the principles of the International Conference on Harmonization's (ICH) Note for Guidance on Good Clinical Practice, however the methodology of such regulation was quite different.

Generally, Phase IV studies in all jurisdictions are not subject to any administration or intervention by the regulatory agency concerned, apart from pharmacovigilance issues.

The role of ethics committees is common to all jurisdictions, however they have slightly differing responsibilities in some, i.e. in Australia, where review of proposals and ongoing monitoring is chiefly the function of the approving ethics committee.

Fees for associated administrative and evaluation tasks, undertaken by regulatory agencies are dealt with essentially in two ways, either by recovery of costs through general fees and charges, such as in the USA, Canada and for the most part, Australia, or via more direct fee charging, such as in the UK and New Zealand.

There are timelines for regulatory review of clinical trial documentation in other jurisdictions. Australia has timeframes for reviews undertaken with respect to the CTX system, however these are not legislated.

Regulation of Clinical Trials by Australia

The review felt that the CTN system has been a great encouragement to the conduct of clinical research in Australia, and the success of the system has now resulted in some areas of difficulty that could be addressed. These include the significant workload of ethics committees in approval of trial protocols and ongoing monitoring; the concerns raised over evaluation of trial biological plausibility and design, with less consideration given to areas

such as toxicology; the requests from numerous stakeholders for more guidance to HRECs in carrying out scientific evaluation; and ethical review as well as costs (for multiple CTNs) associated with multi-centre trials.

The review noted that adequate ongoing monitoring of clinical trials after approval was an area of concern raised by several stakeholders. Currently this is carried out by ethics committees primarily, with some complementary functions undertaken by the TGA. The review felt that, by formalizing a clinical trial inspection function within the TGA, the current system of providing endorsed undertaking to comply with GCP principles signed by sponsors and investigators as part of the CTN form would be strengthened by this hands-on "verification" function, as well as be a method whereby correct conduct of clinical trials to GCP standards could be promoted by the TGA to the research community. This would also increase credibility of trial data generated in Australia and subsequently submitted to regulatory authorities in other countries. The review believed that to allow minimal regulation prior to clinical trial commencement, a more active role of verification of GCP standards was required for ongoing trials.

Human Research Ethics Committees in Australia

The overwhelming number of submissions received by the review in relation to ethics committees commented upon the Australian arrangements. Key findings by the review were:

- The success of the CTN scheme has resulted in a high workload for ethics committees as well as their ongoing monitoring responsibilities.
- The current necessity to obtain ethics committee endorsement from multiple committees for multi-site trials is seen as a considerable waste of scant resources and often results in slightly different conditions being imposed on the trial in question at different sites.
- Committees vary in their timeframes for evaluation given their location and different workloads.
- Costs vary widely between committees for evaluation, from nothing to several thousand dollars.
- Committees desire greater direction in assessing clinical trial documentation and would, for the most part, be amenable to guidance documents outlining data requirements and to assist in decision-making, for example when to send a trial via the CTX route, or request third-party review of certain aspects of the documentation.
- The capacity of committees for the review of serious adverse event reports is considerably limited in comparison to the number of reports received.
- The review heard from several stakeholders that they desired to maintain the deregulated system of the CTN scheme, but conceded that problems with ethics committee workload and multi-centre trials were major contributors to barriers for clinical research.

Although the review has put forward several options for addressing multi-site review of clinical trial documentation, and other measures to alleviate ethics committee workload, it is clear that no single measure will suffice, nor can action by a single entity such as the TGA or NHMRC fully deal with the problems identified above. The current system has a historical, institutional basis, as well as being linked with issues of indemnity and duty of care.

Cooperation at both federal and State and Territory level is seen as necessary to achieve a streamlined ethical and scientific review, as well as monitoring function of clinical trials.

The Special Access Scheme and Authorised Prescriber Scheme in Australia

The review did not note any major concerns from stakeholders with these schemes. It was found that there was some misunderstandings about the schemes, for example that the TGA acted as a "locator" of unapproved goods for medical practitioners, and that the TGA had some role in determination of whether or not medication was provided free of charge under these arrangements. The review felt that medical practitioners perhaps needed to receive more information about the schemes than they currently do, despite comprehensive guidance documents existing on the TGA website.

A Clinical Trial Register

The review team noted from many submissions that several stakeholder groups were in favour of a clinical trial register, however they differed on the scope intended and the information that might be available on it. The review felt that the expectations from a register were somewhat unrealistic. Access to a clinical trial medication is, after all, access to a therapy that is unproven and in some cases may simply be access to a placebo.

While there were valid arguments that a register may address issues of negative publication bias in scientific journals and prevent repetition of research and thus wasting of resources, it was felt that a clear decision needed to be made about what a register would be trying to achieve, and thus frame the scope of the register to suit that objective.

Some industry stakeholders raised concerns regarding the level of information that would be required to be entered on the register, citing commercial confidentiality concerns. While some may refute this, the review was acutely aware that mandating complete details be entered for an Australian register might be a path to ensuring cutting-edge clinical research is carried out in other countries, hardly conducive to obtaining timely access to therapies for the Australian public.

The review believes that that a register should be set up to include all trials with medicinal products in Australia and New Zealand (i.e. this would encompass some trials not presently administered by the TGA or Medsafe), with information sufficient to provide a resource on the trials that are currently ongoing or completed in Australia, and have contact information available such that interested parties may contact trial sponsors or investigators to inquire about the outcomes of the trials. The currency of the information on the register would be the responsibility of the trial sponsor.

Infrastructure Funding, Insurance and Indemnity Issues

The review noted the comments made with respect to funding and is persuaded that an argument exists for increased infrastructure funding for cooperative groups, however, this issue is not within the Terms of Reference of the Review.

There is a clear issue of clinical trial insurance and indemnity, with the provision of this by government across the State and territory health systems varying considerably. A dichotomy exists between investigator initiated trials and those trials conducted by the

pharmaceutical industry, in as much as the industry can more readily afford insurance costs. The review believes that indemnity issues for clinical trials can likely only be addressed at a governmental level and recommends government examine indemnification for clinical trials as part of overall indemnification for health services, at the federal or State level.

The Trans Tasman Joint Agency for the Regulation of Therapeutic Products

The review recognizes the differing systems in New Zealand and Australia with respect to the regulation of unapproved therapeutic products. Clinical trials in New Zealand undergo separate scientific assessment by the SCOTT committee, with ethical review provided by regional Human Research Ethics Committees. Australia has a deregulated system whereby ethical and scientific assessment is undertaken by Human Research Ethics Committees that are affiliated with the Australian Health Ethics Committee of the National Health and Medical Research Council.

Access to unapproved therapeutic goods on an individual basis is subject to more regulation and justification to the regulator in Australia, with a more deregulated system in New Zealand with the sponsor of the goods only required to send quarterly reports of use to the regulator.

The review felt that the clinical trial systems of Australia and New Zealand could ostensibly be “harmonized” by the introduction of scientific assessment for certain trials being carried out by a “Scientific Assessment Panel” (SAP). A SAP would constitute the SCOTT committee in New Zealand, while in Australia it would be represented by institutional ethics committees that currently exist, but fulfil certain additional criteria. This would ensure that, for the higher number of trials carried out in Australia, adequate numbers of such review committees would exist. A SAP in Australia could also provide ethical endorsement as ethics committees do now, allowing a single ethical and scientific review of documentation to continue in Australia. For all other trials outside the defined set for SAP review, other institutional ethics committees could provide scientific and ethical review. Of course, a SAP would be able to provide review for these as well, should they be proposed for the same institution at which a SAP was constituted.

Trials required to be regulated would be similar to those requiring regulation in Australia now, i.e. those which, under the legislation of the Joint Agency, were considered “separate and distinct” therapeutic goods, and thus required an exemption from the legislation in order to be supplied to the public without a product license being issued. The proposed review avenues of various types of trials are summarised in the table on the following page, which appears in Chapter 11, p141 of this document.

Essentially, a harmonised system is proposed which, in Australia, strengthens the scientific review process for trials by having either the regulator or an ethics committee with substantial membership and scope for review assess certain types of trials. This measure, in concert with the further development of clinical trial inspection capability, is seen as necessary to ensure trials are conducted commensurate with international standards of Good Clinical Practice and hence demonstrate the ongoing credibility of research in Australia and that safety and rights of trial subjects are paramount.

	Regulatory System			
	CTN	CTX	NZ	Proposed CTS
Scope	Medicines and medical devices	Medicines and medical devices *gene therapy and related therapies	Medicines	All therapeutic products
Who decides route?	Sponsor, HREC	Sponsor, HREC	Legislation	Legislation stipulates rules trying to identify risk. Rules to be applied by sponsor & HREC.
Scientific r/v	Institution - all	TGA - all	SCOTT committee - NCE, and new formulations only	*Agency* - Gene therapy and xenotransplantation; *Agency or SAP* – High risk trials. *Institution* - All others
Ethical r/v	Institutional HREC	Institutional HREC	Regional HREC	*Single centre trials* Institution HREC or SAP in Australia and Regional HREC in NZ *Multicentre trials*; NAHREC in Australia or several SAPs/Institutional HRECs as currently occurs, regional HRECs in NZ
Agency role	Receives notification Monitors adverse events Inspects trial sites	Evaluates summary scientific data and approves usage guidelines Receives notification of all trials Monitors adverse events Inspects trial sites	Receives notification and approves exemption on basis of advice from SCOTT Monitors adverse events	Evaluates summary scientific data for certain trials mandated by legislation Receives notification of all trials Monitors adverse events Inspects trial sites

*although not mandated in legislation, current NHMRC guidelines require CTX route for all gene therapy and related therapies unless GTRAP advises CTN is acceptable.

With respect to other avenues of access to unapproved therapeutic goods, specifically the Special Access Scheme and Authorised Prescriber Schemes of Australia, the review believes that these schemes should be adopted for use as part of the Trans Tasman Agency, with New Zealand staff administering the schemes in New Zealand. No submissions objected to the use of these schemes for New Zealand, and a specific consultation carried out by Medsafe did not reveal any objection from medical practitioners.

Recommendations of the Review

Chapter 5: 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 multicentre trials should be introduced. The review recognises that this would potentially reduce the range of services available to be provided for clinical trial oversight in Australia.

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 consider establishing a separate Office of Clinical Trials separate from the current branches (particularly the Drug Safety and Evaluation Branch). The Office should have responsibility for all clinical trials. The downside of this recommendation is a potential significant increase in the cost of the program and lack of expertise and connection between evaluators looking at products of different life phases.

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.

Chapter 6: Monitoring and Inspection of Clinical Trials

R16. The Joint Agency should take a more involved role in monitoring clinical trial activity by enforcing existing requirements on reporting and 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 and should aim to audit ~ 1-3% of trial sites and HREC within 3 years.

Chapter 7: 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 studied.

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".

Chapter 8: 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.

Chapter 9: 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 could 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. It is acknowledged such a register would not meet the needs of many using non-medicine interventions as alternatives to therapy.

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.

Chapter 10: 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.

Chapter 11: 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.

Chapter 1: Introduction

Establishment and modus operandi of the review

1. In April 2003, the Therapeutic Goods Administration (TGA) and the National Health and Medical Research Council (NHMRC) jointly established a Review of the Australian Arrangements for Clinical Trials and Access to Unapproved Therapeutic Goods.

2. The Review was given the following Terms of Reference:

Terms of Reference

The Therapeutic Goods Administration and the National Health and Medical Research Council are undertaking a review of the Australian arrangements for clinical trials and access to unapproved therapeutic goods[1].
The review will involve 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 will require wide consultation with relevant stakeholders including consumers, industry, health professionals, researchers, and human research ethics committees.

The review will 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.

3. Oversight for the review was provided by a Steering Committee consisting of relevant Australian and New Zealand representatives, chaired by the Chief Medical Officer of the Department of Health and Ageing.

4. The Steering Committee comprised:

Clinical Trials Review Steering Committee

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
Therapeutic Goods Administration

5. On 24 April 2003, Professor Richard Smallwood, Chief Medical Officer, wrote to a wide range of stakeholders 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.

6. On 18 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.

7. During its consultative phase, the Review also met for discussion with Stakeholders who had expressed a wish to meet with the Review Team and to present oral submissions.

8. 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.

Participants at the Workshops included the Review Team, TGA officials, and a wide range of persons invited from among those who had made submissions or who had participated in the interview program.

9. Wherever appropriate, the Review has, in this Report, reflected the views expressed to it. It places on record its gratitude to the many people who made the time and effort to contribute to this study.

10. The Review Team consisted of Mr Alan Bansemer (Project Leader) and Mr Michael Clarke with significant contributions on aspects of the Review from Dr Susan Alder, Ms Amanda Price and Professor Michael Reid.

11. The Review expresses special appreciation to the TGA staff made available to assist the Review, Ms Jocelyn Kula (until 30 June 2003) and Dr Jon Rankin, who were of great assistance to the Review Team throughout the process.

Context of the review

Overview of access to unapproved therapeutic products in Australia

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

13. 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.

14. A key point noted by the Review is 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 when approving products for supply. These principles would also apply to access for individual patients in need of potentially life saving and enhancing treatments.

15. It is also important to appreciate that unapproved therapeutic goods have undergone essentially 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 as outlined in the NHMRC's "*National Statement on Ethical Conduct in Research Involving Humans*". 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.

The clinical trials environment in Australia

16. Clinical trials in Australia 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.

17. 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.

18. 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 also be given by the HREC, 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.

19. Clinical trial activity is currently averaging approximately 550 trials of therapeutic products per annum (medicines 500: medical devices 50) at 1800 trial sites across Australia. 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.

20. 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 yrs. 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*". Chapter 3 of that document describes repeated changes to the administration and legislative underpinning of clinical trials regulation that have led to reduced involvement of the regulatory agency in the approval of trial protocols and review of scientific data over the last 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, especially of 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.

21. 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 to inspect 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.

22. At the time of announcing this current Review the TGA was considering how, in the face of rapid technological advancements, a formal program for inspecting clinical trials should be implemented and whether such a program, alone, would be sufficient to ensure patient rights, wellbeing and safety are protected adequately into the future. Standards of ethical review of clinical trial documentation in Australia are maintained by the NHMRC, and 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.

International initiatives

23. 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.

24. Firstly, over the last 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).

25. With the move to the acceptance of common data packages across the various jurisdictions, there has been a recognition that the basis of these data packages, ie the clinical trials used to generate 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 consent to undergo such inspections 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.

26. At the time of the initiation of this 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.

27. In addition, the 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 to ensure compliance of clinical trials with GCP principles.

28. 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.

The proposed Trans Tasman Joint Regulatory Agency

29. 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.

30. Formal agreement for the initiative was reached in 2003 and it is the intention of both governments that from 1 July 2005 the joint agency will replace the Australian TGA and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).

31. In recognition of existing differences in the regulatory and ethical frameworks for clinical trials in Australia and New Zealand, the TGA and NHMRC considered the Review should examine the current regulatory provisions for clinical trials and access to unapproved therapeutic goods in Australia and New Zealand. It requested the Review 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.

32. 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. The review understands that it is intended that the Joint Agency shall regulate to similar standards in comparable regulatory agencies around the world.

Other developments of importance arising during the conduct of the Review

33. 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.

34. 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.

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

36. 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.

37. The current Review acknowledges the report and recommendations of the Expert Committee, and sees no need to re-canvass the broad issues already studied by that Committee. However, the recommendations of this Review's report apply to the regulation of complementary medicines as equally as to other therapeutic products.

Chapter 2: Scope of the Review's Deliberations

Overview of submissions

38. As a result of the call for written submissions, 51 formal submissions were received between 23 July 2003 and 28 November 2003, including 2 submissions from New Zealand industry. A list of written submissions is located at Appendix 1.

39. During its consultative phase, the Review also met for discussion with many stakeholders in Australia and New Zealand who had expressed a wish to meet with the Review Team and to present oral submissions. A list of these stakeholders is located at Appendix 2.

Collectively, these responses covered a wide range of stakeholder groups and can be categorised broadly as in the table below. The code assigned to each group is used in the overview.

Affiliation	*Code*	*Written submissions*	*Oral submissions*
Government (Australia, NZ)	G1	3	unclear
Government (State or Territory)	G2	3	4
Consumer advocacy group	C	6	8
Industry (pharmaceutical, biotech, devices)	I		
Industry representative body		5	2
Individual companies		12	16+
Contract Research Organisation	CR	3	7
Researcher (investigators, cooperative groups)	R	11	16
Ethics committee	E	2	2
Institution (hospital, university)	A	3	1
Other (individual, professional group)	O		
Professional group		2	1
Individual		1	1
		51	58+

Issues Covered

40. Many of the submissions raised multiple issues. They were wide-ranging and, in some cases, covered issues beyond the Terms of Reference of the Review. The analysis of submissions has been restricted issues covered by the Terms of Reference. Of the 51 written responses:

- 18 provided comments on the positive impact of the CTN Scheme on the level of clinical trial activity in Australia and/or the benefits to patients in terms of access to treatments. These comments were spread across the spectrum of non-government stakeholder respondents (I-7; R-4; E-2; C-2; O-1; CR-1; A-1). Industry in particularly indicated that the CTN was a key factor in many companies choosing Australia as a site for research investment.

- 23 considered the current clinical trial review processes were either inefficient or in some way presented a barrier to the conduct of clinical trials. These types of comments were made mostly by researchers and industry (R-9; I-8; C-2; E-1; A-1;

G2-1; O-1). Of these submissions, 11 had also identified positive impacts from the introduction of the CTN scheme.

- 20 raised concerns about delays in obtaining ethical approvals for multi-centre trials. These concerns were spread across the spectrum of respondents, including most research groups, both professional groups and both ethics committees (R-7; I-3; E-2; C-2; O-2; G1-1; G2-1; CR-1; A-1). Industry in particular suggested alternative models be introduced to facilitate such trials.
- 13 provided comment on other aspects of the operation of HRECs, such as eliminating the use of different forms and procedures across HRECs to reduce duplication of effort (I-5; C-3; R-2; G1-1; G2-1; CR-1).
- 5 (all from consumer/advocacy groups) raised the need for increased consumer participation in the clinical trial approval process and/or the need for a more transparent process.
- 10 commented on how clinical trials and other mechanisms of access to unapproved products should operate under a Trans Tasman agency. These were received almost exclusively from industry (including 1 New Zealand submission) and contract research organisations (I-7; CR-2; R-1).
- 11 considered there needed to be clearer delineation of responsibilities of the sponsors of clinical trials, HRECs and the TGA with regard to requirements for reviewing adverse event reports and monitoring clinical trials. These comments were common to most stakeholders (I-4; R-2; CR-1; G1-1; G2-1; C-1; O-1). Four of the submissions (R-1; CR-1; I-1; O-1) included comment on the need for or utility of Data and Safety Monitoring Boards (DSMBs).
- 28 provided comment on the need for and/or the possible operation of a Clinical Trials Register. These comments were made by most stakeholders. Researchers, individuals and consumer/advocacy groups provided relatively more comment on this issue than other stakeholders (R-8; I-7; C-6; A-3; O-2; G2-1; CR-1).
- 6 raised concerns over issues relating to either funding of clinical trials generally or clinical trial insurance and indemnity (R-2; I-2; E-1; C-1).
- 15 raised issues relating to the current operation of the SAS and other non-trial access to unapproved products (I-5; A-3; C-2; E-1; G1-2; G2-1; O-1).

41. These issues were explored further in the oral submissions with a view to guiding the development of a workshop issues paper.

42. Of interest to the Review was the nature of responses in relation to its objective of determining whether any improvements were necessary to maximise patient and trial participant safety and maintain public confidence. None of the submissions gave specific evidence to suggest that the standard of clinical trials, their protocols or monitoring of patient safety had declined. However, a number of respondents, including consumer advocacy groups and researchers, considered the current system was close to overloading HRECs. One consumer group felt that, with rapidly emerging technologies and further expansion of trial activity, system failures could occur in the future.

Workshops on Significant Issues

43. Facilitated Workshops were conducted on Tuesday 11 November 2003 (in Sydney) and on Thursday 13 November 2003 (in Melbourne).

44. Participants at the Workshops included the Review Team, TGA officials, and a wide range of persons invited from among those who had made submissions or who had participated in the interview program. At each of these Workshops, participants examined significant issues that had come to light from the submissions received and from the interviews conducted.

45. The issues addressed by the workshops included, among others:
- examination of the current arrangements with respect to the operation of HRECs;
- the possible establishment of Coordinating HRECs (CHRECs);
- the possible establishment of Scientific Assessment Panels (SAPs);
- examination of the current arrangements with respect to the operations of the CTN and CTX Schemes; and
- the need for a clinical trials register.

46. A report on the outcomes of the workshops is located at Appendix 3. It should be noted that not all comments made by stakeholders at the workshops were factually correct in their detail and many lacked an in-depth understanding of the activities of the TGA and the operations of HRECs and the AHEC. Analyses of the issues within the Terms of Reference of the Review are given in subsequent chapters of this report.

Chapter 3: The Current Situation in Australia and New Zealand

Australia – Clinical Trials

Legislation

47. The principal legislation relevant to the manufacture and supply of medical products in Australia is the *Therapeutic Goods Act 1989* (the Act), the *Therapeutic Goods Regulations 1990* (the Medicines Regulations), and the *Therapeutic Goods (Medical Devices) Regulations 2002*, (the Devices Regulations).

48. However, from October 2004, the administration of legislation relevant to clinical trials of and special access schemes for medical devices will transfer to Chapter 4 of the Act and the Devices Regulations, with the completion of the transitional phase for the new medical devices regulatory framework. Nonetheless, the actual operation/processes for the schemes will remain the same.

49. In this context, TGA should complete the development of updated guidelines to reflect this change, and should undertake an educational program for relevant stakeholders.

50. The *Therapeutic Goods Act 1989* and associated regulations establishes a uniform, national system of regulatory controls to ensure the quality, safety, efficacy and timely availability of medical products for human use. Responsibility for the regulatory controls lies with the TGA.

51. Under the Act, medical products for human use that are imported, manufactured in Australia, supplied by a corporation, supplied interstate or to the Commonwealth, or exported must be included in the Australian Register of Therapeutic Goods (ARTG) unless specifically exempted from the operation of Part 3-3 of the Act.

Clinical trials

52. The Clinical Trials Notification (CTN) and Clinical Trials Exemption (CTX) Schemes for clinical trials of medicines and medical devices have distinct legislative bases.

- CTN Scheme – Section 18(1)[2], Section 31A(1)[3], Regulation 12[4] and Schedule 5A paragraph 3[5]:
- CTX Scheme – Section 19 (especially 19(1)(b))[6], Section 31B(1) and (2) [7] and Regulations 12AA-AD[8].

53. The current medical products legislation is restricted in its coverage by the constitutional limitations of Commonwealth powers. It is arguable that it could be enforced in clinical trials sponsored by unincorporated bodies or individuals using medical products wholly manufactured in the State or Territory in which they are used. Such trials would, however, be subject to any relevant State or Territory legislation. As clinical trials, they are also subject to the NHMRC National Statement[9] requirement for review by HRECs, but there is no legal requirement for this. The NHMRC does have considerable influence in ensuring ethical standards are

maintained, however, by its role as one of the major funders of clinical research in Australia. Thus it has the ability to make requirements of such trials prior to funding provision.

54. The CTN / CTX Schemes are required for all clinical trials involving:
    - any product not entered on the Australian Register of Therapeutic Goods; or
    - use of a registered or listed product in a clinical trial beyond the conditions of its marketing approval.

55. Clinical trials in which registered or listed medicines or medical devices are used within the conditions of their marketing approval are not subject to CTN or CTX requirements. Such Phase IV studies or trials, as long as they meet the definition of clinical research in the NHMRC National Statement, still need to be approved by an HREC before the trial may commence. Again, there is no legal requirement for this.

Clinical Trial Notification (CTN) Scheme

56. The CTN Scheme is a notification scheme only.

57. All material relating to the proposed trial, including the trial protocol is submitted directly to the relevant HREC by the researcher at the request of the sponsor. The TGA is not required to review any primary data relating to the clinical trial. The HREC is responsible for ensuring the appropriate assessment of the scientific validity of the trial design and the safety and efficacy of the medicine. It is also responsible, in the context of the trial protocol, for assessing the ethical acceptability of the proposed trial. An HREC may decide that it is not willing to review a trial under the CTN scheme and may advise the investigator that it will review the trial only under the CTX scheme. The institution or organisation at which the trial will be conducted, referred to as the 'Approving Authority', gives the final approval for the conduct of the trial at the site, having given due regard to advice from the HREC.

58. CTN trials cannot commence until the trial has been notified to the TGA and the appropriate notification fee paid. There is no legal requirement for sponsors to wait for acknowledgment of the CTN notification but many do so to ensure that all procedures have been followed correctly. The Therapeutic Goods Regulations require notification to be in a 'form' approved by the Secretary of the Department of Health and Aging, i.e. on the current CTN form.

59. The CTN scheme was introduced in 1990. It was intended to be a notification scheme for those trials that did not require detailed scientific evaluation prior to commencement. Specifically it was intended to be used for trials relating to new indications or patient populations for products already approved for marketing, or for products which had been evaluated and approved for clinical trials by either the US or UK regulatory authority.

60. The current fee for a CTN application is $240. There is some confusion over the fee required for multicentre trials. The current guidelines clearly set out that there should be a separate fee for each act of notification but that there is one fee for all sites notified at the same time.

61. At the present time the TGA is providing a written acknowledgment of the CTN notification within 2-3 days of the receipt of the notification. In addition, it is standard practice for all CTN trials notified to be reviewed by Senior Medical Officers. Additional information concerning the trial may be sought at this point.

Clinical Trial Exemption (CTX) Scheme

62. The CTX Scheme is an approval process.

63. A sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment. A TGA Delegate evaluates the information provided within 50[10] working days and decides whether or not to object to the proposed Usage Guidelines for the product. If an objection is raised, trials may not proceed until the objection has been addressed to the Delegate's satisfaction. Essentially if not addressed the CTX application is rejected.

64. If no objection is raised, the sponsor may conduct any number of clinical trials under the CTX application without further assessment by the TGA, provided use of the product in the trials falls within the original approved Usage Guidelines. Each trial conducted must be notified to the TGA.

65. A sponsor cannot commence a CTX trial until written advice has been received from the TGA regarding the application and approval for the conduct of the trial has been obtained from an ethics committee and from the institution at which the trial will be conducted.

66. There are two forms, each reflecting these separate processes (Parts), which must be submitted to TGA by the sponsor.

- Part 1 constitutes the formal CTX application. It must be completed by the sponsor of the trial and submitted to TGA with data for evaluation.
- Part 2 is used to notify the commencement of each new trial conducted under the CTX as well as new sites in ongoing CTX trials. The Part 2 form must be submitted within 28 days of the commencement of supply of goods under the CTX.

67. The current fee for a CTX application is $15,300 (Phase II and III) and $1,240 (Phase I). There is no fee listed for the submission of additional data should TGA raise concerns over an application. It has been reported that it is TGA practice to charge an additional full fee for the submission of supplementary data. This is not the case; supplementary data within the one application are free. If an application is rejected or withdrawn, and a new application is made, then a new fee is payable. There is no fee for notification of subsequent trials under the CTX scheme.

Sponsor of the trial

68. All CTN and CTX trials must have an Australian sponsor. The sponsor is that person, body, organisation or institution which takes overall responsibility for the conduct of the trial and signs either the CTN form or the CTX form. The sponsor usually initiates, organises and supports a clinical study and carries the medico-legal responsibility associated with the conduct of the trial.

Trials Involving Gene Therapy and Related Therapies

69. Proposals for gene therapy research undergo a process of review and approval which involves an HREC, the NHMRC's Gene and Related Therapies Research Advisory Panel (GTRAP), the TGA (if proceeding via CTX), an Institutional Biosafety Committee (IBC) and, when relevant, the Gene Technology Regulator.

70. Membership of GTRAP includes medical experts, members of the Gene Technology Technical Advisory Committee (GTTAC), representatives of the TGA, an ethicist and a lawyer. GTRAP's role is to assist HRECs to assess research proposals involving gene therapy.

71. All research proposals must be submitted to an HREC for initial ethical and scientific review. Researchers are advised to submit their proposals in the form set out in the GTRAP document *"Guidelines for the Writing of Human Gene Therapy Proposals"*, a copy of which can be found on the GTRAP website: http://www.nhmrc.gov.au/research/gtrap/about.htm - review.

72. When it has completed its assessment, the HREC forwards the proposal to GTRAP, having identified any aspects of the proposal requiring specific comment.

73. GTRAP assesses the proposal. As part of this process the investigators attend a GTRAP meeting at which the proposal is reviewed and specific issues are raised. A representative of the trial sponsor is also invited to attend.

74. Following this meeting, an interim report from GTRAP is sent to the investigators and the relevant HREC(s). This interim report forms the basis of a teleconference between GTRAP, the investigators, the sponsor's representative and a member of the HREC(s). At this meeting outstanding issues are discussed.

75. The final report from GTRAP is issued following the teleconference. Additional meetings or teleconferences can be arranged as required, before final recommendations are submitted to the HREC.

76. GTRAP may consult with other bodies concerned with monitoring the safety of innovative genetic manipulation techniques (OGTR) or the standards for product manufacture (TGA).

77. GTRAP has recommended that, in general, gene therapy proposals follow the TGA's Clinical Trial Exemption (CTX) Scheme, unless GTRAP considers the Clinical Trials Notification (CTN) Scheme suitable, eg if the gene therapy vector had already been approved for a similar clinical trial by a regulatory body such as the US Food and Drug Administration (FDA).

78. Proposals that fall under the jurisdiction of the OGTR must also be submitted to an IBC for initial assessment.

79. When it has completed its assessment, the IBC forwards the proposal to the OGTR, having identified any aspects of the proposal requiring specific comment.

80. The OGTR assesses the proposal and, before giving its recommendations to the IBC, may consult with GTRAP, or other bodies concerned with the safety of innovative genetic manipulation techniques.

81. In the final step of the regulatory process, the HREC ensures that the proposal has been approved by all relevant bodies and decides whether or not the research may proceed.

82. Although GTRAP works predominantly with the HREC, the expertise of this committee is always available to investigators, sponsors, HRECs and the public. In the case of investigators, it is considered beneficial during the early preclinical phases for them to approach GTRAP to determine in advance what will be expected before the gene therapy product can be introduced into clinical trials.

83. Relevant information on these types of trial is contained in the *NHMRC Guidelines for Ethical Review of Research Proposals for Human Somatic Cell Gene Therapy and Related Therapies* and the Gene and Related Therapies Research Advisory Panel's (GTRAP) *Recommendations for the Writing of Gene Therapy Proposals*.

Clinical Trials in Australia

84. It is very difficult to find accurate data about clinical trial activity in Australia. The TGA does not publish information about clinical trial activity on a regular basis. The information in Table 1 is collated from a number of different TGA sources and provides only the bare minimum information about trials approved/notified to TGA.

Table 1: Clinical Trials: 1990 to 2000

	1990	**1991**	**1992**	**1993**	**1994**
CTX Scheme					
Medicines	55	42	36	35	42
Medical devices					
CTN Scheme					
Medicines					
Trials	0	63	257	300	355
Sites	0	155	504	651	678
Medical devices					
Trials	0	2	10	10	16
Sites	0	2	11	13	23

	1995	1996	1997	1998	1999	2000
CTX Scheme						
Medicines	29	11	10	6	5	2
Medical devices	2	0	0	0	0	0
CTN Scheme						
Medicines						
Trials	391	443	484	560	462	541
Sites	997	1162	1382	1830	1766	1676
Medical devices						
Trials	32	23	36	46	45	47
Sites	80	52	90	196	128	113

85. Yet, the record shows that more complete data was presented in the past. For example, at a series of meetings in 1999, a TGA officer presented the following sets of information:

Table 2: CTX and CTN Sites: 1990 to 2000

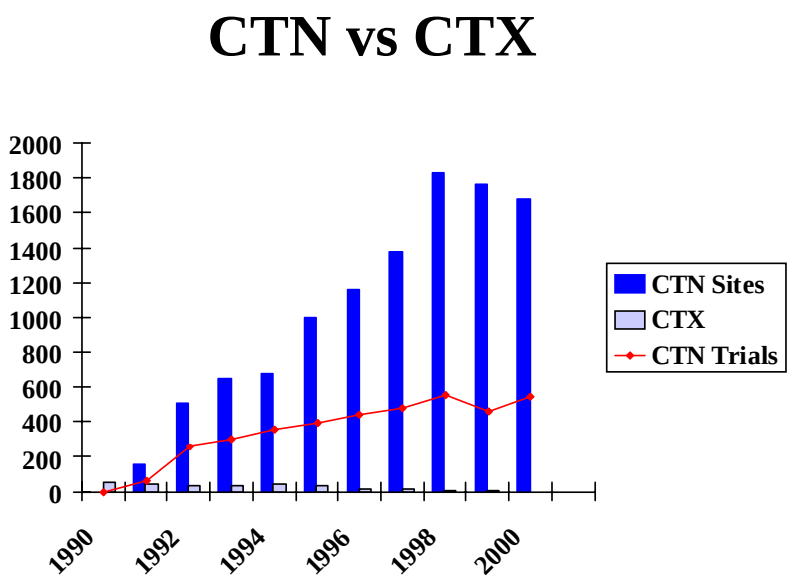


Table 3: Single-Site and Multi-Site Trials: 1991 to 1998

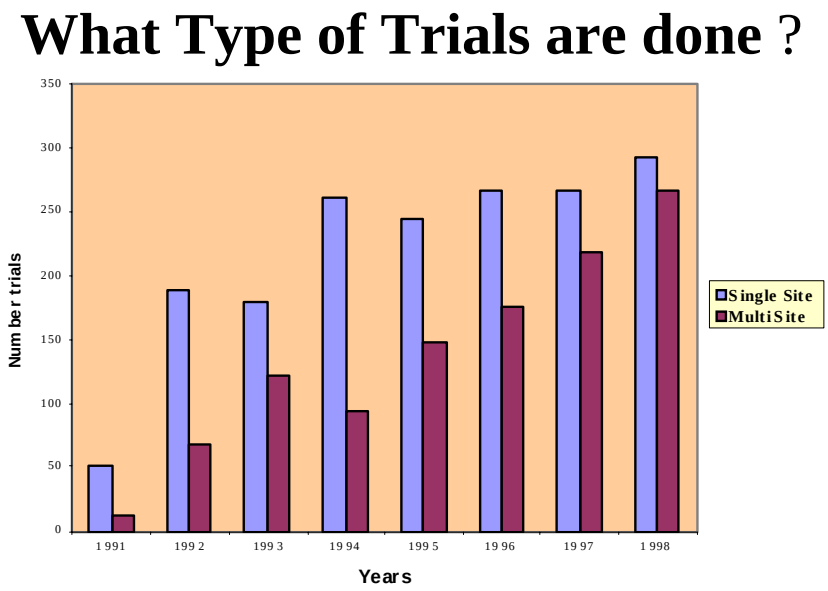


Table 4: Trials by State 1991 to 1998

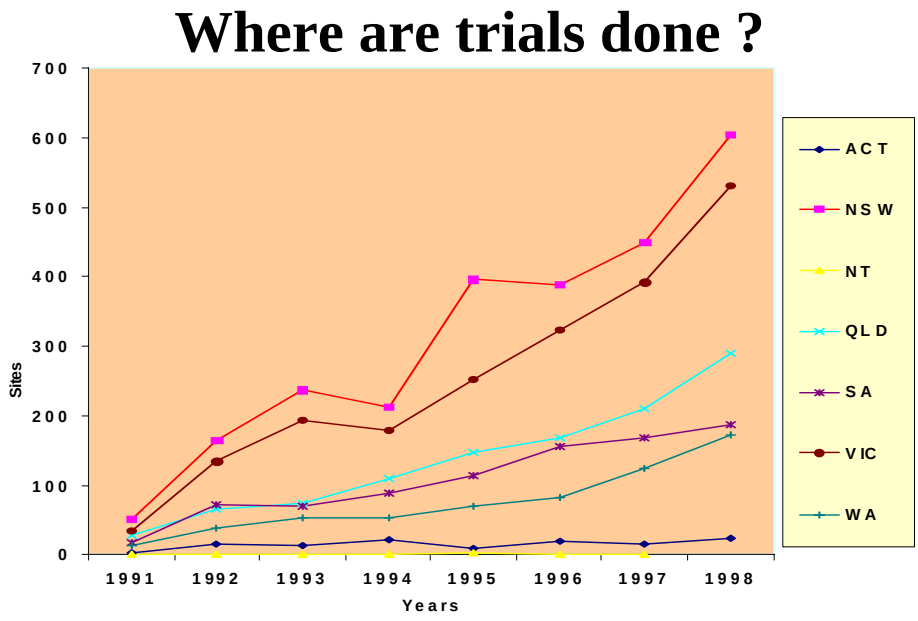


Table 5: Types of Trials: 1991 to 1998

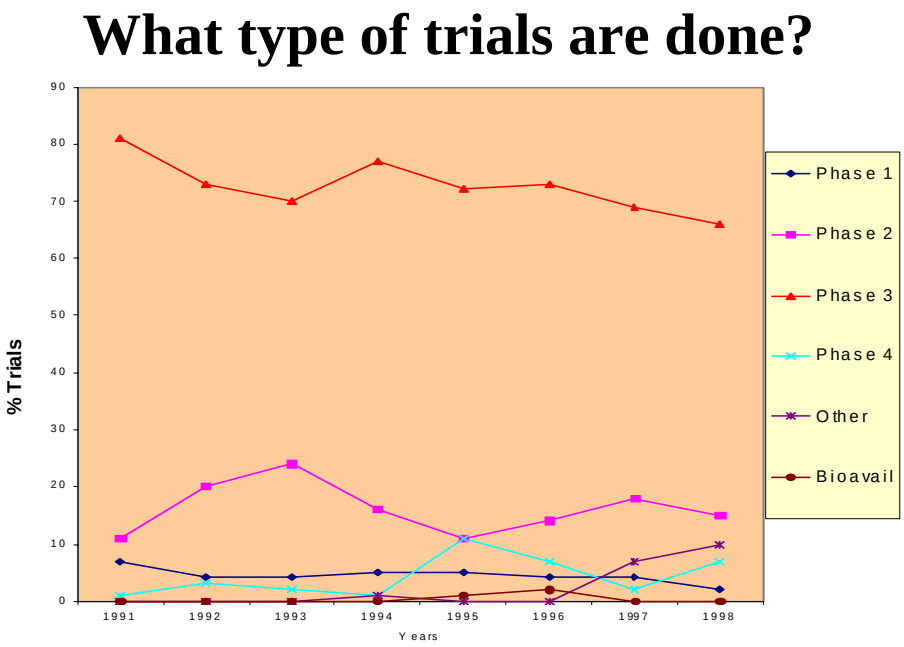
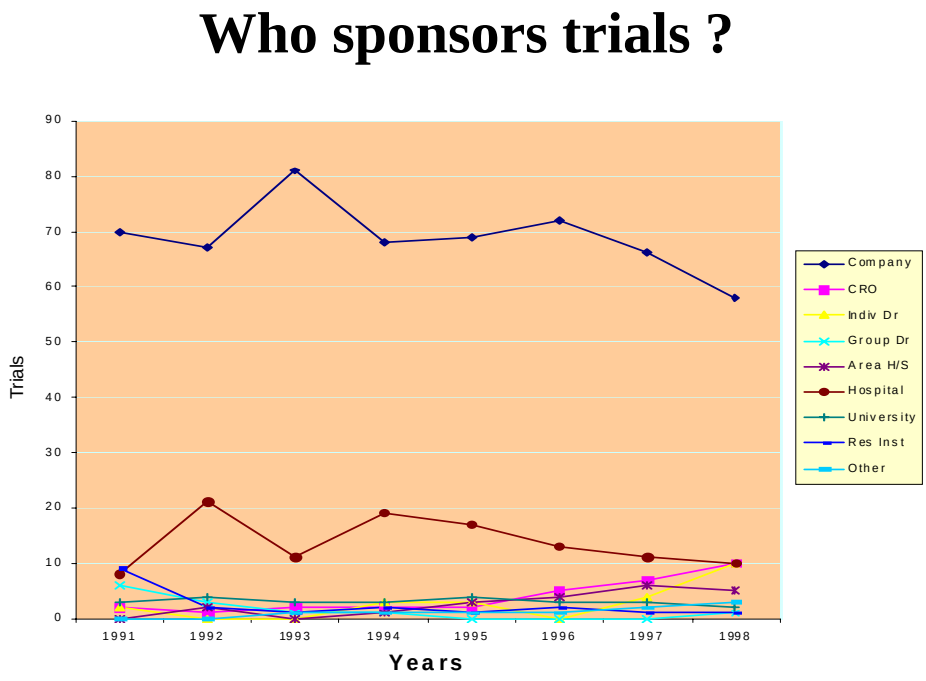


Table 6: Nature of Trials: 1991 to 1998



86. The above exemplifies data that the TGA should compile for public release each year, and have available on request. It provides a level of detail that, while of use to many stakeholders, is unlikely to compromise commercial-in-confidence information.

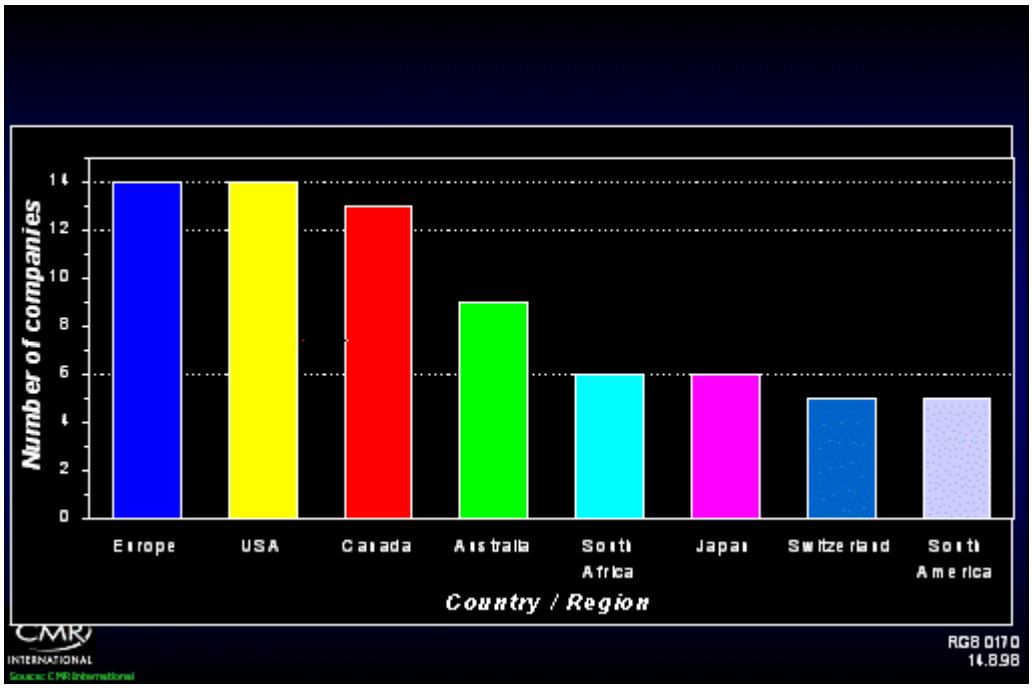
87. How Australia fits within the world context of clinical trial activity is also extremely difficult to determine. With regard to the total number of trials conducted, at the International Conference on Harmonisation held in Brussels in 1997, Dr David Lyon from the Irish Medicines Board presented data on the number of trials conducted in Europe. Table 7 below presents that data, with the Australian and New Zealand numbers for 1998 included.

Table 7: Comparison with CT in Europe (David Lyons, Ireland, ICH 4)

Country:	**No. of Trials:**	**Population:**
United Kingdom	1600	55 MM
France	1500	55 MM
Australia	**560**	**19 MM**
Portugal	200	10 MM
Ireland	250	3.5 MM

88. A survey conducted by the Centre for Medicines Research International in 1997, asked the top 20 international pharmaceutical companies to nominate the countries in which they routinely conducted clinical trials. The results are shown in Table 8 below for the 14 companies that responded to the survey.

Table 8: Where Clinical Trials are Routinely Conducted[11]



89. It is clear from this survey that within some international pharmaceutical companies Australia has attained an important role in the clinical development program. However, input to the Review has suggested that this position is not secure. There continue to be changes to requirements in many overseas countries and strong Government encouragement to improving the clinical trial climate in a number of regions, including the European Union, Eastern Europe, Asia and Latin America. The likely future impact of these changes on the industry in Australia is difficult to assess.

Australia – Special Access

90. There are currently three mechanisms whereby patients may access unapproved products without enrolling in a clinical trial. These mechanisms are:
- The Special Access Scheme (including its two categories - Category A and Category B;
- The Authorised Prescriber Scheme;
- Personal Importation.

The Legislation

91. The different mechanisms have distinct legislative bases:
- The Special Access Scheme:
  a) Category A – Section 18[12], Section 31A(2)[13] and Regulation 12A[14]
  b) Category B – Section 19 (especially 19(1)(a))[15] and Section 31B(1)[16]
- Authorised Prescriber Scheme: – Section 19(5)ff[17], Section 31B(3)[18] and Regulation 12B[19]
- Importation for Personal Use: - Section 18(1)[20], regulation 12(1)[21] and Schedule 5 paragraph 1[22].

The Special Access Scheme

92. The Special Access Scheme (SAS) refers to the arrangements that allow access to unapproved products by individual patients, other than via personal importation. The arrangements rely on different sections of the Act according to whether they are Category A patients or not.

Category A

93. Category A patients are those defined in the legislation as "persons who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment".

94. For Category A patients, use of an unregistered medicine or medical device is obtained via notification. The treating medical practitioner is required to complete the

Category A "Authority to Supply" form and send it to the sponsor of the product. This provides the sponsor with the legal authority to supply the product.

95. The practitioner must send a copy of the "Authority to Supply" form to the TGA within 4 weeks of the date of signature on the form. Failure to do so is an offence with a current penalty of up to $1,000.

96. The "Authority to Supply" form requires the practitioner to certify he/she:
- has reached the conclusion that the patient is Category A; and
- has obtained the informed consent of the patient, or patient's guardian, to the medicine being given to the patient. Informed consent is defined in the regulations to mean consent freely given on the basis of information concerning the potential risks and benefits of the treatment that is sufficient to allow an informed decision whether to consent to the treatment. Consent should be gained in writing unless there are good reasons to the contrary; and
- will prescribe the product in accordance with good medical practice.

97. The Therapeutic Goods legislation was amended in 2000 to provide the TGA with the authority to review and seek clarification of the Category A classification of patients (Section 31A(2)). The current TGA guidelines on Special Access[23] make reference to this change and indicate that ***"This will occur on a case by case basis only if it is believed that the Category A provisions were being used to avoid the process of having to obtain prior approval from the TGA for supply of an unapproved product. In such cases, the TGA may seek advice from relevant advisory bodies and/or specialist medical societies as to the appropriateness or otherwise of the Category A classification. If it is considered that a practitioner is using the Category A provisions inappropriately, the TGA can advise the doctor that similar future notifications will be invalid and that they are likely to release such information to State and/or Territory authorities, such as a Medical Board and/or Medical Complaints Units. When the TGA identifies use of a product for an indication that is considered to fall outside the scope of the Category A definition, the TGA would also inform the sponsor"***. However, the TGA's main powers in relation to questioning a Category A nomination is in referring information to others such as Medical Boards. The TGA has no discretion in law to refuse at a Category A notification from a registered medical practitioner.

Category B

98. Non-category A patients (known as Category B patients) require approval under section 19(1)(a) of the Act either by a TGA delegate or an external delegate.

99. The treating medical practitioner must seek the approval of a 'delegate' authorised under the *Therapeutic Goods Act 1989*. Requests can be made to either:
- a delegated medical officer within the TGA. Applications can be made by phone, fax or in writing. Phone requests are possible but are reserved for cases where there is an urgent medical need for access to the product. A form is provided for written applications. The requesting doctor may wish to contact the sponsoring company or TGA to clarify whether the product has been previously requested under SAS arrangements, though a negative answer does not preclude a successful outcome.

- a delegate outside the TGA. A limited number of delegates have been appointed in hospitals and other organisations (eg Australian Defence Forces) with respect to a limited list of medicines. Applications must be made in writing. Note: an external delegate cannot be the applicant and must act in accordance with a set of treatment protocols. An external delegate can only approve medicines included in the delegation of the Secretary.

100. The TGA is able to request information about unapproved medical products and the circumstances under which they are supplied. In relation to the SAS, these powers are derived from sections 31A(2) (for exemptions relating to Category A use under section 18 and Reg 12A) and 31B(1) (for Category B approvals under section 19) of the Act.

Conditions of the approval

101. Should approval be granted, that approval is almost always granted subject to certain conditions placed on the medical practitioner. The legislation requires the conditions to be met and the type of conditions imposed usually includes:
- the maximum dose and duration of treatment;
- should treatment be discontinued before the end of the treatment period approved, the TGA is to be notified of the reasons for discontinuation within 6 weeks of the treatment being discontinued;
- details of any adverse reactions are reported to the TGA.
- the use of an unapproved product should be regarded as an experimental use and should be used within the context of fully informed consent. The principles set out in the NHMRC's *National Statement on Ethical Conduct in Research Involving Humans 1999*[24] should be observed;
- the doctor and patient, or patient's guardian, accept responsibility for any adverse consequence of treatment. The Commonwealth accepts no responsibility for any defects in the product whatsoever, including defects related to manufacture, distribution, directions for use and dosage;
- on completion of the treatment all remaining supplies of the product should be returned to the supplier;
- any special conditions appropriate to the specific patient and product;
- the period for which the approval is valid, particularly in cases where importation is required (eg: for up to 12 months from the date of the decision);
- that the total quantity imported and supplied is not to exceed that required for the treatment of the particular patient; and
- the approval is for supply for use only by the particular patient.

Reporting Adverse Reactions

102. Reporting adverse drug reaction to unapproved drugs on Special Access is voluntary for practitioners but mandatory for sponsors. This is consistent with the reporting requirements for marketed drugs.

Authorised Prescriber

103. Under subsections 19(5)-(9) of the Act, the TGA is able to grant certain medical practitioners authority to prescribe a specified unregistered therapeutic good or class

of unregistered medical products to specified recipients or classes of recipients (identified by their medical condition). The medical practitioner then becomes an 'Authorised Prescriber' and can prescribe that product for that condition (also known as the 'indication') in individual patients in their immediate care without further approval from the TGA.

104. The Therapeutic Goods Regulations (Regulation 12B) stipulates that in order to be eligible for an Authorisation (i.e. to become an 'Authorised Prescriber'), a medical practitioner must be:
    - a medical practitioner engaged in clinical practice in a hospital and who has been endorsed by the ethics committee of the hospital; or
    - a medical practitioner treating patients outside a hospital setting and who has obtained endorsement from an appropriate ethics committee.

105. Provisions are available to allow for doctors who do not have access to an ethics committee to gain approval via endorsement from a Specialist College.

106. Applications must be made in writing.

107. As for the SAS, 'Authorisations' are subject to conditions. The general conditions applied to all approvals are:
    - The product may be prescribed only for patients under the authorised medical practitioner's immediate care.
    - The authorised practitioner will obtain informed consent from each patient (or guardian) in relation to the proposed use of the unapproved product, and in this context the patient must be informed that the product is not approved in Australia.
    - For unapproved products derived from biological tissue including human blood or plasma, the Authorised Prescriber must document the patient's consent in the form approved by the TGA.
    - The Authorised Prescriber must continue to have an appropriate endorsement in order to continue to supply the product.
    - The authorised practitioner will comply with all relevant State/Territory legislation.
    - The Authorised Prescriber will instruct the patient or patient's agent to return any unused product to the pharmacy on completion of treatment.
    - The authorised practitioner will report any suspected adverse drug reaction/device event to the TGA and to the endorsing ethics committee.
    - The TGA may give notice of revocation of this authorisation at any time. This authorisation is valid only until revoked or until a product with the same active ingredient or in the same therapeutic class is approved in Australia, which ever is the earlier.

108. This means that the Authorised Prescriber must be a medical practitioner engaged in clinical practice in a hospital and who has been endorsed by the ethics committee of the hospital or a medical practitioner treating patients outside a hospital setting and who has obtained endorsement from an appropriate ethics committee for the purpose of supply of the product (as required by Regulation 12B(1) of the Therapeutic Goods Regulations) or from a Specialist College.

109. The ethics committee can withdraw its endorsement of an Authorised Prescriber if, at any time:
    - the committee has concerns about the appropriate use of the product by the Authorised Prescriber;
    - the committee has concern about the safety of the product;
    - the Authorised Prescriber fails to comply with conditions imposed by the committee;
    - the Authorised Prescriber is no longer deemed to come under the jurisdiction of the committee, for example the Authorised Prescriber leaves the institution and takes up an appointment elsewhere, under the jurisdiction of a different ethics committee; or
    - the Authorised Prescriber fails to comply with State/Territory legislation.

110. Withdrawal of endorsement will result in the TGA revoking the Authorisation.

Personal Importation

111. The personal importation provisions allow for a person to import a limited quantity of most medical products for themselves or their immediate family.

112. Personal importation relies on section 18, Regulation 12, then Schedule 5 item 1 of the Therapeutic Goods Act 1989.

113. Personal importation occurs when:
    - an individual either brings a therapeutic good into Australia on their person or arranges from within Australia for a therapeutic good to be sent to them from an overseas supplier; and
    - the goods are to be used by that individual or a member of his/her immediate family and are not sold or supplied to any other person.

114. Individuals may import medicines without the goods being entered on the ARTG where:

    - the goods are either for use by the importer or a member of the importer's immediate family, and
    - the goods do not contain a substance which is a prohibited import under the CPI Regulations, and
    - the product is not an injection containing material of human or animal origin (except insulin), and
    - the quantity imported does not exceed three months' supply per importation and the total quantity imported per year does not exceed 15 months' supply at the manufacturer's recommended maximum dosage; or
    - importation of the goods is approved under regulation 5 of the CPI Regulations or the goods are included in a gazetted class approved for importation under regulation 5, and
    - in the case of prescription medicines (i.e. Schedules 4 and 8 of the Poisons Standard), the goods are the subject of a prescription issued by a State/Territory registered medical practitioner. Note: medicines carried by a passenger on a plane or ship are an exception to this requirement, however, an

import licence is still required in the case of medicines in Schedule 4 of the CPI Regulations if the passenger does not have a prescription.

New Zealand – Clinical Trials

Legislation

115. The principal legislation relevant to the manufacture and supply of medical products in New Zealand is the *Medicines Act 1981*, which defines the parameters and requirements for the sale, manufacture and supply of medicines in New Zealand.

116. The *Medicines Act 1981* and associated regulations establishes a uniform, national system of regulatory controls to ensure the quality, safety, efficacy and timely availability of medical products for human use. Responsibility for the regulatory controls lies with Medsafe.

117. Section 30[25] of this Act describes the process that a study sponsor or manufacture has to follow to obtain an exemption to some parts of the Act for medicines to be used in clinical trials.

118. Exemptions are required only for the following medicines:
- New chemical entities;
- New or different dose forms, delivery systems, or formulations of approved medicines;
- Medicines that do not have consent to be marketed in New Zealand.

119. Clinical trial approval (exemption under Section 30) is not therefore required for the following trials:
- Bioequivalence trials of a new medicine with one which is currently marketed;
- New indications or uses of a product that has consent to be marketed in New Zealand.

Procedure for clinical trial approval

120. In order to conduct a clinical trial requiring an exemption from the *Medicines Act*, an application must be made to Medsafe (a business unit within the Ministry of Health, through the Director General of Health who will grant approval after receiving the following:
- A favourable recommendation from the Health Research Council's Standing Committee on Therapeutic Trials (SCOTT);
- Approval from an accredited ethics committee for the study protocol.

121. The Director General of Health has 45 days from date of receipt to advise the applicant of the outcome of the review. The review has been advised this process typically takes 21 days.

122. The cost of a clinical trial application is currently NZ$2,800 per application. Clinical trials that do not require an exemption are assessed via appropriately constituted ethics committees, accredited by the New Zealand Health Research Council.

Good Clinical Practice

123. New Zealand has not adopted the International Conference on Harmonisation – Good Clinical Practice (ICH GCP) guidelines. However, it uses local Good Clinical Research Practice Guidelines that were released as interim in 1998 and which are almost entirely in keeping with ICH GCP.

Ethics Committees

124. Ethics committees must be constituted and operated according to the national standard of ethics committees and be accredited by the Health Research Council (HRC) Ethics Committee or the Director General of Health as being qualified to review clinical studies involving human participants.

Follow up by Medsafe

125. Following approval by Medsafe the sponsor of a clinical trial must provide the following:
    - 6 monthly progress report, including the number of patients recruited, the number of drop outs and withdrawals and all serious adverse events that do not result in breaking the study blinding code;
    - All serious adverse events that lead to breaking the study code must be reported within 3 working days of receiving the information. Follow up reports are required to assess causality and a discussion of the impact of the SAE on the future use of the investigational medicinal product (IMP);
    - Any new data on the IMP that may have an impact on the conduct and ethical consideration of the study should be included in the progress report;
    - Any study of the IMP in another country which has been stopped duet to serious and unexpected adverse reactions;
    - Withdrawal of the product from continued development or from the market for any reason;
    - On termination of the study a copy of the final study report.

New Zealand – Special Access

Supply of Unapproved Medicines

126. Section 29 of the *Medicines Act 1981*[26] deals with the supply of unapproved medicines to medical practitioners for the treatment of a named patient under their care. The legislation places an obligation on the supplier of the medicine to report details of the supply to the Director-General of Health.

127. To fulfil this obligation, suppliers of unapproved medicines must notify Medsafe, as soon as practicable after the end of every month in which the medicine has been supplied, of the following:
    - International non-proprietary name (INN) and trade name of the medicine supplied
    - Dose form
    - Month and year of supply
    - Name and address of supplier.

128. The Section 29 Declaration/Notification Form includes a declaration that the supplier will also maintain the following records:
    - name(s) of the medical practitioner(s) who requested the supply of the medicine.
    - name(s) of the patient(s) the medicine was required for.
    - dose form(s) and strength(s) of the medicine.
    - date(s) of the month the medicine was supplied.
    - name(s) of the place(s) where the medicine was supplied.

129. These records are audited by Medsafe when they review and issue GMP licences.

Similarities and Differences

Clinical Trials

130. It is apparent that there are fundamental differences between Australia and New Zealand in the regulation of clinical trials due to legislative differences.

131. The most basic differences are in the scope of regulation in terms of the types of trials covered by the schemes and the types of products. The definition of trials that fall under the control of the regulatory agency differs significantly. In New Zealand there is no requirement that Medsafe approve trials investigating new indications and trials investigating bioequivalence. Both these groups of trials are required to be approved or notified in Australia.

132. In New Zealand the regulation of clinical trials covers medicines, while in Australia it covers medicines, medical devices and complementary medicines.

133. In neither country are Phase IV trials required to be approved or notified to the agencies. However, ethics committee approval is still required and the ethical standard applied includes compliance with GCP requirements.

134. New Zealand has not adopted the ICH GCP guideline but has a local interim code of GCP. Adherence to this code appears to be voluntary. Adherence to ICH GCP is, under Regulation 12AB of the *Therapeutic Goods Regulations 1990*, mandatory in Australia for trials conducted under CTN or CTX.

135. New Zealand has a single scientific review process in the SCOTT. This is in reality an outsourcing of regulatory agency review to a single body. Australia has a decentralised, deregulated process that offers the alternatives of the scientific review being done by TGA (for CTX) and by HRECs or other bodies - for example, the Shared Scientific Assessment Panel in NSW (for CTN).

136. New Zealand has a process of accreditation for HRECs by the Health Research Council Ethics Committee or the Director General of Health that consists of a committee filing a report every 12 months. The report is similar to the Australian 'compliance' report. The NHMRC in Australia has noted that the process of accreditation in New Zealand is similar to the notification system in Australia. In Australia, HRECs are obliged to notify their existence to AHEC/NHMRC and

complete a detailed annual statement of compliance with the National Statement. These processes differ from the proposed accreditation system in the European Union.

137. There are differences in the time taken for review of applications and the cost of applications. SCOTT review costs NZ $2,400, while in Australia, fees for trial regulation include AUS$15,300 for CTX and AUS $240 for CTN. Timeframes are typically 21 days in New Zealand, with a 50 or 30 working day timeframe for CTX in Australia (depending on the data required to be reviewed), while the CTN scheme has no regulatory delay, with notification and payment of processing fee automatically creating the authority to supply investigational drug.

Supply of Unapproved Medicinal Products

138. In contrast to clinical trials, the regulation of supply of unapproved medicinal products is more deregulated in New Zealand than in Australia.

139. In New Zealand the focus of control is on the sponsor of the product with no obligations on the prescriber, while in Australia the focus of control is on the prescriber of the product.

140. In New Zealand the only requirement is on the sponsor of a product to notify Medsafe on a monthly basis of details of the products supplied. This is in marked contrast to the Australian situation where the prescriber of the product is required to notify the TGA (Category A) or to seek approval (Category B and authorised prescriber).

141. In New Zealand, the issue of use of unapproved medicines on an individual patient basis is viewed as a matter of professional practice rather than medicines regulation and the NZ “Bill of Rights” and the “Code of Patient’s Rights” issued by the Health and Disability Services Commissioner, under his empowering legislation, set out the obligations of the prescriber to the patient. In general, these require the practitioner to fully inform the patient of the options available for treatment, the risks and benefits of each treatment including the proposed course of treatment, and the need to seek the patient’s explicit informed consent either verbally or in writing where the treatment is considered to constitute a clinical trial.

Chapter 4: Comparison with current Avenues of Access to Unapproved Therapeutic Goods in the United Kingdom (UK), the United States of America (USA), and Canada.

United Kingdom

Clinical Trials

142. Prior to the introduction of the European Union (EU) directive on Good Clinical Practice,[27] clinical trials in the UK were subject to regulation under the *Medicines Act 1968* and the *Medicines for Human Use Regulations 1994*. These regulations required that anyone wishing to supply a medicinal product for a clinical trial had to obtain a clinical trial certificate (CTC) from the Medicines and Healthcare Products Regulatory Agency (MHRA). The legislation, however, provided for various exemptions from the requirement to hold a CTC. Most trials in the UK were conducted under one or other of these exemption schemes.

143. Under the old legislation studies in healthy volunteers (Phase 1 trials) did not require regulatory approval (CTC) and could commence after an ethics committee had given a favourable opinion.

144. The MHRA required a Clinical Trial Certificate (CTC) for all clinical trials unless covered by an exemption. The Agency could also require a CTC for a trial notified under an exemption if it judged the trial to pose an unusually difficult risk to benefit decision. A full submission of data for the CTC was required. The MHRA would normally refer the application to the Committee on Safety of Medicines (CSM) for advice on whether or not to grant a CTC.

145. The exemption schemes that most trials operated under were:

- **Doctors and Dentists Exemption (DDX)** – A doctor or dentist conducting a clinical trial on his or her own patients and not on behalf of a commercial organisation or other third party was exempt from the requirement to have a CTC – they were required only to provide a notification to the Medicines and Healthcare Products Regulatory Agency (MHRA) under the Doctors and Dentists Exemption Scheme.

- **Clinical Trials Exemption (CTX)** – any person other than an independent doctor or dentist conducting a trial had to obtain an exemption by applying for a Clinical Trial Exemption by submitting summaries of the supporting data normally required for a CTC.

- **Clinical Trials of Marketed Products** – notification to MHRA was all that was required.

The Clinical Trials Directive of the EU

146. The EU Directive on Good Clinical Practice (the Directive) came into force in May 2004. It aims to simplify and harmonise the administrative provisions governing

clinical trials by establishing clear, transparent procedures and creating conditions conducive to the effective co-ordination of clinical trials in the European Community.

147. The scope of the Directive is wide. It is intended to cover all clinical trials of medicinal products[28] and medical devices involving human subjects, whether sponsored by commercial companies or non-commercial institutions. It does not, however, include Phase IV studies (i.e. trials conducted with medicinal products or medical devices used within their approved conditions of marketing).

148. The Directive sets standards in terms of general principles. It does not, however, give details of how these principles should be implemented.

149. The Directive requires:

- Member States to establish ethics committees on a legal basis and imposes legal obligations in relation to certain procedures, such as times within which an opinion must be given;
- Certain Licensing Authority procedures for commencing a clinical trial;
- Standards for the manufacture, import and labelling of clinical trials and investigational medical products (IMP);
- Member States to set up inspection systems for good manufacturing practice (GMP) and good clinical practice (GCP) to ensure compliance with the standards;
- The safe monitoring of patients participating in trials by setting out procedures for reporting and recording adverse drug reactions and events;
- Secure networks to be established to help exchange of information between Member States.

Costs and Fees

150. The MHRA has stated that fees will be charged to cover the costs of assessment, authorisation, issuing of manufacturing licences and inspections. These fees will apply to all clinical trials – including academic and investigator sponsored trials. There will be no differential fees for non-sponsored trials. The final fee structure has not been released. The proposed fee (£2,700) is substantially lower than the previous fees for CTC applications (£17,215). There are fees for initial application, supplementary applications and an annual service charge per initial application.

Ethics Committee Review

151. In keeping with the Directive's requirement that all member States establish ethics committees with a legislative basis, the new clinical trials legislation for the UK introduced a new system of establishing and recognising ethics committees. In particular, the legislation set out the criteria for ethics committees to follow in reaching an opinion about clinical trial proposals, and the UK Department of Health established the UK Ethics Committee Authority (UKECA). This body is charged with establishing new ethics committees, and determining their catchment area, as well as the types of trials that each committee may review. The UKECA is also responsible

for monitoring the activities of ethics committees, and providing them with guidance and assistance.

152. Existing ethics committees are able to be recognized by the UKECA, provided that they meet the new requirements.

153. The new legislation also provides a mechanism whereby a chief investigator who is dissatisfied with an unfavourable ethics committee opinion may request that the Authority direct another ethics committee to consider his or her application.

154. The new legislation also imposes statutory time limits for ethics committee opinion, namely a maximum of 60 days for all trials and up to 90 days for trials involving gene therapy, somatic cell therapy, or a product containing a genetically modified organism. A further extension of 90 days is permitted if the ethics committee feel the need to consult an expert committee for advice, such as the Committee for the Safety of Medicines. There is no statutory time limit for ethical review of clinical trials involving xenotransplantation.

155. The EU Directive requires that Member States establish a procedure to obtain a single opinion for proposed multi-centre trials. A single individual is therefore responsible for obtaining an ethics committee opinion in relation to a multicentre trial. The appropriate ethics committee is considered that which is established or recognised for the area in which the chief investigator in "professionally based".

156. The Directive also requires that for trials conducted in more than one European Member State, a single opinion will be given for the UK.

Good Clinical Practice (GCP)

157. The new UK regulations require that all clinical trials must be conducted in accordance with the conditions and principles of GCP. The standards set out in the new regulations do not introduce major changes to the conduct of commercial clinical trials. They do however represent a major change to non-commercially sponsored trials. Compliance with the principles of GCP is now a legal obligation for all clinical trials and all trials (both commercially sponsored and non-commercially sponsored) will also be subject to GCP inspections.

158. The inspections will include both systems and trial specific audits. The audit program will include both commercial and non-commercial clinical research.

159. The inspection program is not intended to cover inspection of ethics committees in the UK.

Manufacturing and Import requirements

160. Under the current scheme the supply of an investigational medicinal product (IMP) for a clinical trial is approved as long as it is in accordance with the specification submitted to the MHRA as part of an application for a CTC or exemption. Thus there is no formal requirement for GMP.

161. Under the new system, there is a requirement for manufacturers to produce IMPs to GMP standards. To ensure this, the manufacturer will be required to obtain a manufacturing authorisation from MHRA to produce an IMP and has to have a qualified person certify that they were manufactured to GMP standards before releasing them. The legislation ensures that these standards are met by requiring GMP inspections of manufacturers of IMPs. Manufacturers are being barred from supplying IMPs to the sponsor or investigator until the trial has received authorisation.

Pharmacovigilance

162. The current legislation requires that CTC (or exemptions) holders must report all suspected unexpected serious adverse reactions to the MHRA. Under the Directive, all unexpected serious adverse drug reactions are required to be reported to the MHRA, but in addition the trial sponsor must also provide a safety update once a year. Furthermore, the new legislation requires the UK to exchange information about safety with other member states by entering all reactions reported to the MHRA into a pharmacovigilance database at the European Medicines Evaluation Agency (EMEA. Industry is able to report the data once – directly to the EMEA, and thus avoid duplicate reporting.

Access to Unapproved Products

163. Unless exempt, all medicines for human use must have marketing authorisation [marketing approval] before being supplied. The legislation however does provide exemption to allow supply of relevant unlicensed medicinal products. Products meeting this exemption are called "specials".

164. The legislation applies to the manufacturer and importer of the product and slightly varies depending on whether the product is manufactured in the UK or is imported into the UK.

165. For products manufactured in the UK, the regulations apply only to the manufacturer of the product and not to the physicians involved in the supply.

166. A "special" may be supplied only in order to meet the special needs of an individual patient. The doctor responsible for the patient's care accepts responsibility for deciding whether an individual patient has "special needs" which cannot be met by licensed products.

167. The conditions applying to the supply of a "special" include all of the following:
- There is a bona fide unsolicited order.
- The product is formulated in accordance with the requirement of a doctor or dentist, registered in the UK.
- The product is for use by his individual patients on his direct personal responsibility.
- It is produced and supplied under specific conditions that apply to all involved in the process eg manufacturers, importers, doctors, dentists and pharmacists. These include:

a) Only doctors, dentists, pharmacists and licensed wholesale dealers may order "specials".
b) All involved in the supply chain are aware of the unlicensed status of the product.
c) The manufacturer of the "special" must hold a manufacturers license from the MHRA specific for "specials". All products must be manufactured according to Good Manufacturing Practice (GMP).
d) Individual "special" product may not be advertised, including inclusion in price lists, circular letters or Internet notices.
e) The amount of stock of any "special" held by an individual doctor or dentist is limited to a total of 5 litres of fluids or 2.5 kilograms of solids (such as tablets and capsules.
f) The supplier of the "special" must keep the following records for 5 years:
    i. The source of the product.
    ii. The person to whom and the date on which the product was sold or supplied.
    iii. The quantity of each sale or supply.
    iv. The batch number of the product.
    v. Details of any adverse reactions to the product supplied of which they are aware.
g) These records must be made available for inspection by the MHRA.
h) The supplier must report all serious adverse reactions that are reported to the supplier to the MHRA via the same mechanisms as for marketed products.
i) Doctors should report serious adverse reactions via the normal voluntary mechanism as for marketing products. (This process is called the 'Yellow Card Scheme'.

168. Where a "special" product is to be imported into the UK, the importer must give written notification to the MHRA in advance of each occasion he intends to import the "special" (no later than 28 days prior to the importation). The notification must include the following particulars:
- The name of the product.
- Trademark (or name of the manufacturer).
- The name of each active ingredient in the product.
- The quantity to be imported, which must be no more than 25 single doses or an amount sufficient for 25 courses of treatment not exceeding 3 months.
- The name and address of the manufacturer.

169. The MHRA must acknowledge each notification and may object to the importation within 28 days of the date of the acknowledgement letter. Reasons for objection may include the availability of an equivalent licensed medicinal product suitable for the patient on the market in the UK or safety and quality concerns.

United States of America

Clinical Trials

Legislation

170. The *Federal Food, Drug and Cosmetic Act* is the primary legislation governing food and drugs in the USA. The associated Code of Federal Regulations (CFR) contains the consolidated final regulations and rules published in the Federal Register. The CFR is divided into 50 titles that represent broad areas subject to Federal regulations. Section 21 of the CFR contains most of the regulations pertaining to medicines and medical devices, as listed below:

- 21 CFR Part 312: Investigational New Drug Applications (IND)
- 21 CFR Part 314: IND Amendment (INDA) & New Drug Applications (NDA)
- 21 CFR Part 316: Orphan Drugs
- 21 CFR Part 58: Good Laboratory Practice for Animal Studies
- 21 CFR Part 50: Protection of Human Subjects
- 21 CFR Part 56: Institutional Review Boards (IRB). (The equivalent of Australian Human Research Ethics Committees within institutions.)
- 21 CFR Part 201: Drug Labelling
- 21 CFR Part 54: Financial Disclosures by Clinical Investigators

Types of IND

171. The United States FDA is the federal agency with overall responsibility for implementing the regulatory controls defined by the legislation listed in the above paragraph. Sponsors and/or investigators wishing to conduct a clinical trial using a medicine or medical device not yet approved for sale in the United States, or carry out a comparative bioavailability study, or carry out a study using a marketed product outside of its approved conditions of use, must file (and have approved) an Investigational New Drug (IND) application to the FDA and obtain approval from the institutional review boards involved.

172. The FDA arguably has a closer and more detailed involvement in the clinical development program of products than any other regulatory agency in the world. While an IND can be submitted at any stage it is generally intended that they will be filed at the start of the clinical program. There are a number of formal meetings between sponsor and the FDA and these are intended to give approval for the progression of the clinical development program, i.e. the “pre-IND”, “end of Phase II” and “pre NDA” meetings.

173. There are three types of INDs:

- **An Investigator IND** – submitted by investigator or sponsor who both initiates and conducts a clinical study;
- **Emergency Use IND** – intended for a single patient until a treatment IND (see below) can be submitted and approved. It allows FDA to authorise use of an

experimental drug in an emergency situation that does not allow time for submission of an investigator IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist;

- **Treatment IND** – submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening condition or if an approved study protocol does not exist.

Procedure for clinical trial approval

174. Before a clinical trial may commence the sponsor of the trial must lodge an IND application with the FDA and obtain IRB approval

The Investigational New Drug Application

175. The IND process is both an approval and a notification scheme. An IND must be submitted prior to the initiation of the first clinical trial in the USA. The FDA reviews this application and if no objections are raised within 30 days the trial may commence. If, however, the FDA raises objections in relation to the information supplied, it can issue a clinical hold which results in the non-approval of the application (i.e. the trial cannot commence), until these outstanding issues are resolved. The FDA has provided written guidance documents setting out the circumstances where a clinical hold may apply and the procedures for sponsors to follow should a clinical hold be imposed.

176. Information submitted in response to any clinical hold is also subject to a 30 calendar day review period by the FDA. Receipt by the sponsor of no additional objection after this time period allows the sponsor to commence their study(ies).

177. All subsequent IND amendments and further trials with the same product are simply notifications to the FDA. The FDA may raise objections and put the amendments or further trials on hold but the trial may proceed immediately the applications are filed. Sponsors are not obliged to wait for a response from the FDA to the receipt of these documents.

178. With respect to medicines, the FDA's approach to the regulation of clinical research is that a stronger clinical development plan will result in a better marketing application and thus quality data for evaluation and a good safety and efficacy profile for drugs subsequently made available to the American public. Regulation of clinical research by the US FDA starts out as an approval process, but becomes more of a notification scheme as evidence to support the safety, quality and efficacy of the investigational product grows.

179. Sponsors wishing to use an investigational product for the first time are strongly encouraged to request a pre-IND meeting with US FDA staff prior to filing their IND application.

Ethical Review of Clinical Trials

180. An IRB must approve all clinical trials before an investigational product can be administered to any human subjects. IRBs must be constituted and operating in accordance with parts 50 and 56 of Section 21 of the Code of Federal Regulations (CFR) described previously. IRBs are not required to be registered with the FDA, nor are they subject to an accreditation process, but they are subject to inspection, carried out under the Bioresearch Monitoring Program of the FDA.

181. There are two instances where IRBs are subject to additional oversight. For research funded by the Department of Health and Human Services (HHS), the relevant IRB must provide written confirmation to the HHS Office of Human Research Protection (OHRP) that it will comply with the regulations pertaining to federally funded research (part 46 of section 45 of the CFR). For research funded by the Public Health Services, the relevant IRB must notify the Office of Research Integrity (ORI), located in the Office of Public Health and Science, that it has authorised a particular research study. In turn, the ORI provides an additional level of scrutiny to the study.

182. A number of bodies in the USA are developing accreditation processes for both IRBs and investigators. These bodies include the Association for the Accreditation of Human Research Protection Programs (AAHRPP), the National Committee for Quality Assurance (NCQA) and the Association of Clinical Research Professionals (ACRP).

183. Part 56 of section 21 of the CFR allows IRBs to delegate their review and approval responsibilities to another IRB, and/or to conduct joint reviews resulting in a single approval for a multi-centre clinical trial. In addition, because there is no requirement that IRBs should be institutionally based, regional and national IRBs (sometimes private commercial operations) have been established, with a view to focussing exclusively on multi-centre trials. The local IRB decides whether or not it will accept a regional or national IRBs decision.

184. The FDA and IRB processes are not required to be sequential and may run in parallel if the sponsor wishes. There is no information that is required to be sent from the FDA to the IRB reviewing the trial.

Data to be submitted in an IND application

185. The data required to be submitted in an IND application is more detailed than that required by other countries. The FDA does a detailed review of the application and the evaluation may form part of the final evaluation of the product (as part of the NDA evaluation).

186. For the subsequent notifications sent to FDA after approval of the IND application, the aim of the FDA review is patient safety. They do not evaluate the trial design or address issues related to adequacy of the clinical development program. They would put a notification on hold only if there were concerns about an unacceptable risk to patients enrolled in the proposed study. Concerns about study design would be addressed at the next formal meeting between the sponsor and FDA.

Costs of FDA evaluation work in Clinical Trials

187. The US FDA recovers no costs for work associated with the processing or review of initial IND applications, the review of information in response to an imposed clinical hold, or activities associated with notifications of trials.

188. There is an acknowledgment by the FDA that work undertaken surrounding review of documentation associated with clinical trials is covered by the fees levied at the time of filing marketing application with the FDA. Clearly not all trials are associated with such applications.

Follow up Procedures - Pharmacovigilance

189. Sponsors of IND applications are required to provide the FDA (and study investigators worldwide) with the following:

- Any adverse event reports that are both serious and unexpected as soon as possible but within 15 days of the sponsor being notified of the event;
- Any unexpected fatal or life-threatening adverse event – as soon as possible but within 7 days of the sponsor being notified of the event.

In addition, sponsors are required to submit an annual report to the FDA consisting of the following information:

- A brief summary of the status of each study in progress and each study completed in the previous year, including the number of patients enrolled in each study;
- Summary information on all clinical and non clinical safety data including all safety reports submitted in the last year;
- A description of the general investigational plan for the next year;
- A copy of any updated Investigator's brochure and a description of the revisions;
- A summary of foreign marketing developments.

Clinical Trial Inspections

190. The FDA has been conducting clinical trial inspections since the 1970s and has the most developed and experienced program in the world.

191. The FDA has adopted the ICH GCP guideline document solely as a guidance document. It has not replaced the FDA GCP guidelines that are enshrined in legislation. Differences between the two documents, however, are relatively trivial.

192. The FDA Bioresearch Monitoring Program is the organisational unit within the FDA that is responsible for a range of inspection activities, including inspection of clinical investigators, research sponsors, contract research organisations, institutional review boards and non-clinical (animal) laboratories. The aim of the inspection program is to ensure the quality and integrity of data and information submitted to the FDA as well as the protection of human research subjects.

193. There are three distinct types of inspections of clinical investigators:

- Study orientated inspections (also called "evaluation" audits) – these inspections are specific to individual studies that are identified as important to product evaluation. These inspections usually occur after the trial is completed. The inspection focuses on the integrity of the data collected during the trial, and the sponsor's intended or completed evaluation of that data in the course of supporting a particular indication in a marketing application.
- Investigator-orientated inspections (also called "for cause" audits) – these inspections are specific to an individual investigator or institution and may arise because of complaints from sponsors or others involved in the research or because the research involves a pivotal study of singular importance in a product approval or its effect on medical practice. They are usually done while a trial is ongoing, and may involve inspection of the IRB involved in the study's approval.
- Bioequivalence study inspections – conducted because one study may be the sole basis of a product's marketing approval.

194. The FDA conducts approximately 700 investigator audits per year and approximately 250 IRB audits per year. Given that there are estimated to be approximately 61,000 clinical investigators in the USA, this constitutes an inspection rate of about 1%.

195. The vast majority (over 90%) of audits in the US, whether study or investigator audits, are concerned with evaluation issues rather than specific patient safety concerns although the number of "for cause" audits is increasing.

196. The FDA conducts inspections both within the USA and in overseas countries where studies have been conducted under an IND. However regulatory action concerning investigators can only be taken against US citizens. Investigators can be disqualified or restricted from participation in future clinical trial activities using products that are regulated by the FDA. Regulatory actions are subject to public disclosure.

197. FDA inspections of overseas sites are carried out if such sites figured in the pivotal trial(s) pertaining to a New Drug Application (NDA) i.e. for approval for marketing in the USA. The only action the FDA would take should problems be encountered with an overseas site or investigator would be to reject the study from submission as part of the NDA dossier.

Clinical Trial Registers

198. Information about IND applications, and about clinical trials conducted under IND applications, is not made public by the FDA.

199. Following pressure from consumers in the USA the US Congress recently passed a specific law which requires that all trials conducted in the USA for life-threatening illnesses must be published on a publicly accessible website (clinicaltrials.com). Being required by law, there are no considerations given for exclusion due to commercial sensitivity. Only trials for specified life-threatening illnesses are required and therefore it is not a comprehensive register of all trials.

200. The aim of the register is to allow patients access to information about current clinical trials – the register includes only currently open trials and includes where the trial is being conducted and a contact point for potential patients to make further inquiries. When the trial is closed to further enrolment is recorded. The results of the trial are not included.

Access to Unapproved Products – Other Avenues

201. Emergency Use INDs and Treatment INDs are the mechanisms in the USA whereby doctors can access unapproved products for use in individual patients.

202. An Emergency Use IND is allowed only for a very limited number of patients and must be replaced by an Investigator IND or a Treatment IND as soon as the investigator or treating physician can locate a sponsor or prepare an IND application for submission.

203. Being part of the IND process, the use of unapproved products is subject to the regulations applying to IND and so all use of unapproved products requires IRB approval and informed consent.

Canada

Clinical Trials

Legislation

204. The *Food* and *Drugs Act* and *Regulations* provide the authority to Health Canada to regulate the sale of drugs for the purposes of use in human clinical trials. Part C, Division 5 of the Regulations defines the specifics for Clinical Trials Application (CTA) and Clinical Trials Application Amendment (CTA-A), requirements for the sale and importation of drugs for use in human clinical trials in Canada.

205. These regulation are consistent with the principles, definitions and standards found in the Health Canada/ICH guidance documents *E6 Good Clinical Practice: Consolidation guideline, E8: General Considerations for Clinical Trials* and *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, which have been adopted by Health Canada.

Procedure for application

206. A CTA must be filed with the Health Products and Food Branch of Health Canada before a clinical trial can commence.

207. Health Canada must review the application and notify the sponsor within 30 days if the application is found to be deficient. If no problems are found the agency will provide the applicant with a no objection letter (NOL) and the trial can start. Health Canada targets review of comparative bioavailability trials and Phase I trials within 7 days of filing, except for trials involving somatic cell therapies, xenografts, gene

therapies, prophylactic vaccines or reproductive and genetic technologies. Trials can start as soon as the NOL is received even if it is less than the 30 days.

208. CTA are required for the following trials:
- Phase I to Phase III;
- Comparative bioavailability trials;
- Trials involving marketed products where the proposed use of the product is outside the parameters of the marketing approval.

209. Phase IV trials (defined as studies within the approval conditions of marketing approval) are not required to be filed with Health Canada.

Ethics Review

210. Prior to the start of a clinical trial, the proposed trial protocol and informed consent document must be reviewed and approved by a Research Ethics Board (REB) as defined in the regulations. The name of the REB that approves the protocol must be submitted to Health Canada prior to the start of the trial.

Follow up by Health Canada

211. Following the initiation of a clinical trial the sponsor of the trial is required to provide to Health Canada the following:
- Updated Investigator's Brochures supplied annually;
- Serious and unexpected adverse drug reactions in line with the ICH guidelines.

GCP Inspection

212. Health Canada has established a formal program of GCP inspections in line with the ICH guidelines. Inspections will be conducted mainly at clinical trial sites, sponsor organisation and contract research organisations (CRO) sites.

213. The inspection program started in January 2002 and included a one-year confidence building and voluntary phase. From January 2003 a formal inspection program was initiated. The aim of the program is to inspect up to 2% of all Canadian sites each year.

214. The agency plans two types of clinical trial inspections:
- Inspection during clinical trials;
- Inspection after completion of clinical trials.

Good Manufacturing Practice

215. Clinical trial products are required to be manufactured at facilities which hold a manufacturing license and are inspected for compliance with GMP.

216. GMP inspections are conducted separately from the GCP inspections.

Access to Unapproved Products

217. The Special Access Program (SAP) provides access to non-marketed drugs for medical practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable or are unavailable.

218. Sections C.08.010 and C.08.011 of the *Food and Drug Regulations* support the SAP.

219. Most of the drugs covered by the SAP are for serious or life-threatening conditions. The examples given in the SAP guidelines include intractable depression, epilepsy, transplant rejection, haemophilia and other blood disorders, terminal cancer, and HIV/AIDS. The SAP is also intended to cover specific heath crises, such as the outbreak of a communicable disease, by providing access to non-marketed drugs.

220. The medical practitioner is responsible for initiating the request on behalf of the patient. A written request for approval must be submitted to Health Canada on a standard form. This form requires information about the requesting doctor, the patient, and the product requested. The level of information is very similar to that required in Australia under the Australian Special Access Scheme.

221. Health Canada endeavour to process SAP requests within 24 hours of receipt. Where it cannot make a decision within that time, it commits to contact the requesting practitioner within 24 hours.

222. When an approval is given, a copy of the Letter of Authorization is provided to the requesting practitioner with a copy sent to the manufacturer.

223. The practitioner to whom approval is given must agree to provide a report on the results of the use of the drug, including any adverse reactions, to both the manufacturer and Health Canada. In addition, the practitioner must agree to provide, on request, full details of all quantities of drug received.

Similarities and Differences between Regulatory Agencies

Role of the Regulatory Agency

224. Outside Australia, it is the regulatory agencies that undertake the primary scientific evaluation of the product to be used in clinical trials and the regulatory agencies which have primary responsibility for the oversight of clinical trials.

225. The FDA has a unique role in that it has much greater control and input into the whole clinical development program. While it does not mandate US studies, given that the USA constitutes approximately 50% of the world pharmaceutical market, most drug development has a substantial (if not total) component of US involvement and it is therefore not surprising that FDA has the role that it does.

226. Other jurisdictions that do not mandate local studies are likely to have only some drugs tested. They therefore cannot exert the same level of control as the USA.

Scope of Trials Regulated

227. The UK was the country with the greatest difference in respect to the level of control of clinical trials. Under the UK's previous system for trial regulation, all phase I trials and all non-commercially sponsored trials were not subject to regulation by the regulatory authority. These trial are now subject to regulation for the first time.

228. In the US, the FDA regulates only those trials that are going to be used for a regulatory purpose but advice to this review is that this tends to be extended to cover almost all trials.

229. Generally Phase IV trials (defined as clinical trials conducted within the marketing conditions) are not regulated in any jurisdiction. However, in some they are still subject to some parts of the regulations (eg in the US they still require IRB approval and informed consent).

230. Comparison of the clinical trial systems of Australia and New Zealand are contained in Chapter 11 of this report and discussed in the context of the likely formation of a Joint Regulatory Agency between the two countries.

Ethical Standards

231. In all jurisdictions, the ICH GCP guidelines (or the FDA equivalent) are required to be followed.

232. The role of ethics committees is common to all jurisdictions and the committees have essentially the same focus and roles. They have a legal basis in the USA and will have in the UK (where they will be established under a new government entity). FDA legislation requires that trials are reviewed by Institutional Review Boards established by the institutions at which the trials are conducted. Ethics committee status in Canada is unclear.

Clinical Trial Audits

233. The issue of clinical trial inspections that have had, since the 1970s, to be conducted in the USA are new to other countries. The programs in Canada and the UK have been instituted only in the last few years and are as yet untested as to their effectiveness. Neither agency has produced clear guidelines as to the nature and extent of the inspections, nor the legal basis of the programs. The UK program is not yet established in legislation.

Fees

234. The charging of fees in relation to regulatory oversight of clinical trials varies considerably between jurisdictions. Australia, the United Kingdom, and New Zealand (see Ch11) all charge fees, with the UK fees having recently been reduced as part of new regulations arising from the EU Directive. In North America, the FDA and Health Canada do not charge fees. Both these agencies consider that fees charged in relation to evaluation of marketing submissions and other regulatory activities are

such that they cover the costs of activities associated with clinical trials. Also, the only agency of these that is fully cost recovered is the TGA.

Timelines

235. All the overseas agencies undertake review within very limited time frames. The USA, which has a review period only for the first trial applied for, has 30 days. It makes no distinction between Phase I trials and any other trial. All subsequent trials (IND application) have a notification scheme. The UK, while the EU directive allows for 60 days, has decided to maintain its previous timeframe and has 30 days (extendable to 60 days under certain conditions). Canada has 30 days but states that it will endeavour to provide approval in less than the stipulated time.

236. The US, UK and Canada work in calendar days.

Chapter 5: Clinical Trial Notification/Exemption.

Submissions to the Review

237. Many submissions received by the Review addressed various issues associated with Clinical Trial Notification/Exemption, as did many of the interviews conducted by the Review Team. However, not all submissions were factually correct in their detail and many demonstrated misunderstandings of the processes involved in the administration of the CTN and CTX Schemes.

238. The introduction of the Clinical Trial Notification (CTN) Scheme in 1991 deregulated the conduct of clinical drug trials in Australia. Under CTN, the TGA is no longer required to assess any data relating to a clinical drug trial prior to trial commencement. The TGA is now notified of clinical drug trials by the sponsor of the trial, who has already obtained HREC and institutional approvals. The TGA may, and does routinely, seek additional information, but this does not delay commencement of the trial.

239. An article published in the Good Clinical Practice Journal in 2003 claimed "***Phase I and II trials are usually conducted under the Clinical Trials Exemption scheme (CTX). Sponsors submit an application to the TGA for evaluation and comment. If the TGA approves the usage, sponsors may conduct any number of trials under the CTX application without further assessments, provided the product is used in a way that falls within the administration's guidelines. Once the HREC review has been completed, final approval for a trial must be obtained from the management of the hospital where the trial is being carried out"***[29].

240. It should be clearly understood that this assertion is not the case - most Phase I and II trials are not done under the CTX, as the numbers given in Table 1 below clearly demonstrate.

241. The Good Clinical Practice Journal article goes on to assert that ***"Phase III trials are generally conducted under the Clinical Trial Notification (CTN) scheme. Under this system, every site submits material relating to the proposed trial, together with a fee, to one of the HRECs, which reviews the trial's scientific and ethical acceptability. The CTN submission is completed by the investigator on the sponsor's behalf, signed by the HREC chairman and the hospital manager, or the approving authority for the host hospital or institution, and submitted to the TGA. Although the TGA is told about the trial, under the CTN system the administration plays no active part in approving it***" [30]

242. Medicines Australia saw the introduction of CTN as a positive move, stating that ***"The CTX Scheme was slow, relatively costly and acted as a disincentive to conduct clinical trials in Australia. However, since the introduction of the CTN Scheme we have seen a significant increase in clinical trial activity in Australia"***.[31] Identifying one of the principal factors that, in its opinion, contributed to this impact, Medicines Australia asserted that ***"It is evident … that the introduction of the CTN Scheme has provided a significant boost to the conduct of clinical trials in Australia because sponsors are able to initiate clinical trials more quickly"***[32].

243. Medicines Australia concluded, however, ***"that the existing regulatory framework comprising both the CTN and CTX Schemes should remain in place in Australia. Whilst there are only a small number of CTX applications submitted to TGA, it is important that this route continues to be available, particularly for early phase clinical trials for which both the sponsor and [HRECs] may desire review by the TGA"***. [33]

Subsequently Medicines Australia advised that the CTX Scheme could be abolished if scientific reviews by accredited third parties could be made available to sponsors. The review acknowledges this approach but doubts any government would be prepared to devolve its responsibility for higher risk trials so completely.

244. As NSW Health, in its submission to the Review, put it, ***"This system has greatly reduced the involvement of the TGA and transferred the workload of review of clinical drug trials to HRECs"*** [34].

245. NSW Health went on to argue that, as well as reviewing the ethical acceptability of a clinical drug trial, HRECs have taken on the responsibility of reviewing (or ensuring adequate review of) the scientific validity of the protocol, which includes trial aims; design; proposed intervention; sample size and analysis; method of drug use; and safety and efficacy of the study medication.

246. According to the NSW Health submission, ***"the introduction of the CTN Scheme has resulted in a major increase in the burden on HRECs and has greatly reduced their capacity to adequately discharge their responsibilities towards protecting the rights and welfare of participants of research"***[35].

247. When the CTN Scheme was introduced in 1991 it was assumed that most clinical trial applications would continue to be made under the CTX Scheme. However, as Table 1 below indicates, ***"since 1991 there has been a steady increase in the number of CTN applications and a rapid decrease in the number of CTX applications. The resources available to HRECs have not kept pace with this increased workload"***[36].

Table 1: Clinical Trials (Medicines) 1990 – 2000

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
CTN Trials	0	70	260	300	380	400	450	490	560	480	559
CTN Sites	0	150	510	650	670	1000	1180	1380	1840	1780	1961
CTX Trials	100	30	30	30	30	20	15	10	5	3	2

Table 2: CTN protocols (NSW) notified to TGA, expected start date 2000

Number of Sites	1	2	3	4	5	6	7	813	17
Number of Protocols	157	50	26	15	10	3	1	1	1

248. According to the Australian Consumers' Association (ACA), "the 1991 reforms not only made it much quicker and easier to establish a clinical trial in Australia; they also made it much cheaper. In a private conversation, one senior pharmaceutical executive

told the ACA that his company's costs of running a trial in Australia were about one-fifth of those in the United States. As a result, his large global corporation has swung as much as possible of its clinical research to Australia. Not all of these cost savings are due to the regulatory changes of 1991, but many are." [37].

249. In view of ACA, "CTX should go. In its present form, the CTX scheme has become redundant. The TGA estimates that only about five trials a year go through this system. That is not enough to justify the maintenance of the process."[38]

250. Taking a slightly different view, Novo Nordisk considers the current regulatory system for clinical trials to be "adequate in Australia and New Zealand, although some improvement would be welcomed." [39]

251. Novo Nordisk "prefers to use the CTN route for our clinical trials, although this usually requires having a UK CTX approval at the time of Ethics Committee submissions in Australia and NZ. We find the SCOTT committee route is more involved and requires a longer lead-time than the Australian CTN route. Usually for phase 1 and 2 trials where only one centre is involved these issues are not too burdensome."[40]

252. With regard to multi-centre trials, Novo Nordisk finds that "the main delaying factor is the time and effort taken to submit packages to each and every EC [Ethics Committee] (usually with different requirements for format and content) and then for each EC to fully review the clinical trial and provide clearance. The actual CTN process is simple and straightforward."[41]

253. Ideally, Novo Nordisk would like to see a "centralised EC clearance procedure for multi-centre trials, where the EC for the Principal Investigator provides the EC clearance that is then adopted by other centres without the need for full review. This would mean that the workload in reviewing all aspects of the clinical trial is done primarily by one centre. All institutions would still require their own ECs, as the Principal Investigator for each clinical trial is likely to be affiliated with a different centre."[42]

254. Failing this, Novo Nordisk would prefer "standard format and content requirements for the EC submissions at different sites."[43]

255. The Clinical Trials Centre at St Vincent's Hospital argues that "the CTX scheme is not voluntarily utilised by industry as a mechanism for the regulatory approval of clinical trials, except in instances where there is a high risk venture (gene therapy, etc). Of note, it is exactly these situations where there may not be sufficient technical expertise available to provide adequate CTX review". [44]

256. The Centre goes on to express the view that "overall, the CTX scheme could be considered an impediment to research as it is potentially slow and an expensive exercise. The issue of time to approval and cost are significant barriers to the implementation of clinical research despite the fact that various Australian bodies are currently trying to promote the biomedical, and especially the biotechnology, sectors

of research. The companies involved in the latter tend to be smaller in size, less well capitalised and undertaking the most high risk ventures."[45]

257. In addition, the Centre does not see the TGA as a body that adds value to the clinical research/drug development process, arguing that "[i]t acts primarily as a regulator and not as an adviser. This is in contrast to the US FDA investigational new drug (IND) system."[46] The Centre would prefer an approach that "provides advice to companies/researchers at the earliest stages of product development and clinical research."[47] (The TGA interestingly, does provide advice to high technology product sponsors using the CTX, where, with its international contacts, it is able to assist in development planning).

258. Discussing general practice research, the Baker Institute explains that "CTN applications require identification of multiple sites at the time of submission to the TGA" [48], whereas "in general practice studies, all sites are not identified at the outset of the study and join the study as the research progresses" [49] with "most general practices act[ing] as screening centres for a large study rather than as a study site." [50]

259. Institute argues that "the definition of a site should be clarified to include a location where –

- Case Record Forms (CRFs), source documents and databases are held and maintained.
- Investigational drug is stored and dispensed.
- Research staff are employed and trained." [51]

260. According to the Institute, ***"general practices are the location at which subjects are screened for study recruitment and as such do not represent a definition of 'study sites' "*** [52]. It goes on to argue that ***"with the current requirements, large-scale general practice-based research will be impossible and overly expensive. For example, if the current rules were applied in the recently completed [the] 2nd Australian National Blood Pressure Study where over 1500 general practices were utilised in the study, … would have cost an additional $330,000."*** [53] According to the Institute, ***"this is likely to jeopardize the prospects of undertaking general practice-based clinical research."*** [54]

278. In a forum organised for the Review by the Victorian Cooperative Oncology Group, the CTN Scheme was seen as ***"a great advantage to … clinical trials in Australia"*** [55] as ***"it allowed competition with international sites by being able to participate in trials without large CTX submissions."*** [56]

279. However, according to Forum participants, ***"there was still lack of clarity about the CTN scheme, including uncertainty about [its] appropriateness for phase I-II trials, and [the] level of overseas review."*** [57]

280. Forum participants were concerned at the costs of CTN applications, and pointed to ***"conflicting advice regarding a single CTN application fee for cooperative trial group listing of multiple centres, or fees for each participating centre"*** [58].

281. The Forum participants were concerned that ***"there were no funds to support each participating centre's application fee in an un-funded cooperative group trial"*** [59], and suggested that ***"TGA confirm batch submissions with a single fee"*** [60].

282. In its submission, Monash University stressed that ***"large-scale clinical trials of international importance can be conducted in Australian general practice. However, uncertainty in application of current TGA requirements, which have obviously been developed with a specialist hospital-based environment in mind, threatens the economic viability of future general practice-based studies"*** [61].

283. The University identified a specific problem, namely that ***"currently CTN applications require identification of multiple sites at the time of submission to the TGA. In large-scale clinical general practice-based studies, practices are recruited over an extensive period of time and are not known at the time of submission. If each practice is to be notified as it is recruited, then a fee is payable at a significant cost. For a trial we are currently negotiating with the National Institutes for Aging in the United States we would have to budget $440,000 for TGA fees"*** [62].

284. Monash proposed, in identical terms to the Baker Institute (cited above) a ***"simple classification of what constitutes a trial site."*** [63]

285. According to the submission, ***"only the national and state-based centres for such a trial would need to be registered as trial sites. … We propose this because general practices act more as screening centres for a large study rather than as a study site per se"*** [64].

286. Monash argued that ***"general practices are a location at which subjects are screened for study recruitment, where study medication is delivered to the subject and where the practice-held medical record is a document of review for subject management and for possible endpoints"*** [65].

Consideration of the Issues

CTN/CTX

287. Notification under CTN and CTX is currently required for clinical investigational use of:

- Any medicine or device not entered in the Australian Register of Therapeutic Goods (ARTG), including any new formulation of an existing product or any new route of administration; or

- A marketed medicine or device beyond the conditions of its marketing approval, including new indications extending the use of the product to a new patient group and the extension of dose or duration of treatments outside the approved range.

288. The current regulations thus include Phase I, Phase II and Phase III trials, but exclude Phase IV trials.

289. The key issues identified by the Review relating to CTX/CTN are:

- Should the CTX and CTN be retained in their current format?
- Should any trials be required to be submitted by CTX?
- Is the current fee structure for CTX and CTN appropriate?
- Should additional guidelines be provided?
- Are the current data requirements for CTX and CTN appropriate?
- Is there a need for a common application form for HRECs?
- Should there be a change in the definition of site under the CTN?
- Should there be a distinction between industry sponsored trials and non-sponsored trials?

290. At the time the CTN Scheme was introduced, the CTX scheme was envisaged to be the predominantly used method by which clinical trials would be authorised and approved in Australia. This view was recorded in the Baume review (1991) and in the CTN review conducted in 1993.

291. Today, however, almost all trials are conducted under the CTN Scheme, rather than the CTX scheme. The reasons for this are not entirely clear. No submission provided any substantial discussion of the CTX scheme.

292. CTN is significantly faster and cheaper with respect to the TGA process, but in terms of multiple site trials & HREC review it is not working as smoothly as was hoped, and many concerns have been raised with the Review.

293. Problems appear to arise when trials are conducted under CTN and the relevant HREC feels it necessary to undertake substantial scientific review. Rather than refer such trials back through the CTX process, there has been an overwhelming willingness by HRECs to undertake scientific review of trials being conducted under the CTN scheme. In many cases this review is likely to be a significantly different review than would have been conducted by TGA (or any other regulatory agency).

HREC Review

294. The depth and nature of the scientific review being conducted by HRECs under the CTN is unclear. No organisation or body who made submissions to the Review has identified any stratification of the process of review by HREC to allow for the different types of trials which were defined at the time of the introduction of the CTN (eg trials of marketed products, trials of products which have been reviewed by the USA or UK agencies, trials where no other review has occurred).

295. There is some concern over the focus of the HREC scientific evaluation of the science of the trial design, and the lack of appropriate attention to the evaluation of the chemistry, the manufacturing process, and the toxicology areas.

296. The TGA has provided guidelines on what should be submitted to an HREC for a CTX application, but there are currently no TGA guidelines provided on what should be submitted to HRECs in relation to CTN trials. This is a serious deficiency.

297. Problems have been identified, especially for the scientific review of multicentre trials. Concern has been raised over the needless duplication of the review process by each HREC, admittedly largely arising out of indemnity considerations for the institutions/sites concerned. There is also concern about single centre trials conducted at institutions that do not undertake many clinical trials or where there is insufficient access to drug evaluation and/or clinical trial evaluation resources.

298. A number of submissions from doctor's cooperative groups raised concerns about the definition of a site and sought to have clarification of this issue as it relates to the CTN. The main issue with the current definition related to the cost of notification of the individual sites. It appears to the review that there is confusion over the issue of costs for individual sites and the TGA should develop an appropriate fee scale to ensure that the costs of notifying individual sites are not prohibitive to large-scale multicentre trials.

299. Overall there appears to be a very strong reluctance to have CT applications reviewed by the TGA. The reasons for this appear to be based solely on historical problems with TGA review.

300. In place of TGA review, a multitude of processes and resulting problems have arisen, primarily due to the decentralisation of scientific review. The current processes being studied are largely State-based, and arise from the State based hospital system. However, they provide no logical solution for multi-centre national trials or trials involving public and private non-hospital institutions.

301. Because scientific review is being conducted by the HRECs, the consensus of the submissions and the workshops was a request for assistance and direction.

302. One way to redress this issue would be to re-establish centralised scientific review by the TGA. However this was not suggested in any submission and much of the reluctance to accept this proposal appears to be concern over a lack of resources at TGA to do this in a cost effective, and time efficient way.

303. Where the overseas agencies (USA, UK and Canada) have a 30 calendar day review time (with maximum extension to 60 days), the TGA currently has a 50 working day time limit (which in reality equates to approximately 75 calendar days). Even this may be extended should additional data be required.

304. For trial variations, the TGA target time is 30 working days (equating to 45 calendar days) for CTX applications.

CTX Issues

305. The submissions to the Review, along with anecdotal comment, indicate that industry wants to keep CTX but almost never uses it, and everyone else wants to get rid of it - but no one has given any reasons for what is wrong with it or why it is not used!

306. It appears to the Review that the CTX is not used because before a product gets finally approved:

- CTX is too expensive, has an initial cost too high for anyone other than companies, and no total cost is legislated.
- CTX takes too long and has no mandatory total time period. The current statutory time period is for each application, and therefore the process may drag on if applications are rejected based on inadequate evidence.
- The guidelines for what is required are too complex and the need for information to go from TGA to ethics committees delays the process.

307. Any change to the current Australian clinical trial review process will present significant challenges to the TGA as well as to an industry that will need to accept the changes and convince their parent companies that this is not a major retrograde step.

308. In order to gain acceptance to any changed process, it may be possible to introduce the changes slowly and in an incremental process which would allow time for TGA to establish credibility by meeting appropriate performance targets.

309. The required documentation to be provided to the TGA under the CTX scheme was based on the UK CTX scheme. This was specifically intended to avoid the production of unique Australian clinical trial applications. With the UK having replaced its CTX scheme with a clinical trial certificate (CTC) scheme, there is a need to re-examine the documentation required for CTX in Australia.

310. During the Review-sponsored workshops, participants discussed a proposition advanced in written submissions that, while the CTN/CTX arrangements should, by and large, be retained, CTX should be used more widely than at present for Phase I trial approval applications, with TGA to issue a clear definitional statement:

- To aid researchers and sponsors determine whether their proposed trial falls into the CTX or CTN category;
- To improve clarity about the CTN scheme and its appropriateness for Phase I and Phase II trials;
- To clarify the level of overseas review; and
- To specify the appropriateness for trials of approved drugs and for phase I and II non-commercially-sponsored trials.

311. The premise of these statements and proposals is that the CTX and CTN are to remain largely as they are. Most submissions assumed no significant change to the process.

312. It would not be appropriate to distinguish between industry-sponsored trials and non-industry sponsored trials. No other comparable regulatory agency now makes such a distinction. The difficulty for non-industry sponsors is their ability to prepare the

application and, in the present system, to pay the CTX fee. If there was to be a distinction, the higher level of scrutiny should be for the non-industry-sponsored trials.

Benchmarking

313. In seeking to maintain comparability of cost and time lines with the rest of the world (as was argued in some submissions), it is difficult to understand how to benchmark and assess comparability when the systems are so very different.

314. The request for inclusion of formal benchmarking performance indicators was widespread in submissions to the Review, but if what was sought was just a comparison of clinical trial systems, on current comparisons CTX looks very bad (being expensive and long) and CTN looks quite good (comparable cost and the fastest).

315. If the comparison is with regulatory agencies and includes the entire system, it would be impossible to do comparisons, as there is no published data on the time taken in either the US or the UK for ethical review. The UK regulatory agency makes no information about agency performance publicly available. That agency has recently been severely criticised for this lack of transparency but has not indicated that any change is likely. The US does not make any information related to clinical trials publicly available. Formal benchmarking is impossible unless jurisdictions make data on clinical trials publicly available.

316. It is common for industry and others to state that benchmarking is a "good idea" but the reality is that it is very difficult to obtain meaningful data with which to benchmark. This is not to say that TGA should not be encouraged to continue its efforts in this regard.

317. TGA should be required to produce general performance information about clinical trials and to make it readily available. It is potentially able to collect an enormous amount of information. There is a cost to providing information, so information collected should have defined public health goals.

Notification and Application options

318. Some respondents proposed the introduction by the TGA of "on-line" application/approval to reduce delay caused by postage of payments. Some believed there is a seven day notification delay time. There is, in fact, no such requirement to wait seven days, and this is clearly spelt out in the current guidelines. Yet it is repeatedly misunderstood and reasserted.

319. On-line notification for CTN or approval for CTX is a good idea and it should be possible for a CTN system to accommodate such an approach. However, the platforms needed for submission of the data required for a CTX application are not yet available in industry or TGA. Certainly acknowledgment of lodging a CTN should be available on-line and TGA and sponsors should be encouraged to develop and use such systems.

Sponsorship

320. It was suggested that a relaxation of the requirements for Australian sponsorship should be done to enable overseas companies to be the sponsors of clinical trials. This, it was claimed, would support smaller contract research organisations (CROs) and cooperative groups to undertake more trials.

321. The issue of Australian sponsorship revolves around legal issues to do with accountability and is one related principally to small CROs. The Review does not consider this issue to be of such a serious nature as to require a change in the legislation. It would lessen the protection of patients if the legislation were to be changed to allow a foreign company to be the sponsor of a trial. The issue and definition of sponsor of a trial was clarified in the guidelines but was not altered.

Reporting and Database capability

322. While significant upgrading of the TGA's IT and database capacity was called for by many respondents, there is in fact a major upgrading process being undertaken at TGA to upgrade the whole IT infrastructure of the TGA (the SIME project). The clinical trial database was not included in the initial phases of this project, but it is intended to be included in later phases of the project. This means that it will be some years before any changes are made. This timeframe should be reviewed.

323. Many argue that the TGA should be required to report regularly and in some detail on clinical trial activity in Australia/NZ and to maintain a database with an appropriate quality system to ensure that analysis and reporting can be done. Reporting clinical trial activity can be done easily without breaching any commercial in confidence restrictions (as can be seen by reference to the Tables in Chapter 3 of this Report). However, reporting costs money and should be related to public health goals.

Fees

324. Introduction of a single CTN application fee for cooperative trial group listing of multiple centres, with TGA confirming batch submissions with a single fee, was a serious issue raised.

325. The issue of CTN fees for multicentre trials is a complex one and extends beyond just cooperative groups. There were changes made in 1999 but these do not appear to have remained in place. The issue relates to the definition of appropriate costs for CTN and whether it is appropriate or necessary for the TGA to recover costs of this activity from its fees. If charges are required, costs are likely to prevent trials from occurring in Australia. Other countries, even the full cost recovery agencies (eg UK) are clearly intending to subsidise clinical trial activity with increased charges on other activities. There should be a close review of the costs of both CTX and CTN to ensure that costs are not a barrier to clinical research. Currently the Australian clinical review regulation system is heavily subsidised by the prescription medicine industry. The appropriateness of such cross-subsidisation should be considered in any review of funding.

326. However, it is recognised that regulatory fees are only one of the costs associated with the performance of clinical trials and these costs are significantly lower than the cost of providing adequate infrastructure and ensuring the trials are conducted in accordance with GCP requirements. There are also costs associated with time spent waiting for ethics and regulatory approval.

Options for change to the Clinical Trial System in Australia

327. There are some options when considering any change to current Australian clinical trial requirements:

- Retain the current process of CTX and CTN as at present, and accept that nothing much will change.

- Retain CTX only for trials where the product has not been approved by one of Australia's comparable countries (EU, USA, Canada).

- Retain CTX and CTN as at present, but improve processes around notification and scientific review. – This is largely the basis for the proposed model in chapter 11.

- Abolish CTX and accept that all trials will be done under CTN - the reality of the current practice, except for high technology products – and do nothing to address the issue of scientific evaluation.

- Redefine CTN to ensure that it is used solely for:
    a) All marketed trials being used for new indications and patient populations.
    b) All trials that have had one trial-related approval by US FDA and/or UK.
    c) All trials testing new dose formulations, and/or significant increases in dosage.

- Adopt one of the appropriate overseas models, such as:
    a) The UK model, where every trial is reviewed in detail;
    b) The US model, where only the first trial is reviewed in detail and subsequent trials are notifications; or

- Invent an entirely new system, still called CTN but having different levels of review.

328. An option proposed by Australian Industry[260] put forward the view that the Scientific Advisory Panels (SAP) of the proposed model in Ch. 11 of this document should conduct review only for a small defined subset of high-risk trials, such as novel compounds in early stages of development, with scientific assessment for all other trials remaining under the review and monitoring responsibilities of currently constituted HRECs, with ethical review done in parallel by the HREC. There was also the widely-held desire to have ethical and scientific review of multi-centre trials be carried out by a single HREC and the decision to be accepted by other HRECs/institutions.

329. The review team believes that the proposed clinical trial model in Chapter 11 allows a parallel review process (ethical review can also be done by a SAP conducting scientific review for specific trials), and the options presented in this report for streamlining of approval processes propose some solutions to the difficulties of

multiple reviews of multi-centre research. Mutual acceptance of reviews by other institutional ethics committees will require federal and State cooperative efforts. The intention is that SAPs shall inspire confidence that scientific review of complex trial proposals has been carried out to a consummate standard, and this coupled with GCP inspection capabilities of the regulator shall promote quality research in Australia while ensuring subject rights and safety are protected.

Possible changes to CTX

330. If there is no change to the current CTX, it would probably not be reasonable to push any more trials through the CTX process as the likely outcome would be that these trials would not be done in Australia. The industry and investigators have overwhelmingly voted with their feet in the last 10 years and have clearly indicated that the current CTX is not an attractive mechanism for doing clinical trials. If no change were to be made to CTX it would be extremely unlikely that anyone would use it, and Australia would lose trials to overseas countries that have better systems.

331. An option is to make CTX more attractive but allow flexibility and not dictate which trials must go under which system. The advantages of this would be that no major change would be made to the system – thus not changing the perception that CTN is still the preferred method - but over time more trials might be done by CTX.

332. The minimum changes that could be made to the CTX to make it more attractive for commercial sponsors are:

- Substantially reduce the time for review of the total submission. If the time taken is longer than 30 calendar days, industry will not use it, to the real detriment of any wish by Australia and New Zealand to be internationally competitive and to attract industry to Australia and New Zealand. For Phase 1 studies it should be no longer than 14 – 21 calendar days.

- Substantially reduce the cost of the CTX, and make it competitive with the rest of the world (where equivalent schemes are either free or at a nominal cost). If CTX stays at its current cost, it is likely that no-one will use it; it is currently the most expensive in the world, yet it is heavily subsidised. Industry would have to be consulted on an increase in cross-subsidisation.

- Make the fee for a CTX application a cost per submission and do not charge for amendments or additions to an initial application.

- Remove the necessity for material from the TGA to go to the HREC (other than in exception circumstances) so that the processes can run in parallel. It should be noted, however, that often ethical review cannot be truly undertaken without completion of the scientific review because this defines what many of the ethical issues are as they arise from the trial design.

- Update the guidelines for what must be submitted under CTX to the TGA to be in line with the European Directive (as interpreted by the UK).

333. Assuming that these changes are made to the CTX and assuming that it is felt that TGA review of the higher risk clinical trial applications is needed (this is by no means supported by the industry or by most of the submissions), other proposals can be addressed.

334. Neither the industry nor most of the investigators will welcome any change that forces more trials to go through CTX. Which trials should then be evaluated by CTX (TGA)? Four obvious options are:

- All trials (this is what the EU Directive requires).
- All phase I trials.
- All first trials in Australia.
- As at present, those trials where additional scientific review is required by HREC.

335. It would be useful to know how many Phase I trials are currently conducted in Australia but this data is not readily available and not routinely collected by TGA. In a rough analysis that was done by TGA in 1999, Phase I trials amounted to about 10% of the new trials each year (about 40-50 trials a year – or one per week). As the data package for Phase I trials is not very substantive, and as there is no human data to evaluate, to encourage use of CTX for all such trials should be feasible. It may however have a huge impact on the total clinical trial activity, and would involve a substantial amount of extra resource allocation by TGA.

336. Another more innovative possibility would be that all Phase I trials should be submitted to TGA, but allow for TGA to accredit some institutions to evaluate Phase I trials (and some later trials). This would recognise those institutions that are clearly doing it satisfactorily now and allow them to continue. It is likely that the accreditation would be for stated therapeutic areas (recognising appropriate expertise). Institutions wishing to continue to do evaluations could apply and an audit of past approvals could be the basis of initial accreditation. New accreditation could be on the basis of establishing appropriate expertise and methodology to ensure quality evaluation is done and meeting performance standards. It may well be that if TGA review is effective and timely, institutions will not want to continue undertaking scientific evaluation of CTN applications. After all, TGA involvement in review would be perceived as reducing institutional liability exposure, even though the reality would be no change in liability. This is likely to increase the cost and delay in timing of trials and to reduce use of Australia as a site for clinical trial activity.

337. Another option is to have all Phase II and III clinical trials go through CTX unless:

- A phase I trial has already been evaluated by CTX, in which case all subsequent trials can be CTN. The drawback in this approach is that the risk of a medicine to a patient group cannot be based only on whether its use in a Phase I volunteer study was without incidence.

- A phase I, II, III trial has already been evaluated by the US FDA or the UK MHRA and allowed to proceed. All subsequent trials could be conducted under CTN. However, there is no documentation available from either agency to demonstrate that the trials have been "approved" (they are both exception systems – the trials are allowed to proceed at the end of 30 days unless stopped by the agency). Since

introducing new forms would lead to excessive delay, there would have to be an acceptance that an assurance from the sponsor would be sufficient. This would in any case cause some delay compared to the current system as it would delay submission of the trial in Australia until after the US or UK process had been completed.

- The "product" (i.e. the same active ingredient by the same route of administration) to be used has already been approved for marketing for any indication in one of the following countries: USA, Canada, UK, Sweden, and Netherlands. (It would not be wise to accept approval from all European nations because Europe includes many countries without adequate registration processes. Consideration could in time be given to a wider list. Of course, access to full reports of these agencies would be necessary to ensure that information on all risks and conditions of use are known.

338. Clarifying the level of overseas review is important but needs to be understood in terms of the criteria for appropriate use of CTX and CTN. The problem with using overseas review is that most people – including investigators and some sections of industry – do not understand how overseas agencies work.

Role of the Regulator

339. There appears to be uncertainty about the role of the TGA in the monitoring of clinical trials. The role of the TGA was not discussed by most submissions except in historical terms. The Review Team believe that the role of the TGA needs to be clarified to ensure that the role of the TGA is to:

- Advise the HRECs and the NHMRC on regulatory requirements for clinical trials.
- Assist HRECs in determining which trials should go CTN and which go CTX.
- Review all adverse drug reactions that are both serious and unexpected.
- Review of some Phase I trials under CTX.
- Conduct an audit program.

340. The role of the TGA is very important in the clinical trial process, but this role is separate and distinct from the TGA role in the evaluation of products for marketing approval. It may be important for the section of TGA responsible for trials is focussed primarily on clinical trials and is seen to be so focussed. However, the loss of life cycle knowledge of drug products would weigh against this suggestion. There are also cost efficiencies and careful consideration should be given as to whether the clinical trials section should be established outside the Drug Safety and Evaluation (DSEB) Branch, which may be a more expensive and less efficient option.

Review Recommendations

R1. The Key elements of the CTX and CTN Schemes, and the New Zealand regional ethics committees 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. Consideration should be given to reducing or abolishing fees for clinical research and loading the costs onto other fees and charges. If fees are maintained, more appropriate fees for large multicentre trials should be introduced. The review recognises that this would potentially reduce the range of services available to be provided for clinical trial oversight in Australia.

R9. Phase I trials are recognised by the Review to (at times) involve products of higher risk, and significant technical data may be required to describe 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 consider establishing a separate Office of

Clinical Trials separate from the current branches (particularly the Drug Safety and Evaluation Branch). The Office should have responsibility for all clinical trials. The downside of this recommendation is a potential significant increase in the cost of the program and lack of expertise and connection between evaluators looking at products of different life phases.

R14. The Office of Clinical Trials should be proactive 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.

Chapter 6: Monitoring and Audit.

341. It is important to ensure that all parties are clear about the definitions of both monitoring and auditing and are clear about what is embraced by these activities. The words have specific meaning within clinical trial terminology but were used with different "lay" meanings by many stakeholders in their submissions to the review.

342. Within the ICH GCP Guidelines, monitoring is defined as: ***"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements."***

343. ICH GCP defines audit as: ***"A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements."***

344. Under the ICH GCP monitoring is the responsibility of the sponsor of a trial and is mandatory. Where the sponsor and the investigator are the same person, the investigator is responsible for organising the monitoring. The ICH GCP guideline states: ***"The sponsor should ensure that the trials are adequately monitored. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP."***

345. Under the ICH GCP guideline, the audit function is not mandatory but may be conducted by the sponsor. Its function is essentially to ensure that the monitoring has been conducted and has been adequate.

346. Currently no regulatory agency conducts monitoring as defined under ICH GCP.

347. ICH is concerned with harmonisation of regulation of medicines but not medical devices. The corresponding body for medical devices is the Global Harmonisation Taskforce (GHTF). At present GHTF does not have its own GCP document but 'recognises' the ISO Standard 14155 as the standard for design, conducting, recording and reporting of clinical investigations of medical devices.

348. Monitoring is defined in the National Statement as: ***"The review by an HREC of ongoing research. Such monitoring can take a variety of forms including review of annual reports, formal review of the informed consent process, establishment of a safety monitoring committee, a periodic review by a third party of the documents generated by the study, a review of the impact of the research on a collectivity, a review of reports of adverse events, or a random audit of a particular processes."***

The details of the monitoring responsibility are set out in Sections 2.33-2.38, 12.8 and 12.9 of the National Statement[66].

349. Monitoring as defined in the National Statement is not the same as monitoring as defined in the ICH GCP guideline.

350. Regulatory agencies have a number of different methods for oversighting clinical trials, usually by requiring the regular provision of written reports on the progress of clinical trials and the reporting of adverse events.

351. Currently the TGA has a difficult role in the monitoring of trials. As the only information provided to TGA in the CTN form is the title of the trial and details of the site, the TGA initially has very little information about the trial. With changes to the legislation in 2000, the TGA is able to request information about the trial including the protocol and Investigators Brochure. TGA also receives details of any adverse reactions that occur at Australian sites but does not receive copies of individual adverse reactions that occur overseas. This was a deliberate decision, based on experience of the limited value of the individual reports. Companies are required to report any new signals arising out of review of ADR internationally and to inform the TGA of any significant safety issue that has been taken by another country's regulatory agency. The TGA would then ensure that the sponsor provides this information to the appropriate HRECs in Australia.

352. The monitoring function with respect to clinical trials is thus predominantly undertaken by the sponsors and the HRECs, with the TGA having several complementary review and monitoring activities.

353. Overseas regulatory authorities carry out a separate role of audit. When conducted by a regulatory agency, an audit is conducted to ensure compliance with regulations and imposes significant legal liability on the sponsor and investigator. The TGA has the power to audit, but has undertaken only a small number of audits to date.

Submissions to the Review

364. Monitoring and audit of clinical trials (including review of adverse events) was addressed by a number of submissions received by the Review, as well as by many of the interviews conducted by the Review Team.

365. NSW Health, in its submission to the Review, pointed out that, ***"in approving a clinical drug trial, an HREC accepts responsibility for monitoring the progress and conduct of the trial. The Therapeutic Goods Regulations impose this responsibility on the HREC and the TGA is not required to undertake any routine monitoring of clinical trials. The TGA does not give any guidance about how monitoring of clinical drug trials should be undertaken by HRECs"*** [67].

366. NSW Health went on to say that ***"clinical drug trials undertaken by large pharmaceutical companies are usually monitored closely by 'Monitors' who make regular visits to study sites and look carefully at the protocol documentation to ensure that the study is being performed accordingly and that data is accurate. Sponsors of clinical drug trials have responsibilities to notify the TGA about***

adverse drug reactions that are serious, could be drug related and are unexpected and/or fatal or life threatening" [68].

367. In this area, the National Statement[69] provides minimal guidance on monitoring (paragraph 12.8). HRECs within NSW ***"monitor to the basic level recommended in this document, that is, reports on research in progress musts be provided to the HREC annually"*** [70]. Researchers also have certain other responsibilities with regard to notifying the HREC of amendments to protocols and events that may impact on the ethical acceptability of a protocol. However, HRECs rely on the integrity of the researcher to inform the HREC of such instances.

368. The *National Statement* allows for a tailored approach to monitoring, stating that there is an obligation to ' … determine the type and frequency of review appropriate to the drug … being investigated and to the degree of risk to participants.'[71].

369. According to NSW Health, the major reason for the low level of monitoring is the ***"lack of resources available to HRECs to devote to this task. In addition, there are no standard procedures for HRECs about how to monitor, apart from the requirement for annual reports. The opinion has also been expressed by some HRECs that the responsibility for monitoring of clinical drug trials should lay outside of the HREC, such as with the institution at which the research is being undertaken."*** [72]

370. With regard to adverse event reporting, the *National Statement* mandates the HREC to require a researcher to 'inform the HREC and the TGA of all serious and unexpected adverse events that occur during the trial and may affect the conduct of the trial or the safety of the participants or their willingness to continue participation in the trial'.[73]

371. TGA guidelines also recommend that HRECs require researchers to advise them of any serious unexpected adverse events that occur during a trial, including those that have occurred at other sites involved in the study. HRECs must consider a serious adverse or unexpected event in the context of information on the drug as well as the underlying disease. NSW Health comments that ***"whether or not HRECs are in fact receiving all of the safety information about a particular trial drug that is necessary for them to make informative and timely decisions about the continued use of that drug is not known"*** [74].

372. NSW Health argues that ***"the exact responsibilities of an HREC in relation to … review of adverse events are therefore unclear. The increasing complexity of clinical drug trials and the volume of adverse events generated, particularly in large multi-centre trials, has led to major difficulties in the handling of adverse events by HRECs"*** [75].

373. Similarly, ***"the responsibilities of the TGA in relation to review of adverse events and dissemination of information to HRECs are … unclear. A central independent review mechanism(s) that can provide information in a timely manner about the safety of an unapproved therapeutic good that is being trialed in Australia would***

greatly enhance the ability of HRECs (and researchers) to know more about the safety of unapproved medical products. It would also decrease the workload of HRECs and enhance their ability to protect participants of research" [76].

374. The Department concludes that ***"although monitoring is only one aspect of the overall strategy to protect the participants of research, HRECs are uniformly concerned about the adequacy of monitoring of human research"*** [77].

This is a significant issue overseas, where the EU Directive requires HREC to be notified of all adverse events. There are moves to try to simplify and enhance the level of communication to both regulatory and HREC from the sponsors, who during development have access to all data accumulated internationally.

375. In its submission, Quintiles argues that, ***"before the TGA embarks on conducting its own audits of clinical trials, or scaling up its staff to enable it to do so, it should consider … alternatives"*** [78].

376. Medicines Australia saw monitoring capacity as essential. It argued that ***"it is important that Australia does have the capability within TGA to monitor, and investigate where necessary, clinical trials about which it has concerns"***.[79]

377. One such alternative would be, according to Quintiles, for TGA to ***"establish through a survey of numerous current studies the means by which compliance is being achieved (or otherwise) for the key legislative standards"*** [80], namely:

- ICH GCP and monitoring of clinical studies;
- ICH GMP and labelling of investigational products;
- ICH Note for Guidance on Clinical Safety Data.

378. Another alternative would be for TGA to ***"engage an outside organization familiar with clinical trial auditing procedures (where there is no conflict of interest) to audit a small number of studies presently being undertaken by or for international pharmaceutical manufacturers"*** [81].

379. Where deficiencies are identified as a result of such a survey or contracted audits, Quintiles argues that AHEC and the HRECs (rather than TGA) should be charged with correcting those deficiencies in the first instance.

380. The Quintiles submission puts forward the view that ***"there should be wider endorsement and encouragement by AHEC and the HRECs of the use of drug safety monitoring boards (DSMBs) – especially for international clinical trials – to provide the assurance that there is proper management of incidents involving serious, unexpected ADRs"*** [82].

It should be noted that Quintiles, in making this suggestion would be a candidate for this role and may be perceived as having a conflict of interest.

381. In similar vein, Novo Nordisk argues that ***"Clinical Trial SAE reporting should be centralised in order to facilitate information flow (and preferably heading towards electronic submission)"*** [83]. In the view of the company, this could be done by submission to ADRAC or ***"the 'Principal' Ethics Committee, similarly to the way we currently report to Medsafe"*** [84].

382. According to the submission, Novo Nordisk conducted a survey of the Australian ECs that it has been involved with and discovered a wide range of what ECs want reported, who they want it reported by (sponsor/investigator), when they want the reports, and in what format they wish to receive the reports. The company believe that ***"simply standardising the reporting requirements of the various ECs to define responsibility for reporting, a standard timeframe in which to report, the level of required information and format (eg. CIOMS/blue card, etc) would improve information flow enormously"*** [85].

383. In its submission, the Clinical Trials Centre at St Vincent's Hospital suggests that ***"adverse event reporting to HREC is currently an activity that generates a paper-trail and consumes HREC and investigator time but does not improve the safety of the clinical trial participant"*** [86].

384. The Centre argues that ***"uniform procedures should be implemented to expedite clinical trial submissions - universal ethics applications forms and adverse event reporting forms would aid investigators and sponsors"*** [87].

Consideration of the Issues

385. The issues that have emerged during the Review include the following:

- The specific role of the TGA and the HREC in oversighting clinical trials.
- The role of the TGA in auditing clinical trials.
- The role of the TGA and the HRECs in reviewing Adverse Events.
- The role of the TGA and the HRECs in monitoring clinical trials.

386. As outlined in the previous chapter, the significant difference between the Australian setting and that found in comparable countries is the level of involvement of the TGA as the national regulator in the process of clinical trials. The deregulation of clinical trials in 1991 largely removed the TGA from the initial steps in clinical trial approval and conduct, but the recent changes to the legislation require it to function as an additional protector of clinical trial participants and empower it with the legal muscle to ensure compliance with Good Clinical practice standards.

387. Given the desire of most stakeholders to maintain the deregulated process, it has been difficult for TGA to establish the right level of balance between its role and that of the HRECs in oversighting clinical trials. Any additional activities undertaken by the TGA in clinical trial oversight will have to be cost recovered, either from general fees and charges or in the clinical trial notification and exemption fees.

388. The level of criticism of the HREC process and the unlikelihood of additional resources being made available to HRECs mean that it may be necessary to shift some of the balance back to the TGA in this monitoring role.

389. Concern has been raised in a number of submissions that all parties involved do not currently conduct the monitoring function adequately. The practice overseas is for regulatory agencies to conduct audits of clinical trials. One response to concern over the monitoring of clinical trials by investigators, HRECs and sponsors has been to strengthen the role of regulatory agencies.

390. Monitoring and auditing of clinical trials is a critical issue facing regulatory agencies worldwide and is a key component of the EU Directive.

391. While adverse event reporting and monitoring was addressed in some of the submissions and interviews, the wider issue of monitoring and audit of trials was not raised during the workshops, and was raised by only a few of the written submissions.

392. Regulatory agencies have a number of different methods for oversighting clinical trials, usually by requiring the regular provision of written reports on the progress of clinical trials and the reporting of adverse events. In Australia, the primary monitoring function is undertaken by the HRECs. Currently the TGA oversights clinical trial activity in Australia through regular review of CTN notifications and the use of its legislative capacity to request information about trials and inspect clinical trial sites. Although GCP inspections have been performed by the TGA, there is no large scale formal program in place as yet. In addition, the TGA is able to release information that comes into its possession to specific third parties, such as State and Territory governments or medical boards, where it has concerns about the standard of use of unapproved products by clinical trialists.

393. Overseas regulatory authorities carry out a separate role of inspection. When conducted by a regulatory agency, an inspection is conducted to ensure compliance with regulations and imposes significant legal liability on the sponsor and investigator.

394. The USA has the longest history of conducting audits, having had a formal inspection program in place since the 1970s. Audits are conducted to check compliance by investigators, sponsors and ethics committees with FDA regulations. The emphasis in clinical trial auditing in the USA is on the integrity of the data and, therefore, most audits are conducted some time (often years) after the trial is completed. Only a very small fraction, approximately 1%, of clinical trial sites is inspected.

395. It is proposed in the UK documentation that, under the new EU Directive, there would be auditing of clinical trials by the UK regulatory agency. This is proposed to ensure compliance with the GCP guidelines but it is unclear to date how this will be done and what would be the consequences of any failure to comply. It is further proposed that the audits would include cyclical review (similar to regular cyclical review of GMP) as well as targeted review where there were issues of concern. The level of monitoring is not stated.

396. The issue of systems review (that is, a review of Standard Operating Procedures and processes) is similar to a process of accreditation. There was some discussion of the accreditation of HRECs in the submissions to the review but not of accreditation of investigators or institutions.

397. Similar programs for auditing for compliance with GCP guidelines have been established by a number of countries in Europe and Asia in the last few years. For example, Sweden's program is fully operational, auditing around 3% of trials per year, both routine and for cause.

398. New Zealand does not have the legislative power to inspect clinical trials, however it does require sponsors of clinical studies to submit reports every six months updating Medsafe and the HREC concerned on the progress of the trial. HRECs in New Zealand also have an ongoing monitoring role.

399. In Australia the power of audit was granted to the TGA only with the change to the legislation in 2000.

400. Since that time the TGA has had discussions with industry but has not made public any definite proposals with regard to a large scale auditing program. In this regard it is now significantly behind the rest of the world.

Review Recommendations

R16. The Joint Agency should take a more involved role in monitoring clinical trial activity by enforcing existing requirements on reporting and 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 and should aim to audit - 1 to 3% of trial sites or HREC within 3 years.

Chapter 7: Ethics Committees and Scientific Assessment.

The Role of Human Research Ethics Committees in Australia and New Zealand

401. Ethics committees are pivotal to the regulation and management of clinical trials in both Australia and New Zealand. In Australia, ethics committee review is required for trials that progress either via the CTX or CTN route. For CTN trials, the TGA does not review any data before the trial begins. This role lies with the Human Research Ethics Committee (HREC) and the principal investigator. The HREC(s) and the institution(s) concerned are responsible for establishing what information should be provided in support of an application and how that application will be handled by the committee. In CTX trials, the TGA reviews summary data about the therapeutic good, and then provides advice to the HREC(s), who then review the trial documentation in a similar manner to that of a CTN-type submission. Once a CTX submission, which includes usage guidelines, is reviewed and approved by the TGA, subsequent trials conducted within these usage guidelines are not required to undergo TGA review, but remain the purview of the HREC, and a "notification" of intent to conduct a trial under the CTX is sent to the TGA after HREC approval for the first and each subsequent trial conducted under the CTX.

402. Ethics committee endorsement, by a committee that has notified its existence to AHEC and undergoes annual review by the AHEC via annual reporting of activities and committee conduct, is a legislative requirement for the use of the CTN and CTX Schemes. Ethics committees that do not have this association with the AHEC are not recognised as committees under the Therapeutic Goods legislation. Such committees therefore cannot provide the endorsement required for an unapproved therapeutic good to be granted an exemption from the need for entry onto the Australian Register of Therapeutic Goods, in order to allows the good's supply in the context of a clinical trial. In this way, the work of the NHMRC and AHEC in setting standards and issuing guidance to ethics committees is given a form of legal standing. The TGA worked collaboratively with the NHMRC in the development of the AHEC Handbook for HRECs, and produced its own publication, "Human Research Ethics Committees and the Therapeutic Goods Legislation", to assist ethics committees in their deliberation of matters related to unapproved therapeutic goods.

403. Clinical trials, conducted via either the CTX or CTN routes, must be conducted according to the approved protocol and associated documents, the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) that has been adopted by the TGA, and the National Statement on Ethical Conduct in Research Involving Humans, developed and maintained by the AHEC and NHMRC. These requirements are both enshrined in legislation (in the case of CTX) and applied via written undertakings (in the case of CTN). The NHMRC in collaboration with the AHEC regularly reviews the National Statement, and such a review is currently underway.

404. Notification under the CTN scheme or application under the CTX scheme is required for:

- any medicine or device not entered on the Australian Register of Therapeutic Goods, including a new formulation, route of administration; or

- The use of a registered medicine or device beyond the conditions of its marketing approval, including new indications extending the use of the product to a new population group and the extension of doses or duration of treatments outside the approved range.

405. Section 16 of the Therapeutic Goods Act 1989 delineates what constitutes a separate and distinct therapeutic good, thus making clear when an exemption for authority to supply an unapproved good, (and hence a CTN or CTX submission in the case of a clinical trial), is required.

406. Trials which do not need to make use of CTX or CTN routes (eg. a post-marketing safety study for a registered therapeutic good, or trials not using therapeutic goods, eg. comparison of two surgical methods) still undergo ethical review despite the TGA having no role in the approval or ongoing monitoring, beyond the usual post-market adverse drug reaction reporting requirements. Hence ethics committee review is the one dominant factor in all clinical trials conducted in Australia, whether using unapproved therapeutic products or not.

407. The National Statement produced by AHEC and the NHMRC outlines requirements and obligations of HRECs when they consider and reach decisions regarding clinical trials. It contains both general guidance as well as specific requirements in relation to some issues, for example monitoring obligations. By endorsing a notification form in relation to a clinical trial conducted under the CTN or CTX schemes, the HREC concerned undertakes to monitor the progress and conduct of a clinical trial. This is a significant, time-consuming and ongoing role. The primary monitoring role for clinical trials conducted in Australia is thus shouldered by ethics committees.

408. In addition to their role in clinical trials in Australia, ethics committees also play a part in access to unapproved goods via their endorsement of authorised prescribers as described earlier in this report. This involves ethics committee endorsement of a medical practitioner as an appropriate person to be prescribing a particular therapeutic good for a specific indication in set clinical circumstances.

409. In New Zealand, ethics committees have a similarly important role in oversight of clinical trials. These committees are regionally based and provide services to the District Health Boards. Trials using new chemical entities that are progressed via the SCOTT committee must still receive ethical endorsement by the regional ethics committees prior to commencement. In addition, clinical trials using “existing” medicines (medicines already evaluated or marketed) that are not required to have scientific assessment, must still receive ethical approval. Although ethics committee constitution in New Zealand consists of more lay persons than medical or scientific personnel, the role and structure of ethics committees in New Zealand is consistent with the requirements of the ICH Note for Guidance on Good Clinical Practice. There is an equivalent substantial monitoring role for ethics committees in New Zealand that parallels that of Australia and thus both New Zealand and Australian ethics committees play a crucial role in ensuring participant safety and well-being in clinical trials.

Issues Raised Regarding the Role of Ethics Committees in Submissions to the Review

410. Submissions discussed several issues in relation to the function of ethics committees. Not all submissions were factually correct in their detail, however a number of ideas were raised as opportunities to enhance the ethics committee review process. Primarily, the comments received were in relation to the role of Australian HRECs, although reference to New Zealand arrangements was made by several stakeholders, particularly with reference to the SCOTT committee for the review of the scientific basis of clinical trials in New Zealand.

411. Key points raised were:

- The high workload that HRECs, largely consisting of voluntary members, are expected to shoulder in the light of the considerable success and thus higher volume of clinical trials that the CTN Scheme has achieved.
- The current climate of obtaining multiple HREC endorsement for multiple sites for a single clinical trial, and the slightly different imposed conditions that such methods can result in, as well as differing requirements in relation to format and content of submissions for approval.
- Differing times taken for review of submissions given the differing workloads of committees at various centres (a problem raised again in the case of multicentre trials).
- The varying costs of having a submission reviewed depending on the committee.
- Perceived lack of expertise in reviewing some submissions and perceived lack of understanding that this could be "outsourced" if necessary.
- The few resources that many operating HRECs have available and the consequent impact on review times for submissions, and monitoring, in particular adverse events notified to HRECs.

Submissions received raising issues related to Human Research Ethics Committees

412. The following represents a comprehensive summary of the issues elucidated by the submissions received by the Review team. While comments may be attributed to particular stakeholders, they in no way represent solely the views of those stakeholders, but are representative of the issues raised by all submissions.

413. As NSW Health put it in its submission[88], "HRECs are responsible for ensuring the protection of research participants by ensuring that research protocols are considered in light of the NHMRC *National Statement on Ethical Conduct in Research Involving Humans (National Statement).* HRECs are comprised of mainly voluntary members who are provided little financial support or training. The workload for HREC members and their Secretariats is often very large and the traditional level of support provided by the institutions is becoming inadequate to maintain the committee's increasing responsibilities".

414. A 1996 report to the then-Minister for Health identified "The fundamental role of an [Institutional Ethics Committee] IEC [as] … to protect research subjects from unethical research, whether in formulation or conduct. The NHMRC *Statement on Human Experimentation* no longer applies narrowly to medical experimentation but

applies more widely to health research. The role of IECs has altered accordingly. IECs no longer consider only the ethical validity of experimentation involving humans but also research "on" or "abut" humans. Other IECs have been established to offer policy advice to the institution. This expanding jurisdiction has dramatically increased the workloads of most IECs[89].

415. Anita Kamat's article made the following summary of the current position: "In Australia, studies are approved by several human research ethics committees (HREC) simultaneously. There are three types of committee. The first is funded by the institution hosting the research. The second is the regional committees, which often represent several local research institutes – the Central Sydney Health Ethics Committee is an example of such a committee. And the third sort is the private ethics committees, such as the Thoracic Society of Australia. Australia has no accreditation programme for HRECs, but committees are encouraged to register with the National Health and Medical Research Council (NHMRC)".[90]

416. "In New Zealand final approval for multi-centre trials applies nationally, and there is just one scientific body for assessing trials of unregistered products. A principal researcher and primary ethics committee are nominated. The primary committee is the committee in the area/locality where the principal researcher is based, and is responsible for the general administration of the approval process on behalf of all committees involved for the proposal. There are also a number of regional committees providing secondary opinions, to which the investigator also submits applications".[91]

417. "Each secondary committee reviews the application and forwards its comments to the primary committee, which collates the responses and corresponds with the primary investigator. Any changes the investigator makes are returned to the primary committee for consideration. The primary committee is then responsible for approving or declining the application on behalf of all the centres involved".

418. "Primary committees are empowered to approve minor amendments to applications that have already been passed, as well as requests for re-approval on behalf of the secondary committees. However, if a primary committee decides that certain amendments are significant – changes to a dosing regime, for example – then the primary committee circulates the request to the secondary committees. Serious adverse events and study progress reports are only submitted to the primary committee. Indemnity and financial aspects of the trial are reviewed both by the ethics committee and by the hospital management team".

419. "In Australia, ethics committees give scientific approval to trials based on their own knowledge or advice from scientific sub-committees within each constituent institution. In New Zealand, the Standing Committee On Therapeutic Trials (SCOTT) provides the primary scientific assessment of unregistered products. However, as the SCOTT and ethics approval process are conducted in parallel, the ethics committees invariably conduct their own scientific assessment, particularly in relation to risk/benefit of the new compound".[92]

420. In its submission, GlaxoSmithKline Australia focused on human research ethics review and scientific review, stating that the company's "concerns with the current

processes of Human Research Ethics Review (HREC)/scientific review include issues which result in unnecessary inefficiencies and time delays while having negative cost, resource and quality implications".[93] These concerns included:

- "Significant variance between HREC submission requirements between investigator sites. This demands significant internal resources, both human and financial, whilst also adding to the resources needed at investigator-sites. [94] Unnecessary duplication of effort is particularly evident in multi-centre trials.
- Review time varies significantly between centres and can cause significant delays in commencement of clinical trials.[95] Experience indicates that time for review can range from 1 month to more than 6 months, resulting in Australia's performance falling short of international best practice.
- Trivial and inconsistent requirements at sites.[96] Differences in requirements can create many unnecessary delays. These can include requirements for minor changes to informed consent forms, poor documentation of approvals and changes to indemnity forms.
- Inadequate administrative support for processes at HRECs.[97] Again, these can create unnecessary delays through, for example, inadequate documentation or back-up resource support.
- Review costs. [98] These vary significantly but are spiralling upwards with no relationship between increased costs/activity and efficiency or the effectiveness of a review. Costs vary from a nominal charge to upwards of $4,400.
- Compliance of HRECs with ICH and NHMRC standards. [99] Some committees lack appropriate quality assurance procedures.
- Appropriate expertise. Some HRECs lack appropriate expertise, [100] nor do some of them have clear understanding of their roles and responsibilities.
- Scientific Sub-committees. The increasing complexity and specialization of research has triggered the establishment of scientific subcommittees, creating a two-tiered process which can cause delays,[101] particularly when not synchronized with HREC meetings.
- Adverse drug events/expedited safety reports. Management of these situations by HRECs seems unclear and therefore raises concerns that compliance is compromised".[102]

421. The company identified a number of potential improvements in the process of conducting HREC/Scientific reviews including:

- "A simple and efficient national standardized HREC.[103]
- Scientific reviews to be undertaken by appropriately qualified and experienced personnel, to be coordinated at either a regional or national level and for shared assessments to be strongly recommended or mandated.[104]
- Consideration of Trans-Tasman mutual recognition of reviews.[105]
- HRECs and scientific reviews to be undertaken in parallel.[106]
- Provision of adequate resources to HRECs to enable them to comply with appropriate standards.[107]
- HREC and scientific committees to meet frequently, either face-to-face or virtually, to review submissions promptly. These meetings should strive to achieve international best practice benchmarks of approximately 2 weeks from submission time.[108]

- Provision of adequate training for HRECs.[109]
- Reduction in number of HRECs through the implementation of fewer 'regional HRECs'.[110]
- Reduction of overall costs through centralisation".[111]

422. In their submission, the industry association Medicines Australia made clear the distinction between the importance of the role of the ethics committees and problems with their procedures. "While we consider that the standard of ethical review by Australian HRECs is very high, consistent with world's best practice, the administrative processes supporting the ethical review are inefficient and result in unnecessary delays to start clinical trials."[112]

423. Medicines Australia has supported that statement with the results of a survey conducted by the association in December 2002. The aim of the survey was to gather information from the association's member companies on their experience of the performance of various HRECs. Twelve member companies responded, providing information on 119 HREC applications to 46 individual HRECs.

424. The survey found that "of the 119 applications only 10 were reviewed and approved in less than 1 month. 56 were approved in 1-2 months, 33 were approved in 3-4 months, 14 approved in 5-6 months and 6 took more than 6 months to approve. Of the last 6 applications only one was due to delays caused by the infrequency of the HREC meeting dates."[113]

425. Further issues with HREC procedures identified by Medicines Australia were:

- Lack of uniformity of HREC application requirements – "There is currently no standard form or format for applications to HRECs to conduct clinical trials.[114] Whilst some HRECs in major university teaching hospitals in Sydney and Melbourne have collaborated to produce a standard form for their respective jurisdictions, this form is not widely adopted by other HRECs. Also the application form developed by the different groups in Sydney and Melbourne are significantly different." [115]
- Inconsistent information requirement – "For more than half of the occasions where a clinical trial proposal was not approved on first review by a HREC, this was due to issues related to the patient information document or informed consent (56 out of 91 instances)."[116]
- Lack of acceptance of a standard Form of Indemnity.[117]
- Resources of HRECs.
- Inconsistency of HREC approval documentation that meets regulatory requirements for Good Clinical Practice.[118]
- Interpretation of Declaration of Helsinki – [particularly the 2000 version which has caused problems worldwide].

426. Problems with HREC consideration of multicentre clinical trials have also been documented in a recent letter to the Medical Journal of Australia.[119] The letter (headed *'Multicentre research: Negotiating the Ethics Approval Obstacle Course'*) outlined the time taken to gain approval for a retrospective review of the medical records of women included in a multicentre study investigation of the outcomes of hypertensive pregnancies in a cohort of 1620 women. The medical records were held in a number of hospitals, and a submission was made to the NSW Department of

Health Ethics Committee and the HREC at the area health service that held 85% of the records. Eight other area health service HRECs were involved for the remaining patients. It took a total of 8 months to gain approval for the complete study. The timeframes for the individual HRECs are given in the following table:[120]

Table 1: Summary, by area health service (AHS, coded S-Z) of different requirements for gaining ethics approval for a multicentre study:

AHS	S	T	U	V	W	X	Y	Z
No of pages of application form	19	20	19	20	12	23	2	11
No of copies of form required	1	1	17	15	20	16	1	14
No of hospitals in AHS covered by approval	2	2	4	1	3	5	3	5
Approval covered by private hospitals in AHS also	na	na	Yes	No	No	na	No	na
No of contacts made (phone/letter/email) to gain approval	20	15	20	15	20	30	10	20
Time taken to gain approval (weeks)	12	20	168* [121]	8	6	6	1	3
Special requests during approval	A	F	A, B, C, E	A	A, D	A		G, H
Approval after first submission	Yes	No	No	Yes	Yes	Yes	Yes	Yes

na = not applicable
A = asked for local researcher to be a contact person for the study
B = charged a $33 fee to submit application
C = requested scientific protocol with references
D = requested budget form
E = reviewed by scientific advisory committee before human research ethics committee (HREC)
F = requested consent and subject information forms
G = University HRECs approval as well as approval of area health service committee required
H = Final approval required from chief executive officer of major hospital in that AHS
[*number appears to be an error as it does not match narrative in full letter]

427. Quintiles[122], too, acknowledged problems with the current HREC arrangements. "There is a great deal of duplication of effort which could be reduced by centralising or regionalising ethics approvals. Individual institutional HRECs should continue to be responsible for their own institutional requirements – especially content of patient information sheets and informed consent procedures."

428. However, in a cautionary note, the company argued that "rationalisation of ethics approvals … must precede any similar centralization of scientific approvals. The availability of regional centres for scientific evaluations will only result in HRECs declaring their unwillingness to do their own scientific assessments".[123]

429. In the view of the company, "judging the ethical acceptability of a study is the major role of every HREC but they must come to be seen as approved or 'hosted' by the institution at which they are based without in any way being 'answerable' to that institution. Mutual acceptance of decisions between HRECs will become possible only when HRECs are perceived as making objective decisions on ethical issues consistent with the needs of the community each one serves".[124]

430. Novo Nordisk[125] argued "that the main barriers to further development of clinical research in Australia are due to the current set up of the Ethics Committees", particularly:

- The cost of preparation and submission of HREC Submissions.
- Requirement to make individual submissions to multiple HRECs with differing format and content requirements, and the need for a standard approach or appropriate guidelines.
- Inability to submit electronically.
- Discrepancies in timelines within and between sites, with many HRECs not meeting monthly.
- The use of a 2-tiered system, with submissions having to go through the scientific committee and then the ethics committee.
- Lack of ability to make minor administrative changes to informed consent/patient information sheets without full re-submission.

431. Dr Winston Liauw identified ***"potential barriers to the efficient implementation of clinical trials"***. According to him, ***"whilst the CTN scheme is a rapid mechanism for regulatory 'approval' at the national level, the human research ethics committee (HREC) is the actual regulatory body"*** [126].

432. Dr Liauw saw HRECs as significantly under-resourced, leading to ***"delays in study approval and possibly even … inadequate review of study protocols"*** [127]. The chief responsibility of the HREC is ethical review of clinical trial protocols and oversight of the studies once they are approved. According to Dr Liauw, HRECs spend a significant amount of time reviewing adverse events but have little information or power to act on the data supplied by sponsors and therefore are not in a position to act as data safety monitors. ***"Typically, the HREC [is] not in a position to undertake other activities such as ensuring adequate training of investigators and other study staff, undertaking appropriate audit of clinical trials, or undertaking other education and QA/QC activities related to the clinical trial arena"*** [128]. Dr Liauw believed that there is a need for more substantial resource allocation in this area.

433. Dr Christopher Reid of the Baker Institute argued for the ***"development of a single ethical review process for multi-centre clinical trials at either a national or state level"*** [129]. He stated that the ***"current situation requires each participating site to submit individually to each respective ethics committee. The replication of work and resources involved in this process is a major drain in clinical research funding. Approval of the study protocol and the use of therapeutic agents through a central body would facilitate this process."*** [130]

434. In addition, Dr Reid sought a ***"central or nominated ethics committee at either a national or State level", with "individual sites … providing a copy of the protocol and notification of approval from the central ethics committee", and with "individual consent forms for each site [being] approved by the local committees"***[131].

435. The Australian Consumers' Association(ACA)[132] noted that "the NHMRC statement concerns itself, appropriately, with the fundamental ethics of research in humans: the imperative that the needs of the research subject should be paramount, that researchers should be asking a question worth answering, that participants should give their informed consent, and so on. It discusses what should, and what should not, be regarded as research for the purposes of ethical control."

436. The ACA sees this approach as "appropriate and sensible for dealing with research conducted by specialist institutes, universities and hospitals – with, in other words, not-for-profit research" but as "inadequate in addressing the pressures and distortions of commerce that arise when all those involved in a project (except the research subject) intend to make money from it, and where profit is their principal motivation".[133]

437. Addressing the resourcing and capacities of ethics committees, the ACA argues that "institutional ethics committees are frequently ill-equipped and under-resourced to undertake the considerable tasks demanded of them by the current regulatory system. Mandatory guidelines should be established to ensure all committees are properly resourced."[134]

438. Further, ACA believes that "Australia has far too many ethics committees. There is a limit to the pool of high-quality, experienced people available to take part in this process. The need for researchers to gain the separate approval of several institutional ethics committees in order to run a multi-centre trial should not be necessary: while we believe trial regulation has generally become too lax, we do not support unneeded regulation. Individual institutionally based ethics committees should be replaced by a much smaller number of committees based on states, regions or therapeutic areas. Legal protection should be provided, if necessary by statute, for institutions taking part in trials approved by ethics committees other than their own. The increased workload on individual committees should be met by each committee having the backup of expert subcommittees and the support of properly funded secretariats and professional support units. These operations should be resourced by matched Commonwealth-state funding on a 50-50 basis."[135]

439. Cancer Trials Australia (CTA) identified as a problem "the usual process for obtaining ethics approval for multi-centre clinical trials" which "involves separate submissions to all participating sites and duplication in the reviews conducted by the HRECs." According to CTA, "the inefficiencies of this process are widely acknowledged within the clinical trials community".[136]

440. CTA points to "several projects being piloted around Australia (including the Mutual Acceptance of Ethics Approval program, initiated by the CTA and based on Sections 3.5 and 3.6 of the NHMRC's National Statement) that attempt to streamline this repetitious and inefficient process. The federal government should endorse and reward participation in such schemes. This would be best received by the HRECs in the form of administrative assistance - as all require additional help in this area - which could in turn be linked to improved outcomes eg time to approval or engagement in streamlining initiatives, etc. Streamlining this process, not only state-

wide but also across the whole of Australia, is essential to encourage more multiple centre trials to Australia."[137]

441. In CTA's experience, "some HRECs can be progressive enough to recognize the need for efficiency driven change" but "other HRECs do not embrace change as readily and require considerable encouragement to do so". CTA concludes that, "if there is not an improvement in the near future, legislation may be required to force efficiency in this area. It would of course be preferable for change to come from within the HREC community, but there needs to be some demonstrable gains made soon before Australia looses too much research business."[138]

442. Professor Gary Jennings argued that "there is an urgent need to foster mutual recognition and enhanced harmonization of EC approvals. This is a major barrier to further development of clinical trial research in Australia."[139]

443. He also saw a need to "encourage uniformity in EC processes – submission documents, indemnity (standard text for indemnity), patient information. legal rights and privacy"[140], "to develop and provide a standard, robust clinical trial database at all EC sites that will allow the capture of standard, consistent and relevant clinical trial information",[141] and "to provide adequate human resources to enable ECs to enter/capture meaningful clinical trial data, perform efficient reviews, follow-up and re-review of the clinical trial process."[142]

444. His submission argued that HRECs should be enabled "to set fees commensurate with the cost of review"[143], and recognized that "there is a need for resources to allow flexible EC meeting dates as requested by the market. Being able to schedule more frequent meetings (than monthly) is requested and required by the market".[144]

445. Servier proposed that "the arrangements for the conduct of clinical trials in Australia be reviewed to include a provision for a single ethical opinion to be delivered and applicable to all centres participating in the same trial whatever the location in the country."[145] This could be organized either through a process of mutual recognition between existing institutional review boards, or through the creation of a network of national ethical committees (for example, one or more in each state), or any other scheme that would ensure valid evaluation of the project by a single ethical committee.. Procedures and timelines for the review of multi-centre trials should be uniform between ethical committees."[146]

446. The company believed that "such a clinical trial authorization system would strengthen the reliability of the evaluation of clinical trials, through enabling each ethical committee to dedicate its resources to fewer clinical trials being submitted to it; and through creating the basis for an auditing and validation process of nationally operating ethical committees".[147]

447. Servier advocated that "performance data for the current clinical trial authorization system should be gathered to enable Australia to be accurately benchmarked against other Western countries. A performance target should be established with ongoing monitoring against both this and other Western countries".[148]

448. Dr. Mark Nelson of Monash University identified as "another long recognised problem for multi-centre clinical trials … the need for multiple applications to each site's Ethics Committee. Development of a single ethical review at either a national or state level would obviate this".[149]

449. At a Victorian Cooperative Oncology Group (VCOG) forum held to have input into the Review(1), the issue of ethics committee processes came under discussion, especially the practice of subjecting one trial protocol to multiple submission to institutional ethics committee. While the "NHMRC Ethics Statement suggested this did not have to occur, … the process of individual institutional ethics approval was still continuing. In Melbourne, a "shared obligation" process around four ethics committees for multi-centre trials had been instituted". [150]

450. The forum suggested a "central ethics review for national collaborative group trials … with institutional ethics committees receiving/accepting that approval".[151]

451. For Victoria, the complexity of Ethics Submissions was a real issue. "The Department of Human Services Victoria had designed a core ethics application form for all clinical trials, but for some centres the form had increased from 2 pages to [a] 34 page application form. This has required additional staff to be appointed at some centres". Similarly, the time taken to obtain Ethics Committee approval was of concern, with "the process [able to] … be as long as 3 months at some participating trial centres".[152]

452. There was concern that "Ethics Committees may be being placed in a position of conflict where they were acting on behalf of patient participants, as well as on behalf of the hospital in regard to resources and medico-legal issues". [153]

453. AusBiotech welcomed initiatives "to enable institutional Human Research Ethics Committees (HRECs) to more effectively fulfil their responsibilities".[154] Its submission expressed "concern over the number of Ethics Committees – which currently rank at a higher number per head of population than any other OECD country".[155] While AusBiotech did not advocate for a reduction in the diligence undertaken by the ethics process in Australia, it suggested "that consideration be given to processes that have long been established in other leading international communities in order for Australia to be globally competitive in this area".

454. The "numbers of Ethics Committees and timeframes imposed" [156] were suggested as a reason "for not conducting clinical trials in Australia, to avoid resultant barriers and time impediments".[157] International companies wishing to conduct clinical research in Australia "often cite the specific requirements and difficulties in securing ethics approval as obstacles. In an environment where it is becoming increasingly competitive to attract and retain clinical development, increasing complexity and demands are creating larger barriers".[158]

The Australian Health Ethics Committee

455. The Australian Health Ethics Committee, a Principal Committee of the National Health and Medical Research Council, undertakes considerable work in formulating national guidelines for the constitution and functioning of Human Research Ethics

Committees. These guidelines currently include the "National Statement on Ethical Conduct in Research Involving Humans" and "Values and Ethics: Guidelines for Research Involving Aboriginal and Torres Strait Islander Peoples'. Via these guidelines, the Human Research Ethics Handbook for ethics committees, a regular HREC Bulletin and the provision of other advice, AHEC promotes a minimum standard of ethical review by such committees, regardless of their geographic location or members. In addition AHEC provides both regional and national training workshops for HREC members.

456. Although having no powers to compel ethics committees to accept these standards, the conduct of clinical trials via the CTN or CTX arrangements in Australia requires the HRECs concerned to have notified their existence to AHEC and to be conducting themselves in accordance with the National Statement. Therefore, committees that do not accept these standards would be unable to endorse the vast majority of clinical research protocols in Australia.

457. Professor Gary Jennings argued that "Currently, AHEC has no teeth to implement or enforce any changes to the current system. The decision to give AHEC some legislative powers should certainly be considered."[159]

458. Quintiles argued that "AHEC should adopt … more formal systems for accreditation of HRECs and … for training of their members and keeping them abreast of ethics developments".[160]

The issue of Scientific Assessment

459. A number of submissions raised concerns in relation to the scientific assessment carried out by ethics committees in relation to clinical trial submissions.

460. It should be emphasised here that, while ethics committees carry the responsibility for ensuring adequate scientific assessment is carried out, it is by no means required that the committee themselves carry out the scientific review. The committee is free to use whatever resources or individuals at their disposal to ensure adequate review of a trial's scientific methodology, and, ultimately, need not endorse the trial if they feel they cannot provide this by whatever arrangement.

461. The option is also always there should the committee feel a particular trial ought to progress via the CTX route. HRECs in Australia are largely voluntary bodies and may not possess a breadth of scientific knowledge sufficient to review all clinical trial submissions presented to them. However, membership of HRECs includes people with expertise in those areas that are normally considered by the committee (in accordance with the National Statement). Thus, at least some of the members do have expertise. In addition the National Statement makes it clear that an HREC may and must gather information from whatever source it chooses to ensure that it is fully informed prior to making a decision. This means that a committee can invite expert advice from a range of sources.

462. For a given submission, an HREC may be able to review the scientific content themselves, (particularly an HREC within a large institution, for example), or refer the scientific review to a specialised sub-committee or other individuals.

463. NSW Health, in its submission to the Review, identified one major issue facing HRECs as "the review of clinical drug trials, specifically relating to ensuring scientific validity prior to approval and then ensuring adequate monitoring post approval".[161]

464. According to NSW Health only some HRECs have a scientific sub-committee to perform the scientific review prior to ethical review. "The majority of committees rely on the expertise of the HREC members or other 'experts' within their own institution to perform the scientific review. In many instances the expertise is not available via these mechanisms and/or those who do have the expertise are being unreasonably utilised. Clinical pharmacologists, critical to the review of the safety and efficacy of the trial medication, are particularly difficult to access."[162]

465. Clinical drug trials carried out at multiple sites usually require review by the HREC responsible for each institution. While the Review was advised that national figures could not be provided, NSW Health was able to make available data in relation to trials in that state. In NSW in 2000, 596 CTN notifications were made to the TGA, representing 263 individual clinical drug trials. 157 of these protocols were conducted at one site only. However the remaining 106 protocols were carried out at multiple sites.

466. NSW Health asserts that ***"repetition of review adds to the burden placed on HREC members and local scientific reviewers in reviewing research that is concurrently being reviewed by multiple HRECs. Researchers are often faced with inconsistent feedback with regard to the scientific protocol and spend considerable time and effort in aligning successive changes to the protocol at each of the trial centres."***[163]

467. In NSW Health's view, in that state, at least, lack of access to appropriate expertise is common to most HRECs, but is particularly difficult for rural HRECs.

468. NSW Health is, consistent with the recommendations of the 1996 Report of the Review of the Role and Functioning of Institutional Ethics Committees[164], currently piloting a Shared Scientific Assessment Scheme (SSAS) for multi-centre clinical drug trials. The key component of the scheme is centralised scientific assessment of multi-centre clinical drug trials by a single committee. Methodological and safety issues are resolved prior to submission to local HRECs. Local HRECs then accept the scientific review of the committee as one aspect to be considered in their ethical assessment of the trial. This pilot scheme commenced in February 2003 and will continue for 12 months.

469. Taking a contrary view, Medicines Australia ***"expressed concern that the introduction of another review step, i.e. separate scientific review, will cause delays to the initiation of clinical trials. It is of particular concern that these systems have been established by individual States, so that if a multicentre trial is proposed to be conducted in these different States, potentially the trial must be reviewed by three scientific assessment committees as well as by the individual human research ethics***

committees at each trial site. This will result in significant delays to the initiation of clinical trials".[165].

However, Medicines Australia was supportive of the establishment of a mega EC to simultaneously undertake the role of the HREC and high level scientific assessment for high risk trials.

470. The Society of Hospital Pharmacists of Australia saw use of internal institutional scientific review as an appropriate mechanism, stating that ***"We do not consider that it should be mandatory for institutions to use an external expert scientific review committee as many hospitals have expert scientific review, or drug trial subcommittees, which in some instances seek external review from expert(s) within Australia or overseas if required"***.[166]

471. Dr Winston Liauw of St Vincent's Hospital addressed the Pilot Shared Scientific Assessment Scheme being undertaken in NSW. ***"The concept of centralised institutional review boards or HREC is being rapidly adopted in North America and is a promising mechanism for providing uniform review across disparate sites, increasing the speed of the approval process if the [review boards'] decisions are recognized by local sites, and providing a higher level of adverse event oversight for clinical trials. Consideration should be given to the establishment of a national [Shared Scientific Assessment Scheme]"*** [167].

472. The 1996 Report of the Review of the Role and Functioning of Institutional Ethics Committees had germane comments on this issue. In its Report, that Review stated that ***"A major issue for consideration … was whether an IEC should be involved with a scientific assessment of the research protocol presented to it. Submissions to the Review differed on whether the role of an IEC should include an assessment of the scientific validity (methodology, safety etc) of a research proposal. Some argued that the focus should be on ethics and not methodology and cited examples of ethics committees rejecting research proposals because of an apparent bias towards particular research methodologies (this concern was prevalent among social researchers). Other submissions argued that ethics and science are inseparable, bad science being unethical"***[168]. Following release of that Report, the National Statement was released, addressing many of the recommendations of the Report (particularly in paragraphs 1.13-15).

473. The 1996 Report went on to say that ***"it is not appropriate for an ethics committee to approve research that is methodologically unsound. However, a distinction needs to be made between the poor or inappropriate use of an established methodology and the use of new research methods with which the IEC may not be familiar. In the first instance this may constitute "bad science"; in the second, "innovative research". In either case, the ethics committee's responsibility is to research subjects through an assessment of the ethical appropriateness of the project. Where methodological or safety issues are relevant to this assessment, additional information should be sought by the IEC"*** [169].

Consideration of the Issues

474. The prime issue that has been highlighted to the Review is the need to improve the efficiency and effectiveness of the HREC system while maintaining the deregulated notification system for clinical trials.

475. The ethical review process has arisen historically in Australia as an institutionally based system.

476. This historical perspective has been the strength of ethical reviews in Australia but it is also a barrier to the development and acceptance of cooperative practices by HRECs, in as much as institutions require independent ethical review in many instances for several reasons, but a prime one being litigation concerns.

477. Generally, despite the problems outlined above and not negating the need for some revision, it is clear from the number of trials being conducted each year that HRECs are managing a high workload of submissions for review, and the standard of that review remains high.

478. Concerns centre more on subsequent monitoring capability and the capacity for review of Adverse Event reports.

479. The major complaints have revolved around the following issues:

- The role of the HRECs in the scientific review of applications.
- The role of HRECs in multicentre research.
- The legal basis of HRECs and the role of mandatory procedures and accountability.

480. It is clear that Human Research Ethics Committees (HRECs) may be able to improve their functioning and discharge of responsibilities under the leadership of the Australian Health Ethics Committee (AHEC). Some of the issues that have been raised are:

- Achieving consistency in approach and standards.
- Adhering strictly to the NHMRC *National Statement on Ethical Conduct in Research Involving Humans*.
- Eliminating duplication of effort by a greater preparedness to cooperate and share review of material.
- Better provision of resources (including fees for sponsored trials and Australian/State Government and institutional contributions).
- Holding regular, frequent meetings, and paying sitting fees and time-based remuneration to Members. (It is recognised that this is already occurring in some cases, but as a more widespread notion, stakeholders thought this may alleviate HREC workload).
- National mandatory use of a standardised application form developed in full consultation with stakeholders utilising an optimal data set. It is noted that AHEC is close to piloting an electronic version of such a form which will also provide guidance to researchers in its use

- National mandatory use of standardised (as far as possible) patient consent forms developed in full consultation with stakeholders taking into account both legal and ethical viewpoints.
- National mandatory use of standardised indemnity and compensation guidelines.

481. The Review feels that a notification scheme similar to the CTN scheme may be retained, but that there could be measures taken to potentially improve ethical and scientific review of clinical trial documentation. It must be borne in mind that, at the commencement of the CTN and CTX arrangements, the number of clinical trials conducted in Australia with involvement by the TGA was around 50-100 per annum. While the exponential increase in clinical trial activity may be lauded as a success of the CTN scheme, the requirements and administrative burden that HRECs now face is substantial and is unlikely to have been anticipated when the CTN/CTX schemes commenced. This workload requires consideration of several potential methods in order to alleviate it.

482. Potential methods of alleviating the volume of tasks undertaken by ethics committees with respect to scientific evaluation include:

- Expansion of the TGA's (or future joint agency's) capability to undertake greater volume of scientific review of clinical trial proposals. Several stakeholders reported verbally that they felt the CTX system, although expensive, was a useful mechanism for some trials, particularly those researching an entirely new therapeutic class or method, and TGA advice gave assistance in refining the drug development program for the therapeutic good. It was also felt that this was a mechanism of obtaining excellent toxicology commentary which can be difficult to obtain elsewhere for some sponsors.
- Formation of specialty-based HRECs (or renamed Scientific Assessment Panels [SAPs]), for both medicines and medical devices that may undertake scientific assessment of clinical trial submissions in instances where local HRECs feel they need to obtain scientific review from outside their committee. Such HREC/SAP assessment would be on an equal footing with the scientific review carried out by the New Zealand SCOTT committee, in the context of a joint regulatory agency. This measure would require Australian State and Territory cooperation to create such HREC committees, in order for scientific review conducted in one State or Territory to be recognised by another, and may require endorsement by the Australian Health Minister's Advisory Council (AHMAC).
- In a slightly different vein to (b) above, the formation of one or several "Nationally Accredited Human Research Ethics Committees" (NAHRECs) that could approve ethical acceptability of clinical trial submissions following scientific assessment by either the Joint Aus/NZ Regulatory Agency, a specialty-based HREC/SAP as described above, or an institutional ethics committee that has chosen to conduct its own scientific assessment. A number of issues would need to be canvassed prior to acceptance of the NAHREC model. These include mutual recognition, indemnity, monitoring and complaints handling, and the place (if any) of local review.

483. Many of the issues raised in this section are inter-related but are dealt with here separately. It is important that the recommendations made here be considered in conjunction with the recommendations made in other Chapters of this Report.

Scientific Review

484. Many of the industry submissions commented that they were not in favour of a 2-tier system of review because of concerns that this would lead to delay in the process of application review. Despite strongly expressed views on this issue, no submission provided any suggestions as to how a single review could be achieved. Indeed, in many instances, a 2-tier system is effectively in operation in Australia at present for many trials, given that ethics committees cannot always provide scientific review from within their own membership in all instances and seek review by other committees or individuals. This practice may run in parallel or sequentially, depending on the specific case.

485. In looking at overseas practices, it is clear that every one of them has a 2-tier system. The scientific review is conducted by the regulatory agency and an ethics committee conducts the ethical review. In most of the systems the reviews are sequential – companies get regulatory approval and then apply to ethics committees. However this is not mandatory and the two processes can be done in parallel. However, anecdotal evidence suggests that where this occurs, many if not most ethics committees also undertake some degree of scientific review.

486. The more important issue is that the role of the regulatory agency is to review the trial proposal from a safety viewpoint, particularly in regard to issues related to the quality aspects of the product and to ensure appropriate compliance of the protocol with GCP.

487. It is accepted that there can never be complete separation of the two review aspects in a philosophical sense – an unscientific trial is unethical. However, there should be greater clarity as to the role of the scientific assessment and the ethical review. 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. While the Review team believes that the *quality* of ethical and scientific review in Australia and New Zealand is consistent with other regulatory agencies around the world and of a high standard, it is the *process* that is thought to have room for standardising also, in an effort to streamline and speed up approvals, particularly in the case of multicentre research.

488. Many HRECs have addressed the issue of scientific assessment and ethical review over the last 10 years by building into their HREC review a 2-tier system under which the protocol is first reviewed by a clinical trial committee (or similarly named/functioning committee) before review by the HREC. Other institutions have expanded the membership of the HREC to include appropriate members to ensure capacity to fulfil this function. Many of these institutions are conducting well-coordinated reviews with appropriate timing in the current clinical trial climate.

489. The Review Team recognises the value of a notification scheme as an attractive proposition in terms of minimal *regulatory* requirements for the conduct of clinical research in Australia and recommends that elements of it are retained in a proposed new system.

490. However, the review feels more guidance could 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. This guidance has already been provided in general terms by AHEC and TGA publications, but could be expanded to detail courses of action in specific instances. This information would prove complementary to the proposals in item 483 above.

491. There are a number of possible criteria such guidance could recommend, although this level of detail would be determined by the TGA, NHMRC and Medsafe in collaboration. Some possibilities might include:

- Redirect trials at highest risk to require scientific assessment by the TGA or SCOTT committee, or an HREC/SAP as described in item 483 above. The structure and legal standing of such committees could be determined by the TGA, Medsafe and NHMRC in collaboration. However, financing of such committees is an issue that will likely require the cooperation of the Australian States and Territories.
- Expansion of scientific assessment capability by the Joint Agency such that an HREC could refer scientific issues to the Joint Agency if required. In this way, the regulator would act as any other body or individual the HREC approached for scientific comment.
- The TGA, Medsafe, NHMRC and HRC in collaboration could also devise more detailed guidelines on what should be submitted to HRECs following completion of scientific review. This should be consistent with that which is proposed in the EU directive. It would also be complementary to the current efforts of AHEC and the NHMRC in the design of a standardised HREC submission application form.
- There should be better information provided to HRECs at the time of review about the overseas status of regulatory review of products being studied. This information is already provided to the Gene and Related Therapies Research Advisory Panel (GTRAP) - an advisory committee established under the Research Committee of NHMRC - in relation to proposed gene therapy trials. Such information can provide valuable data about the known safety profile of the proposed product.

Multicentre trials

492. While the National Statement aimed, in the last revision, to give support to voluntary cooperation between HRECs, it is clear from the many submissions that addressed this issue that there has been little real success in achieving effective cooperation. This is hardly a failing of the National Statement or AHEC, but has more to do with issues of indemnity and litigation concerns prompting institutions to err on the side of caution and have their own committees review submissions for trials that are intended to be conducted at their facility.

493. Given the strong local focus of HRECs, there is a real danger that local ethics committees will not easily accept the establishment of regional and/or national ethics committees. Legal issues, coupled with a desire to "know what is going on in one's own institution" are very real impediments to any form of widely accepted or mutually accepted ethical review. Such a reaction could lead to the addition of another layer of ethics review without increasing efficiency or effectiveness, which would be highly undesirable.

494. Despite these reservations, the Review sees merit in:

- 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.
- The establishment and "accrediting" in some way (perhaps including accreditation of some existing, large institution-based HRECs) of a small number of specialty-based (eg oncology, general practice) HRECs/SAPs, that could be approached for scientific review, if the HREC reviewing the submission thought it necessary.
- Making submission to a NAHREC available as an option where any trial is to be undertaken at two or more sites.
- 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.
- Providing for mutual recognition of the decisions of NAHRECs by all other HRECs if they wish.
- Providing for the establishment of a NAHREC review for national collaborative group trials, with local HRECs receiving/accepting that approval.
- The provision of resources for the establishment of NAHRECs and specialty-based HRECs (including fees for sponsored trials and Australian Government contributions through NHMRC).

Legal Basis of HRECs

495. The issue of accountability of ethics committees and the lack of a legal basis was not directly raised by the submissions, but has been raised with the Review in other forums and is notable when comparison is made with overseas countries.

496. The current legal basis for HRECs in Australia derives from their linking with the Therapeutic Goods legislation. Only HRECs that have notified their existence to AHEC and function according to AHEC guidelines are recognised by this legislation as being able to endorse a trial via the CTX or CTN route. Thus, only such committees can form part of the conditions that ultimately create an exemption from the operation of Part 3-2 of the Therapeutic Goods Act 1989, and allow supply of an unapproved therapeutic good in Australia in the context of a clinical trial.

497. It may be prudent to more fully to establish the legal basis for the role of HRECs in relation to trials of therapeutic goods by better detailing that role in relation to

therapeutic product trials in the Therapeutic Goods legislation. It would be possible to set out in the legislation the requirement for the establishment of HRECs, the format of submissions to HRECs, and the requirement for mandatory use of common forms for applications, consent, and indemnity and compensation. This would achieve more standardisation and consistency of process than at present. These standards may well be those currently recommended or under development by the NHMRC, for example a lot of work has already gone into developing a generic form for ethics committee submissions for clinical trial approval.

498. An additional option in relation to HRECs would be to strengthen the role of AHEC to have a more "accrediting" function in addition to its current function of standard setting and provision of guidelines. The Review team sees this taking the form of a more substantive verification of adherence to guidelines and conduct etc. than the current annual checklist from HRECs provides.

499. Another (and least preferred) alternative would be to try to achieve the same outcomes, but maintain the voluntary system that is presently in place. The development of more appropriate guidelines on the role of HRECs in reviewing trials of therapeutic goods is possible but it may take some time to achieve consensus and agreement. If this option was to be followed, it would not be possible to put in place mandatory requirements, and the whole process could remain very much as it is today.

Role of AHEC

500. The role of AHEC is pivotal to the process of clinical trial regulation, but there is a strong need for a closer working relationship between TGA and AHEC.

501. AHEC presently meets for 2 days 4 times a year, with major projects being undertaken by working parties which meet in person or by teleconference as often as needed. Working parties regularly contain co-opted members with special expertise. In addition an AHEC executive committee meets by teleconference approximately every 6 weeks. The part time nature of appointees to AHEC and its working parties and the requirements of extensive public consultation mean that key tasks such as the pending review of the National Statement can take between 1-2 years.

502. The previous collaboration of TGA and AHEC in producing guidance for HRECs is acknowledged. In view of the complimentary roles of TGA and AHEC in the regulation of clinical trials, the practice of inviting TGA representatives to meetings of AHEC should be continued. This should be extended to representatives of the Joint Agency when issues related to trials of therapeutic goods where the regulator plays a role, are being discussed.

503. It is clear from the submissions to the review that there is a need for more communication of information about clinical trial regulation to HRECs and to other stakeholders from both TGA and AHEC.

504. The issues raised with the Review – and supported by the Review - to strengthen the role for the Australian Health Ethics Committee (AHEC) were to enable it to:

- Set mandatory standards and operational guidelines governing the establishment, membership, processes, procedures and standards of HRECs and NAHRECs, consistent with the NHMRC *National Statement on Ethical Conduct in Research Involving Humans*, and using as a model the European Union *Directive of the European Parliament and of the Council on …the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*.
- "Accredit" all HRECs and NAHRECs.
- Ensure the provision of appropriate training and education to HREC and NAHREC members by the use of current guidance documents, additional information as proposed, and where necessary face-to-face training or visits to HRECs by appropriately qualified staff of the TGA or NHMRC.
- Mandate time limits for HRECs, specialty-based HRECs and NAHRECs (if appropriate resources have been made available to allow this), with a reasonable maximum time for consideration of a submission for the conduct of a clinical trial.

505. In addition, respondents drew to the attention of the Review some of the recommendations made in the Report of the Review of the Role and Functioning of Institutional Ethics Committees[170] as having not yet been appropriately implemented.

506. Among the specific desires expressed by many respondents were:

- All institutions with an HREC must nominate an independent complaints handling officer.
- Institutions should make available sufficient (ongoing) funding to enable its HREC members to avail themselves of opportunities for relevant in-service training and development.
- Institutions should ensure the provision of adequate resources for their HRECs. A new HREC should not be established unless the institution can provide adequate means for resourcing the committee.

507. The Review is concerned that these responses demonstrated a lack of basic understanding of the functioning of HRECs. For example, all institutions must have a complaints officer as must each HREC. This has been a formal requirement at least since the National Statement was published in 1999. The National Statement also clearly states that it is the responsibility of an institution to properly support its HREC, which includes appropriate funding.

Recommendations

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 studied.

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".

Chapter 8: Special Access Scheme (SAS) and the Authorized Prescriber Scheme.

508. The Special Access Scheme (SAS) provides for the import and/or supply of unapproved medical products on a single patient, case by case basis. Usually, approval to supply is granted by the TGA. However, in some circumstances, approval from an 'external delegate' to supply an unapproved therapeutic good is sought. In this circumstance, an application approved by an 'external delegate' must be approved by an HREC. In practice, such external delegations are rare and HRECs are not routinely asked to deliberate on such issues.

509. However, in the rare instances where an approval from an HREC is required, the Committee must address the following issues: assess the efficacy and safety of the product; the condition for which it is being prescribed and an assessment of the seriousness of that condition in the patient to be treated; the mode of use/treatment and whether it conforms to the treatment protocol; and the clinical justification of using the product in light of available alternative treatments. The HREC must also consider their knowledge of the practitioner wishing to supply the goods and should comment on the appropriateness of the consent arrangements.

510. The TGA is able to grant a medical practitioner authority to prescribe a specified unapproved therapeutic good to specified recipients or classes of recipients. However, the medical practitioner must first obtain endorsement from the HREC at the institution at which the good is to be used.

511. The information that should be reviewed by HRECs is similar to that necessary for SAS. In addition, HRECs are responsible for monitoring the approval by provision of regular reports from the 'Authorised Prescriber', including assessment of suspected adverse reactions.

512. In its submission, the NSW Department of Health addressed the Special Access Scheme (SAS). ***"Lack of expertise and unfamiliarity with … applications may prohibit an HREC from making thorough assessment of such applications. It must be remembered that HRECs are established to review research proposals involving human participants. Review of applications other than for research, such as those required by the SAS, is inappropriate and burdensome"*** [171].

513. Turning to the Authorised Prescribers Scheme, NSW Health argued that ***"as with the SAS, lack of expertise and unfamiliarity with such applications may prohibit an HREC from making a thorough assessment of such applications. The addition of such applications to the workload of an HREC, when it is outside of their function according to the National Statement, increases the burden on HRECs and decreases the time available for the review of human research proposals"*** [172].

514. In its submission, Novo Nordisk found ***"in general that the SAS in Australia is an adequate system for providing access for unapproved drugs. The issues we find with the SAS include a lack of understanding by prescribers regarding the Category***

(A/B) and the length of approval provided for patients on long-term medication for a chronic condition." [173]

515. The company believed that ***"SAS is used for two distinct groups of Novo Nordisk goods - unregistered medicines and 'non-actives'. … We recognise the need for ongoing evaluation of patients taking unregistered medicines, however, we would prefer these patients be given a longer SAS approval, as they are being treated for a chronic condition. … Ideally, we would prefer that TGA allow the sponsor to provide SAS items used in chronic conditions to 'pre-approved' patients (or prescribers) on an ongoing basis – with a regular report to TGA on the prescriptions/orders filled. This would reduce the administrative workload for the TGA and prescribers as well as the sponsor"*** [174].

516. This was a view shared by the Society of Hospital Pharmacists of Australia: ***"The current Special Access Scheme (SAS) and authorised prescriber scheme should be maintained as the model for any joint Australian and New Zealand scheme"***[175].

517. The Clinical Trials Centre at St Vincent's Hospital believed, on the other hand, that ***"access to unapproved drugs should be more stringently regulated. Currently, there is no assessment of whether an unapproved drug … meets even minimal quality manufacturing requirements … . Regulators should make a greater effort to scrutinise the rationale for using an unapproved drug. There are drugs in clinical trial (i.e. where there is sufficient doubt [as] to their efficacy) that patients are receiving through [the] SAS scheme. It seems appropriate that these recipients themselves should be offered or have access to a clinical trial, and/or the drug should not be available off the auspices of a clinical trial unless other supportive evidence can be supplied by the prescriber or manufacturer"*** [176].

518. The Centre argued further that ***"the supply of drugs that have proven effectiveness in pivotal studies but are undergoing ADEC and then PBAC review needs to be addressed. Arguably, these drugs should become orphan drugs until such time as the appropriate regulatory decisions are reached"*** [177].

519. It is unclear what is being proposed here, as an orphan drug is one that is used to treat a very small number of patients. Its use in regulatory terms relates to the data package that is to be submitted and the evaluation process and cost issues. Drugs that are currently under evaluation or PBS assessment may or may not include orphan drugs.

520. The Centre concluded with the view that ***"the issue of off-label or unapproved uses of drugs should … be addressed. Closer regulation of this area and of unapproved medical products, through the use of a pharmacovigilance database collating both efficacy (in a specific indication) data and adverse reaction data would be a way of improving the knowledge-base for use of these agents"*** [178].

521. The issue of "off-label" use of approved products is a difficult one, and the suggestion to collect data on such may be academically interesting, but is complex. For very practical reasons the TGA (in line with overseas agencies) does not require SAS for "off-label" use of approved products. This use comes within the province of medical

practice. No other submission raised this issue and there does not appear to be sufficient justification to introduce any change to current practice.

522. The VCOG forum addressed the SAS that ***"allowed medical practitioners, under certain circumstances to prescribe drugs, for individual patients, not yet approved in Australia. These drugs could be prescribed with or without a treatment protocol. It was noted that whilst the SAS program generally worked well, there were some problems in that clinicians were not always experienced in using that mechanism, and that the clinician takes the liability for use of the drug. Compassionate access clinical trial s provided access to drugs either through SAS or another system"*** [179].

523. In the view of the Forum, ***"the SAS provided for drugs to be imported for a specific indication because they were not registered by TGA, but had been approved overseas. … [A] fast-track system with review by national experts may be useful". The forum "suggested [the] develop[ment of] additional guidelines for SAS, particularly for multiple and longer term usage"*** [180].

Consideration of the Issues

524. The Review has found that the submissions have not identified any major concerns with the procedures for SAS and Authorised Prescribers.

525. There is, however, an indication that there is not a good understanding of the procedures, especially the changes made in 2000, and TGA should be encouraged to be more proactive in promoting the current guidelines.

526. At the Workshops conducted by the Review[181], there was discussion on a proposition that "the SAS and the authorised prescriber scheme, under which patients are able to access the drugs they need, should be retained in its current form, but be improved by the current somewhat time consuming process to be simplified, including the use of "on-line" application and approval, and approval of patient, not of prescriber".

527. SAS Category B is an approval process, and sometimes the TGA staff need time to evaluate the request and to request additional information to be sent in by the requesting doctor. Not all requests are granted approval. This is as it should be.

528. It is not appropriate to have the approval given to patients rather than doctors, as was suggested in one submission. In most cases, requests for SAS are for what would be prescription only medications. If the permission was given to the patient then there would be no way that the TGA could ensure that the patient actually saw a physician or had medical supervision for the use of the product.

529. The current wording of the legislation is that Category A and authorised prescriber requires the involvement of a medical practitioner but category B does not. It is TGA practice to give approval to a medical practitioner, but there have been cases where entirely appropriate approval is given to dentists or oral surgeons in the setting of a hospital use.

530. Many of the issues raised in submissions were addressed in the changes made to the schemes in 1999/2000, and the current guidelines reflect these changes. It is apparent from the submissions that many stakeholders have not fully understood the changes that were made to the scheme at that time.

531. The Workshop considered the suggestion that "ongoing use of SAS for multiple patients [should] require HREC approval, together with an approved treatment protocol and patient consent".

532. Under the current guidelines both are already required. The difficulty arises in determining how many patients are required to be approved under Category B (which requires informed consent but not HREC approval). Information about the authorised prescriber scheme is sent to practitioners after a second patient is approved, but it is up to the practitioner to apply for authorised prescriber status. The practitioner is in a better position than the TGA to decide this. There are advantages for practitioners in less paperwork and in avoiding the inconvenience of requesting individual approval, so they are more likely to apply for authorised prescriber when appropriate.

533. There was very little criticism of the post-2000 changes to the SAS/authorised prescriber schemes in the submissions, and therefore there appears to be little reason for change.

534. The Workshop considered the view that "category differentiation … be used as intended, with "very seriously ill" as the sole criterion". However, Category A is reserved for imminently life-threatening conditions and authorised prescriber for seriously ill patients. It is not prescribed in the legislation or in the guidelines that Category B should be used only for "very seriously ill" cases. There are many examples of the need for access to unapproved drugs, especially service items (drugs removed from the market for commercial reasons but supplied for a few patients who are unable to take alternative products). There would be many patients who would be seriously inconvenienced if this restriction were to be introduced.

535. No evidence was presented to the Review that there was inappropriate use or abuse of the SAS process.

536. Some respondents proposed to the Workshop that "a link … be established between the end of Phase III, licensing and PBAC listing by earlier involvement by TGA to take into account likely PBAC implications". This is to fundamentally misunderstand the whole process of TGA and the PBS.

537. To involve TGA in any way in the process of PBS listing would be completely at odds with the legislation and would seriously damage the credibility of the TGA as an independent regulator, as opposed to the PBAC/PBS as a government reimbursement scheme for pharmaceuticals.

538. The issue of continuing access to free medication at the end of the clinical trial process, and any possible delay in access to subsided medication if a product is not successful in achieving PBS subsidy, is not an issue that should be addressed by TGA.

539. The current TGA clinical trial guidelines suggest that the issue of ongoing access to medication for chronic conditions or serious illnesses should be addressed in clinical trial protocols, and may be an ethical issue that needs to be addressed by HRECs when considering Phase II or III trial protocols. Making it mandatory in all circumstances is not possible and may be counter productive – it may actually deny access to product. Where a company is not confident of achieving a PBS listing, it may choose to not undertake a clinical trial in Australia if that trial could expose the company to on-going mandatory provision of a free drug. This could also be seen as the government avoiding listing expensive products on the PBS if it can arrange to have all patients receive medication free on never ending clinical trials or SAS arrangements.

540. The Workshop considered a proposition " … many SAS and authorised prescriber arrangements are 'clinical trials'" (albeit, despite protocols, with poor data collection and unclear end points) and that, therefore, "access before licence (including to orphan drugs) [should] be tied to monitoring and routine clinical evaluation with clinician and patient to agree to more formal data collection for assessment".

541. A clinical trial is a scientific experiment with a clear scientific question to be answered related to the safety and efficacy of a product. As most clinical trials are comparative, it would be unethical to conduct a clinical trial where the answer to the scientific question is known. That is, if the doctor knows that one therapy is better or more appropriate than another for a particular patient, then it would be unethical to enrol that patient into a randomised clinical trial where s/he may not get the most appropriate therapy.

542. The current TGA guidelines for SAS and authorised prescriber make it clear that these are not appropriate mechanisms for clinical trials. They are mechanisms for treatment of individual patients. There do exist clinical trial designs that collect appropriate data from small numbers of patients. These are clinical trials and must meet the standard for clinical trials.

543. The TGA and the industry have on a number of occasions developed protocols for the use of SAS drugs. Treatment protocols were seen originally as an important resource for use by external delegates (ie, practitioners delegated by the Secretary of the Department of Health and Ageing to consider SAS applications for access to specified medicines at an institutional level). However, this mechanism was not popular and it was largely unused. In contrast, the protocols have proved to be of assistance for prescribers accessing approvals for products through the TGA.

544. The only advantage to the proposal is to a company that might achieve data collection of "clinical trial standard" through the SAS or authorised prescriber without having to pay investigators for the time spent in collecting data, and without having to provide the product free. (Product provided on a clinical trial is required to be free - according to the National Statement - but companies can charge for product under the SAS and authorised prescriber schemes).

545. There is a difficult balance that must be aimed for in considering any process of access to unapproved medicines, namely to balance the necessary regulatory scrutiny

with encouragement to companies to submit products for evaluation. One difficulty in this process is that TGA cannot force companies to make submissions, and for many of these products it is the physician/hospital that is involved in the process of importing the product or encouraging a company to supply. It is therefore extremely difficult to take stringent regulatory action against doctors/hospitals for non-compliance with procedures. Regulatory action against doctors, or even companies, appears to have had little effect and disadvantages only the patient. The change in 2000 that allowed TGA to refer problems with doctors to the State Medical Boards was an appropriate move but has yet to be found to be effective.

546. One respondent proposed to the Workshop that "the current prohibition of the promotion of SAS drugs … be relaxed to permit advice to physicians and pharmacies as to the availability of such drugs, perhaps by way of a national register of available drugs".

547. The prohibition on the promotion of SAS drugs is maintained in order to provide a disincentive to companies to use SAS for an indefinite period rather than to apply for marketing approval for their products. If any company were able freely to promote products that had never been evaluated, the company would hardly be likely to seek marketing approval.

548. The Review can see advantages to pharmacists and doctors in having a list of SAS products available, but on balance is convinced that such a practice would likely lead to inappropriate use and to active promotion by some companies.

549. Any pharmacist or doctor can at present contact the appropriate company and ask whether a particular product is available on SAS. The prohibition does not prevent companies answering such an inquiry. For products without an Australian sponsor, the pharmacist or doctor can contact TGA and ask whether approvals have been given. The Review does not believe that the advantages of the proposal outweigh the disadvantages.

Recommendations

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

Chapter 9: Clinical Trials Register.

550. One proposition under widespread debate across all sectors is that there should be a comprehensive Register of all clinical trials conducted with medicinal products in Australia and New Zealand.

551. The NSW Department of Health, addressing the Clinical Trial Register proposal, argued that ***"the development of a Clinical Trials Register may lead to a number of important benefits for HRECs. … The ability to identify when clinical trials are submitted to other HRECs may improve communication between HRECs and reduce repetition. Facilitation of effective monitoring of clinical trials, including safety data and publications [would be enhanced]"*** [182].

552. The Society of Hospital Pharmacists of Australia shared that view, arguing that ***"We support the establishment of a clinical trial register readily accessible to health professionals and patients. Such a register could facilitate cooperation between groups who may not be aware of similar research proposed at another institution"***.[183]

553. Quintiles proposed that ***"the existing CTN database needs to be expanded to include all clinical studies (and study sites) involved in clinical trials in Australia whether initiated under the CTN or the CTX and be able to include in due course all studies running at New Zealand study centres"*** [184].

554. The company went on to argue that ***"such an expanded database should not be publicly accessible but should be available to all HRECs accredited to the AHEC under strict rules of preservation of confidentiality. The perceived advantages are the ability to monitor study outcomes in the long term. … Those advantages are not of such magnitude as to justify the costs of servicing such a register and responding to public and media requests for information or comment on individual studies or studies in a particular disease which could also breach confidentiality"*** [185].

555. In its submission, the Australian Consumers' Association (ACA) argued that ***"two national registers should be established, the one to provide a guide to all clinical trials approved for conduct in Australia, and the other to provide a guide to results"*** [186].

556. Novo Nordisk ***"considers that the Health Authorities need a commercial-in-confidence clinical trials register. This would contain the information that is currently required via the CTN"*** [187].

557. However, Novo Nordisk ***"would not be prepared to support a clinical trial register system that was open to the public. It would act as a deterrent for placing early phase trials in Australia and encourage unreal hope in some patients that they may be able to access medicines via a clinical trial, when in reality they may not meet inclusion criteria. It is important for clinical trial site staff to be able to select appropriate patients for inclusion in any clinical trial"*** [188].

558. The Clinical Trials Centre at St Vincent's Hospital put forward a view that ***"the CTN scheme has served as a useful mechanism for encouraging clinical trial activity in Australia. However, there is little transparency as to how the notification information is utilised, if utilised at all. It seems appropriate that there should be an internet-accessible clinical trial register that arises from the CTN scheme. This would serve the purposes of increasing transparency of the system, decreasing the duplication of some research activities and could serve as an information portal for clinical trial participants – so increasing participation in clinical trials"*** [189].

559. Speaking as the peak industry body, Medicines Australia expressed the view that it ***"is open to discussions regarding the establishment of a clinical trials register in Australia"***.[190]

560. Medicines Australia did caution, however, that ***"The overarching concern of the pharmaceutical industry is that commercial-in-confidence information should not be disclosed about their research. With this caveat, we are willing to consider the establishment of a clinical trial register if the real need can be demonstrated, appropriate consultation with all interested parties occurs, and appropriate funding is provided to establish and maintain the register"***. [191]

561. In a significant contribution to the proposal to establish a register, Dr John Simes provided detailed arguments for the establishment of a National Clinical Trials Registry. He argued that ***"the proposal to establish a national register for all controlled trials in Australia has enormous national and international support"*** [192].

562. Simes went on to state that ***"the arguments to establish such a national registry are many and include:***

- ***The need to provide a complete register of all trials prior to publication to ensure that evidence-based medicine is based on a complete and unbiased review of the trial evidence;***
- ***To ensure doctors and patients have access to ongoing trials for increased trial participation;***
- ***To allow better planning, funding and priority setting for future trials research; and many other important reasons"*** [193].

563. Simes argued that ***"the steps to put a national register in place in Australia are already well underway"***[194] and that ***"almost all new trials (at least phase II and phase III) could be registered with the National Register on a voluntary basis. Issues related to confidentiality and commercial sensitivity could be handled in a simple manner without concern to sponsors"*** [195].

564. In Simes' proposition ***"Trial registration could remain voluntary"***[196], ***"Sponsors could request details related to trial protocols to remain confidential. This could even mean restricting public information just to the trial title and contact"***[197], ***"Sponsors could request a trial be registered 'in camera' – this would mean the***

trial would eventually be known to the public but not while the fact of the trial was regarded as still confidential"[198], and ***"Phase I trials (where this was more of an issue) need not be included in the register"***[199].

565. Identifying a 'pilot phase' in the establishment of any national Register, Simes proposed a series of measures to facilitate its initial operation:

- ***"Complete the establishment of the web clinical trials register database.***
- ***Demonstrate the feasibility of collecting new trials in an efficient manner through ethics committees, TGA, major sponsors and cooperative trials groups.***
- ***Establish a core data set (after agreement with each sponsor) to be made available on the web.***
- ***Work with international groups to build a unique identifier of each trial (avoid international duplication of the same trial) for international register.***
- ***Provide the core data set via web to interested groups (eg. via cancer councils for cancer trials) to improve patient/doctor access***
- ***Maintain more detailed information (subject to sponsor approval) on issues related to trial design, patient groups, treatment, etc. for descriptive/planning purposes.***
- ***Make register information available to groups undertaking systematic reviews of trial evidence***
- ***Demonstrate to sponsor, government and users the value of the system for long-term use.***
- ***Review progress of the National Register in 18 months together with the results of the TGA review and make recommendations/refinements on a long-term national clinical trials register"***[200].

566. In a similar vein, the Health Research Council of New Zealand - Te Kaunihera Rangahau Hauora o Aotearoa addressed the issue of registration of clinical trials. The Council believed that ***"registration in New Zealand could:***

- ***Inform patients and clinicians about trials in which they could participate;***
- ***Optimise use of resources by reducing duplication of effort and funding;***
- ***Optimise use of expertise by encouraging collaboration;***
- ***Assist in identifying gaps in research activity"*** [201].

567. The Council saw the stakeholders in the development of a register of clinical trials as being the Health Research Council, ethics committees, pharmaceutical companies, biotechnical companies, clinical researchers and consumers.

568. Among the most important issues, according to the Council, was ***"The scope of registration: what clinical trials should be registered? [It is] widely accepted that Phase III and IV studies should be registered and this would be relatively simple to achieve with the existing SCOTT and Medsafe databases. If establishing a register is contingent on obtaining the agreement of stakeholders responsible for conducting Phase I and Phase II trials, this may delay the creation of a register"*** [202].

569. The Council addressed the issue of whether trial registration should be mandatory or voluntary. ***"Whether trials registration is mandatory or voluntary, each poses implementation problems. Mandatory trials registration would be easier to achieve with [randomised controlled trials] (RCTs), but more difficult for Phase I and II trials because of stakeholder concerns. Mandatory registration of RCTs would be most easily achieved through ethics committees. Voluntary registration overcomes many stakeholder concerns, but is generally perceived not to work, as there is no motivation to register"*** [203].

570. GSK cautioned that ***"before the listing of all trials on a trial register can be done, further consultation and discussion needs to occur regarding:***

- ***The purpose of the register;***
- ***Data elements and associated details that would be required;***
- ***Accessibility and the maintenance of appropriate confidentiality;***
- ***Location of the stored information;***
- ***Responsibility for the maintenance of the register;***
- ***Resource implications for sponsors;***
- ***Implication for time-lines for study initiation and study cycles"*** [204].

571. In its submission, the Baker Institute proposed that ***"a register be developed for the use of 'experimental' drugs in clinical research" with "the register … accessible to investigators via the TGA website. Investigators planning on using … experimental drugs can identify and access approval documentation on the website"*** [205].

572. At the VCOG forum, participants expressed a view that ***"an aim of a register should be to document all trials so there was no bias in reporting, especially regarding early closure or whatever reason. Another aim should be to prevent duplication of trial design. Patients were increasingly seeking/demanding access to information on clinical trials. The arguments for a register were persuasive, however the difficulty lay in its establishment and maintenance. It was noted the TGA already had the ingredients for a simple register as it received all trial notifications, and this could be expanded, and supported through the ethics approval process. There was a very powerful ethical imperative for patients to have assurance that the research they are participating in leads to something"*** [206].

573. Some participants recognized that ***"a separate issue was the confidentiality of pharmaceutical company sponsored trials and … unwillingness to have trials listed on a public register".*** [207].

574. It was suggested that ***"trials that were not registered by TGA (eg non-drug/device trials - surgical or psycho-oncology trials) but [that] still required ethics approval could also be referred to the register through … the ethics committee process"*** [208].

575. There was, then, general support at the forum for a trials register, and it was suggested that TGA raise the issue of confidentiality of pharmaceutical company trials being listed with Medicines Australia. The forum believed registration should be a mandatory process, initially for all publicly funded trials, and that industry would be likely to follow-on. It was suggested the register include publication details, and that a single national register could be categorised by disease and access level. Finally, the forum agreed registration be included into ethical approval process.

576. In its submission, NAPWA argued the move towards tagged and listed central clinical trial registries has gained significant momentum internationally in recent years, with the growth in internet use and access a prime trigger. ***"The USA maintains a publicly funded online register, as does the UK, which maintains a meta-register of controlled trials through the joint auspices of the UK Medical Research Council and the National Health Service Research and Development Programme. Canada maintains a variety of online registries, including the My Health Canada website and a variety of disease-specific registries. The European Union is currently considering processes that might allow for the merging of various member nation registries into a nascent combined register"*** [209].

577. According to NAPWA, ***"The arguments for a central record of current clinical research endeavours are compelling. Without a publicly accessible centralised facility, the ability to find out what is being studied where – and for whom – will remain elusive to all except those conducting and authorising each specific trial. This clearly has the potential to militate against patients and their health providers knowing about trials that might be of benefit. Researchers could be unaware of existing or current research that might replicate their own, plus the ability to set and monitor national research priorities is clearly not optimised in the absence of a total research picture. It is also worthy of note that the chances of unpublished research simply vanishing without trace becomes more difficult to envisage under a publicly accessible centralised register system thereby enhancing holistic safety parameters. It is useful to recall that the disappearance of preliminary UK research, linked to the dangers of prophylactic anti-arrhythmia drugs in people with heart attack, contributed to significant avoidable morbidity and mortality in this area"*** [210].

578. NAPWA saw significant potential ***"to widen trial recruitment pools via online information linked to a centralised register site and to concurrently engage consumers with a range of associated health education resources and information. Canada, in particular, has developed strong online consumer health networks linked to clinical trial registries. NAPWA would be fully supportive of any***

proposals aimed at investigating the feasibility of the development of a centralised trials registry" [211].

579. NAPWA recognised that developing a national clinical trials registry raises some important ethical and practical questions. ***"How do trials get listed? How is the information updated and maintained in a rapidly developing and changeful research environment? How are consumers to be kept informed, but at the same time protected from poor quality or misleading research?"*** [212]

580. NAPWA concluded that ***"these practical problems, real as they are, do not outweigh the substantive benefits to be gained through a well-maintained high-quality register"*** [213].

Consideration of the Issues

581. The primary question about a register relates to what it is trying to achieve.

582. The overseas registers have had a very clear purpose - they were established primarily for the consumer. That is why in the US, the register was included in separate legislation and not in the FDA legislation. The register is concerned with active trials only - so patients can have access to "unapproved" drugs. The context within which the register has been established in the USA is quite different from that in Australia. In the USA approximately 40% of the population are uninsured. Enrolment in a clinical trial provides access to what would otherwise be expensive treatment at significantly lower or no cost. The need for access to cheaper treatment rather than to clinical trials *per se* is one of the drivers behind the register in the USA.

583. The arguments in favour of a register around issues of 'access' need to be balanced against several important realities that were lost on a number of submissions. Firstly, clinical trials are conducted because the efficacy and/or safety of the product in question are as yet unproven. Thus, while enrolment in a trial may improve a participant's chance of accessing a particular treatment, there is no guarantee there will be any beneficial health outcome. Secondly, and more fundamentally, is that in a randomised controlled clinical trial, a participant may receive placebo or a comparator, rather than the product they had hoped to receive by entering the trial.

584. One significant outcome of the establishment of the registers in the USA has been that patients have become aware of trials and possible avenues of access to medication. If they are not able to access the trial, there has been an increase in the demand for the US equivalent of SAS (treatment IND). FDA has accepted this. It is reasonable to expect that there would be, in Australia and New Zealand, a similar increase in awareness of and desire to participate in clinical trials, should such a register, with trials entered at least at the recruitment stage, be accessible to the public.

585. Many of the submissions requesting a register had somewhat unrealistic expectations as to what a register could deliver, at least at the outset - expectations that detailed information about the drugs would be included, information about the results of the trials, including overseas trials etc.

586. While many people feel strongly that a register will ensure that trials are completed and reported, there seems to be no evidence to support this, including advice from within the FDA. The ability to ensure that the register is up to date will depend on good will from investigators and sponsors.

587. What is to be included in the register will depend on the primary reason for its existence. If the primary function of the register is to provide access to patients, the minimum would be the nature of the disease being treated and a contact for the principal investigator to facilitate requests for information.

588. However, it can be argued the primary purpose of the register should be in relation to (a) avoiding over use of human participants if trials are already in place (b) reassuring participants that they truly are contributing to the public good – and not just to industry profits, and (c) reducing the problems of publication bias (where trials with positive results are published in preference to those showing no treatment effects).

589. It must be accepted that, if the register were to provide all of the information requested by all stakeholders - full details of the product involved, the protocols, the dates of trial start and finish etc - it is possible that the perception of disclosure of confidential information not released anywhere else in the world may lead to sponsors of products choosing not to bring trials to Australia. If the number of trials were to fall significantly, this would have the opposite effect to the intention behind the proposal as it may inadvertently lead to a reduction in access to products.

590. One issue raised by industry is whether the posting of the results of a trial on a register would cause problems with publication or with patent applications. This is unlikely to be a problem with large multinational companies who are likely to have patents well in place before trials are started, but could be a problem for smaller biotech companies.

591. None of these are reasons for not having a register, but there needs to be a clear understanding of the purpose and the limits of what a register is going to collect and when, as well as a clear understanding of the impacts that the register is likely to have on the conduct of trials.

Recommendations of the Review

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 could 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. It is acknowledged such a register would not meet the needs of many using non-medicine interventions as alternatives to therapy.

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.

Chapter 10: Infrastructure Funding, Clinical Trial Insurance and Indemnity

592. While the issues of clinical research funding and insurance are outside the terms of reference of the Review, a number of submissions and oral presentations to the Review either addressed the case for increased infrastructure funding for cooperative groups or identified problems with obtaining clinical trial insurance and indemnity. As these two issues are closely linked it is appropriate to address them together in this Report.

Infrastructure funding

593. In a 2002 study made available to the Review, Oceania Health Consulting made the point that ***"in the clinical management of cancer, the practice of evidence based medicine is almost totally reliant on the findings of previous clinical trials. While industry-sponsored trials are important, the vast maj-ority of advances in cancer care are made through clinical trials conducted by cooperative groups"*** [214].

594. Oceania warned that ***"Australia risks losing the capacity to continue 'world's best practice' cancer treatment as comparable countries increase the role, standards and capacity of cooperative groups in conducting clinical trials in cancer. This outcome could retard the practice of evidence-based medicine in Australia as trials are integral to its practice. It could also compromise Australia's access to advanced therapies"***. [215]

595. The study pointed out that ***"randomised controlled trial[s] … are complex, difficult to conduct, require substantial infrastructure and expertise, and are therefore costly compared to other forms of research (although not when compared to the overall cost of clinical care). Due to the need for substantial numbers of recruits into such trials, they are mostly conducted on a multi-centre basis, and the national cooperative groups (essentially large virtual networks) make this possible. Trials conducted by cooperative groups have substantially contributed to the spectacular progress in improving the survival of cancer patients"***. [216]

596. Turning to an assessment of the benefits of clinical trials, the study identified benefits to the trial participant, to the general community and to science. ***"Patients benefit from early access to new therapies; improved outcomes (on average) for patients who enter the trials, irrespective of which treatment they receive; improved quality of care from the patients' perspective; and improved therapies in future. The broader community benefits from better health outcomes; a decrease in premature death and disability; improvement in the evidence behind cancer care; and a health system that is both cost-effective and "world's best practice". Science and clinical scientists benefit from access to new therapies; improved clinical practice as a result of the discipline that a trial imposes; and a more rewarding professional life. Trials improve clinical practice in the institutions that conduct them, i.e. they improve the organisational culture through enhanced clinical rigour, which in turn benefits the patients"***. [217]

597. The study concluded that the ***"conduct of national cancer trials and participation in international cancer trials necessitates [the] formation of national cooperative groups with substantial expertise and capacity"***. [218]

598. According to Oceania, Australia's seven national cancer cooperative groups[219], all of which are conducting world-class research despite severe financial constraints, ***"have shown they can be sustainable and effective, the members are committed, their contributions provide substantial leverage on their existing but extremely limited funds, and the groups are flexible and efficient. The shortage of funding, however, means that there are some weaknesses in the cooperative group arrangements, e.g. there are areas for which there is not a cooperative group (such as lung and prostate cancer) and groups have different approaches based on what they can afford rather than what is optimal practice. More fundamentally, this shortage of funding is threatening the sustainability of the groups that do exist"***. [220]

599. The study warns that ***"Australia's low cost base but high level of scientific expertise makes Australia an excellent place to conduct trials on these new therapies but a potential lack of capacity to conduct trials to contemporary international standards in future is a threat to this opportunity"***. [221]

600. One of the gaps in capacity identified by the study is the ***"operational cost of the cooperative groups themselves. … Cooperative groups are small businesses with expenses that include organising and attending meetings of the executive, other communication expenses, staff costs, insurance charges, legal agreements, etc. as well as the cost involved in the pursuit of the group's goal, i.e. identify suitable clinical questions, seek members' involvement in the particular trials, and ensure they are conducted efficiently"***. [222]

601. Similarly ***"the ability to manage data and other aspects of the trial locally is key to trial recruitment and quality. … Additional support for local data management is required if increased recruitment is to occur"***. [223]

602. Oceania points out that ***"coordinating centres manage trials; provide input to trial design and protocol development, database design, etc; as well as trial management, data management, biostatistical analysis and reporting, education and training, and long term follow up of cases. They train and support study nurses, data managers and principal investigators"***. [224] It argues that ***"funding arrangements should reflect the actual cost of each of these activities"***. [225]

603. Cancer Trials Australia (CTA), in its submission to the Review, argued for increased and targeted funding for research infrastructure ***"that will increase research capacities"***, [226] and for ***"targeted funding … to support HREC Secretariats"*** [227]. The submission argued that ***"it is inappropriate for HRECs to apply market forces to their fee structure, when they are performing what could be described as a community service, as this could potentially discourage the conduct of clinical trials within Australia"***, [228] and suggested ***"administrative funding targeted to provide***

HREC Secretariat support … [to] improve efficiencies and reduce timelines associated with the process". [229]

604. In addition CTA argued for increased funding to Co-operative Groups, stating that ***"although co-operative group studies are often under funded, the research undertaken by them is particularly significant in understanding both existing and new treatments. These groups also have an important role in determining the use of treatment modalities that are not usually supported by a commercial sponsor. Australia should encourage this type of research by offering financial assistance to co-operative groups"***. [230]

605. In a paper made available to the Review, Professor John Zalcberg drew upon the Oceania study (see above) to argue that ***"there is a risk that the limited number of major Australian research centres will drop out of Australian trials groups and focus on international trials. This may mean that in future even major regional centres and possibly the smaller capital cities will have no access to clinical trials and modern treatment options"***. [231]

606. Zalcberg identified the existing gaps in capacity as:

- ***"Funding for the operational cost of the cooperative groups themselves;***
- ***Resources for recruitment and local data management at the institutional level***
- ***Central trial coordination, management and analysis of trials;***
- ***Audit and quality assurance of trials"***. [232]

607. He proposed ***"funding in the range of $5 million to $6 million per year … as being required to make a meaningful difference to capacity. Departmental funding for an initial three year period, with a review of the whole program in the third year is recommended. The NHMRC is examining capacity issues in medical research but it will take some time yet, although in other respects the NHMRC Review of Clinical Research in Australia and this proposal are consistent and complementary"***. [233]

608. The VCOG forum also addressed the issue of resources for clinical research, and stressed the current ***"totally inadequate funding for clinical trial groups"***. [234] The forum supported ***"a proposal for A$5 million to increase infrastructure for central and local trial management to underpin Australia's collaborative clinical research trial activity"***. [235]

609. It pointed to ***"the UK's decision to allocate 20 million pounds into a national clinical trials framework to improve outcomes from cancer"*** [236] and while it recognised that ***"the UK models were different to the Australian cooperative groups"*** [237], it stressed ***"they were both about investigator-initiated national collaborative research. The fact was that clinical trials research informed clinical practice"*** [238].

Insurance and Indemnity

610. At the VCOG forum, the Review heard discussion of a peculiarly Victorian aspect to the insurance / legal review issue involving a single source of legal advice to ***"DHS Victoria, the hospitals and the insurance company providing indemnity"*** [239], with ***"all CTN phase I-II trials [being] reviewed by [that] legal firm prior to approval. There had … been conflicting advice [given] about patient consent forms from the legal and ethical viewpoints. Additional costs and time was incurred for this process"*** [240].

611. AusBiotech expressed concern about the impact of clinical trials insurance. ***"The increasing difficulties and costs in obtaining clinical trials insurance are adding another barrier for both local and international companies to undertake clinical research in Australia. For local biotechnology companies, the costs associated are often too great to obtain sponsorship for such insurance"*** [241].

612. AusBiotech advised the Review that ***"there is currently only one insurance company that will offer clinical trials insurance within Australia. This insurance company is based offshore and their credit rating is very low. In this year alone, the insurance premiums and fees have increased by a factor of 3-4, making access for biotechnology companies very difficult. Australian biotechnology companies at present have few alternatives available and therefore are often forced to look at overseas clinical trial opportunities"*** [242].

613. According to AusBiotech, ***"awareness of companies of the insurance requirements and their liability in accepting the role of sponsor for insurance appears to be low"*** [243].

614. Addressing insurance and indemnity issues, Jeremy Kenner of the Peter MacCallum Cancer Institute stated that ***"Victorian public hospitals that conduct clinical research currently labour under an unnecessarily restrictive arrangement with the Victorian Managed Insurance Authority, as agent for the Victorian Department of Human Services. Under this arrangement, the major impediment to the promotion of clinical trials is the requirement that a commercially sponsored clinical trial must be indemnified by an Australian legal entity that may not act as an agent for the commercial sponsor. This requirement means that an overseas sponsor that does not already have an Australian subsidiary must 'find' an organisation (generally an organisation that monitors clinical trials and does not have significant assets) that is able and willing to act as a 'front' for the commercial sponsor. For innovative European research companies this is particularly onerous"*** [244].

615. The Institute went on to say ***"clinical trials that are not commercially sponsored must still be insured. The current system requires that a hospital conducting research must, in essence, indemnify itself against any potential claims arising out of the trial. Many hospitals are unwilling to take this risk, whether or not they are covered by their ordinary malpractice policy issues, in the case of a public hospital, by the State"*** [245].

616. Turning to co-operative groups that conduct research, the Institute argued that they ***"are concerned with addressing clinically important questions that are not necessarily of commercial interest … . One of the major impediments to such research is the increasing need for these groups to carry increasingly expensive clinical trials insurance. … [M]any hospitals are unwilling to approve such research without such insurance, despite the fact that these trials are often the most important from the patient's perspective"*** [246].

617. The Institute suggested two ways in which the current arrangements could be modified to better facilitate such research: "***To … consider shifting indemnification of clinical trials away from individual organisations and toward State or Commonwealth government in those instances in which indemnification by a commercial sponsor is not available; To provide for government indemnification of co-operative group-based … research"*** [247].

618. Cancer Trials Australia also addressed the situation in Victoria. ***"The CTA together with the HRECs of its affiliate health institutions recently piloted the Mutual Acceptance model to expedite multi-centre clinical trials. Nevertheless, Phillips Fox, which undertakes legal review on behalf of the Victorian Government, required that each HREC submit what was essentially identical documentation for separate review. … [T]he time taken to gain approval is extended by unnecessary duplication and there are unnecessary costs. The CTA understands similar situations exist in other States"*** [248].

619. CTA stated that it is not aware of any successful legal action by trial participants related to clinical trials in Australia. It suggested that time and cost inefficiencies associated with extensive legal review could be greatly reduced without diminishing rigour and quality. It suggested that ***"a check list of standard legal inclusions that must be incorporated in to an application could be developed, with only those studies that do not include these provisions, or fall outside certain parameters having to undergo legal review. Under the current system efficiency improvements are not in the interest of lawyers undertaking these reviews as this reduces their fees"*** [249].

620. In CTA's view, ***"it is imperative that streamlining occurs within the legal review process for clinical trial protocols, preferably through negotiation, consultation and agreement between the State jurisdictions to give a system that can work on a nationwide basis"*** [250].

621. Turning to standardized indemnity statements, CTA was of the view that the ***"ethics review process could … be improved by consistent and/or enforced use of a standardized indemnity statement similar to that produced by Medicines Australia"*** [251].

622. According to Professor Garry Jennings, Victorian hospitals are required, as a condition of their insurance (if insured by VMIA) to submit all Phase I and II clinical drug or device trials (regardless of whether they are commercially sponsored or not) and all non-sponsored or non-commercially sponsored Phase III trials to VMIA and

its lawyers for review, advice and approval before the trials can be approved to start. The insurer's lawyers have 14 days to review the documentation. This, according to Jennings, ***"represents yet another step in the approval process in which delays can occur"*** [252].

Consideration of the Issues

623. The Review has carefully noted the comments made to it in submissions and in interviews in relation to infrastructure funding and is persuaded that there is a case for increased infrastructure funding for cooperative groups. Nonetheless, as this issue does not fall within the Terms of Reference of the Review the Review is unable to make specific recommendations.

624. The Review also recognises the urgency of addressing the issue of clinical trial insurance and indemnity, particularly in relation to sourcing research insurance for 'public good' clinical trials. At present the support provided by Governments in terms of insurance coverage for clinical trials conducted within the public health system varies across the States and Territories.

625. There is a dichotomy between investigator initiated trials (or 'public good' trials), where research insurance is often hard to come by, and those trials which receive industry sponsorship, for which insurance is readily available. The Review heard of several examples where credible, high-profile research institutions, attempting to undertake credible, public-good research independent of industry were unable to obtain insurance and indemnity for that research. Such research is important for enhancing health care and patient outcomes.

626. One possible remedy may be for the NHMRC to develop 'public good' criteria under which it may be appropriate for Government to provide support for industry-independent research. In some cases this may be the only way for non-industry supported clinical trials to be conducted.

627. The Review recognises the positive aspects of New Zealand's no-fault insurance scheme, whereby trials that are not conducted primarily for commercial benefit are covered by the New Zealand Accident Compensation Scheme, which is a state insurance scheme that covers all personal physical injury caused by an accident (unintended event). Furthermore, the review is cognisant of the work that has been done by surgeons in relation to personal professional indemnity insurance.

628. Clearly the issue of insurance and indemnification is much broader than just the clinical trial context, and one which the Government needs to address in relation to the provision of health services generally.

Recommendations of the Review

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.

Chapter 11: Trans-Tasman Joint Agency

629. Following in principle agreement in June 2000, the New Zealand and Australian Governments agreed formally in late 2003 to establish a single trans-Tasman therapeutic products agency to regulate medicines, medical devices & other therapeutic products. It is the intention of both governments that there should be a single system for the regulation of medicinal products which will operate in both countries. From 1 July 2005 the joint agency will replace the Australian Therapeutic Goods Administration (TGA) and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).

630. The Australian and New Zealand Governments signed a Treaty in Wellington on 10 December 2003 to establish the bi-national agency to regulate therapeutic products, including medical devices and prescription, over-the-counter and complementary medicines. To this end it is necessary to redraft the legislation pertaining to medicinal products in both countries to ensure the same policy and practices will apply under the joint agency. A project team of Australian and New Zealand officials will develop the final details of the regulatory framework and the legislation to regulate therapeutic products in both countries. Clearly it would be desirous to have a harmonised system for dealing with "unapproved" therapeutic goods (making use of the Australian definition), including methods of access to therapeutic products for clinical trial use as well as individual patient use.

631. The two countries currently have different systems for granting ethical and scientific approval for clinical trials. While both have their origins in the Declaration of Helsinki and conform to the International Conference on Harmonisation's Note for Guidance on Good Clinical Practice (GCP), harmonising these arrangements as far as possible is clearly preferred in the context of a single regulatory agency.

632. This joint agency initiative will harmonise the regulation of therapeutic products between both countries under the Trans Tasman Mutual Recognition Arrangement (TTMRA), in which Australia and New Zealand have agreed to take steps that will lead to a more integrated Trans Tasman economy.

633. The primary role of the new Joint Agency will be to safeguard public health and safety in Australia and New Zealand through regulation of the quality, safety and efficacy (or performance) of therapeutic products. The Agency will be accountable to the Australian and New Zealand governments. The ongoing cost of regulation will be recovered from industry.

634. In discussing the soon-to-be established Trans-Tasman Regulatory Agency, Clinical Trials Victoria "fully endorse[d] this project. A joint agency and streamlining the process to gain approval in different jurisdictions would allow access to a wider ethnic group base. The joint market of New Zealand and Australia will be incredibly favourable to conducting clinical trials in these countries and would accelerate international competition for clinical trial business".[253]

635. There has been much speculation about this development. In one published view, "the new joint agency would be a unified body similar to SCOTT that would provide

a single scientific assessment of new molecules. It would prevent the duplication of effort that currently happens, rid the Australian ethics committees of the huge responsibility of making scientific assessments, and ensure there was government involvement in the evaluation of the quality, safety and efficacy of unregistered products".[254]

636. According to this line of opinion, "The joint committee might function along similar lines to the TGA under Australia's CTX scheme, which means that it would approve or reject the product and its intended usage rather than the protocol. This would eliminate the need to seek expert scientific advice for every new protocol with the same molecule. The CTN scheme would apply to trials for registered medication".[255]

637. Kamat's perception is that "Australia rejected the opportunity to establish regional ethics committees despite the recommendations of a 1996 report submitted to the Australian Minister of Health. The review committee decided to retain the multi-centre process largely because it believed many institutions with ethics committees would not want to relinquish their decision-making powers. However, the joint system will be more streamlined as it will operate through a single scientific and safety assessment body and administrative consistency will be encouraged. A pilot study using this new system is currently underway in New South Wales. The results will determine the feasibility of this system in Australian states. Regional ethics committees are preferred in New Zealand, a much smaller country, where the system would not compromise ethics committees' ability to deal with local issues".[256]

638. She predicts that "a joint application form will be introduced along with the new system. In New Zealand, applications are made on a national ethics application form, which helps reduce discrepancies in the information submitted for ethical review. Implementing a similar system in Australia would be an extensive and challenging, albeit worthwhile, task, considering that Australia has around 250 ethics committees compared with the 14 that exist in New Zealand".[257]

639. She concludes that "both Australia and New Zealand will benefit considerably from a joint agency. It will give New Zealand access to a greater pool of scientific expertise, while Australia will gain a less complex approval process. Trans-Tasman harmonisation may also attract more multinational pharma companies to New Zealand, where for economic reasons few firms have an R & D presence".[258]

640. Many of the issues canvassed by Kamat are at the forefront of the current Review, conducted in the seven months after the publication of her article.

641. While some submissions expressed positive opinions about the concept of the Joint Agency, none addressed the issue of what changes should be made to accommodate the different practices in the two countries with respect to regulation of unapproved therapeutic goods. These differences are explored further, below.

Clinical Trials and the Trans-Tasman Agency

642. As noted elsewhere in this Report, there are marked differences between Australia and New Zealand with respect to how clinical trials and supply of unapproved products are regulated. Throughout the consultation period and in the submissions to

the Review, the general opinions expressed were that Australians wanted to maintain the Australian system and New Zealanders wanted to maintain the New Zealand system.

643. There are a number of issues that the Review has discussed in other parts of this Report that would require changes to the current Australian legislation. It is logical at this stage that the changes be incorporated into the new legislation for the joint agency.

644. The Australian systems for access to unapproved therapeutic goods have been described in detail elsewhere in this report. In New Zealand, currently there is a two-tier system for clinical trials, with one route requiring both ethical and scientific review for trial approval (ie. local/regional ethics committee approval for ethical issues and scientific review by the centralised SCOTT committee [a sub-committee of the Health Research Council (HRC)]), and the other requiring only ethical review.

645. Applications requiring both ethical and scientific review before proceeding are as follows:

- New chemical entities;
- New or different dose forms, delivery systems, or formulations of approved medicines;
- Medicines that do not have consent to be marketed in New Zealand.

646. Application is made essentially for the substance, with the SCOTT committee's review focussing in the main on the safety of the substance in question, and the validity of the scientific method (ie. study design) proposed.

647. The second clinical trial route in New Zealand consists of trials using "existing medications', ie. medicines that have already been approved for marketing. This includes situations where marketed medicines are being studied for new indications. These are subject only to ethical review, and in fact Medsafe is not made aware of the existence of such trials in a formal manner.

648. Medical devices are not captured by the current New Zealand legislation, and consequently, clinical trials using medical devices, at present, are not regulated in New Zealand. Trials involving a medical device, therefore, are subject solely to the second route of review for clinical trial proposals, ie. ethical review only.

649. Medsafe *per se* does not undertake scientific review of clinical trial submissions, although they do receive trial protocols and associated documentation. The evaluation is done by members of the SCOTT committee. The chair of the committee distributes the relevant papers to three members who each assess independently and send their report back to the chair who collates the findings into a recommendation for approval or not to be provided to Medsafe.

650. Approximately 70 applications per annum are processed via the SCOTT committee. Evaluation timeframes are set at 25 days, however review is usually complete within 18 days for most submissions. A fee of $2500NZ is charged, with some avenues available for waiver of this.

Other Avenues of Supply of Unapproved Products

651. Australia has developed a complex system for the regulation of unapproved products, which recognises different levels of risk and different levels of access. It is focussed on the prescriber of the product rather than the sponsor (as many products do not have sponsors in Australia). For conditions that are not considered life-threatening, justification for the proposed use, as well as some degree of efficacy and safety data, must be provided in order for approval for use to be obtained. It also recognises a need for ethical review of the use of experimental products by medical practitioners who wish to treat specific conditions. Reliance is placed on ethics committees because of their developed expertise in assessing risks and precautions in research involving humans.

652. The Australian Special Access Scheme and Authorised Prescriber arrangements have been discussed in considerable detail elsewhere in this report.

653. The New Zealand system is totally deregulated and requires notification after the fact, with listings of unapproved goods supplied each quarter sent to the regulator by the sponsor of the products, listing the details of the medicines, doctors and patients involved. It does not appear to place any obligations on the prescriber and does not require ethical review for supply.

Human Research Ethics Committees

654. The most difficult Trans-Tasman issue to address is the role and function of ethics committees in endorsing use of unapproved products. The history and experience of the two countries are different and the role and function of ethics committees have been shaped by that history.

655. It is recognised that ethics committee review is somewhat different in New Zealand. Ethics committees in Australia are expected to be responsible for ensuring that submissions to conduct clinical trials are appropriately reviewed for scientific content as well as ethical matters, whether by members of the committee itself or via consultation with external persons or organisations. The greater proportion of scientifically trained personnel on Australian ethics committees provides enough talent in many instances for this review to be undertaken without consultation with third parties. In New Zealand, this function is solely the province of the SCOTT committee, for those medicines requiring an exemption from the *Medicines Act.* However, it should be noted that trials with medicines in New Zealand that have already undergone evaluation for a particular indication do not require an exemption from the *Medicines Act,* and assessment of trial proposals are undertaken solely by the ethics committee with jurisdiction over the trial.

656. The NHMRC National Statement clearly does not apply in New Zealand. New Zealand has developed its own oversight and requirements for HRECs. ICH GCP has been adopted in Australia but with amendment in relation to HRECs, as the standard required by the NHMRC's National Statement is higher than that required by the ICH.

Consideration of the Issues

657. The Review understands the focus for the regulation of supply of products by the Joint Agency will be based on the requirement for licensing of 'separate and distinct' products. Generally, before being able to be supplied lawfully a new therapeutic product will require a separate product licence from the Joint Agency if it has a different sponsor, manufacturer, product name, dosage form, indications, formulation etc. Products will be required to have such a licence unless they are specifically exempted from that requirement (such as through supply under clinical trial arrangements etc).

658. Currently in Australia, trials of medicines and medical devices classified as "separate and distinct therapeutic goods" under the Therapeutic Goods legislation, are required to progress via the CTN or CTX system in order to obtain an "exemption" for the substances such that they may be lawfully supplied in Australia in the context of a clinical trial.

659. It is the understanding of the Review that in New Zealand, clinical trials for new substances or medicines that are materially different from that marketed in New Zealand (except in the case of "indication") are required to progress via both regional ethics committee and SCOTT committee review. While this is a two-tier system of review, it is recognised by the review that such a method can, in the New Zealand context, provide a streamlined method for ethical and scientific assessment across several trial sites, given the differing ethics committee arrangements in New Zealand, with regional spheres of responsibility. Given the smaller number of clinical trials conducted in New Zealand, review by the SCOTT committee of scientific content of clinical trial proposals has not led to a bottleneck in evaluation and thus increased timeframes for review.

660. The review proposes that trials regulated by the Joint Agency and requiring an "exemption" in order to be conducted, shall encompass the definition currently in place in Australia, ie. a trial with a marketed medicine or medical device that is proposed to be used in a way that renders it a separate and distinct therapeutic product, including for a different indication, shall require an "exemption" from the Joint Agency. This need not raise concerns for New Zealand sponsors, as under the proposed model, many such trials may still proceed under similar arrangements that are already in place.

661. The various mechanisms available currently in both Australia and New Zealand for supply of unapproved therapeutic products are seen as vital for providing access to treatments for patients. Submissions were generally in support of retention of these schemes that provide access to unapproved therapeutic goods largely on an individual patient basis.

662. It would, therefore, be appropriate for the Joint Agency to adopt and adapt these schemes for the purpose of regulating access to unlicensed products. The scope of these schemes should cover medicines, medical devices and complementary medicines.

663. It has been agreed via the Trans Tasman Treaty that the primary objective of the new Joint Agency will be to ensure timely availability of therapeutic products that are of acceptable quality, safety and efficacy/performance. In addition, a vital component of the overall regulatory framework is that there will be **no lowering of the standard** of regulation following harmonisation of practices across the two countries.

664. Thus, the Review considers that the Joint Agency should have, as the basis of its administration of access to unlicensed therapeutic products, the following core principles that currently underpin the operation of the Australian system:

- Maintaining a balance between ensuring timely access to important new therapeutic developments and protecting broader community interest by ensuring that products available are of appropriate quality, safety and efficacy/performance.
- Encouraging sponsors to apply for licensing of products and prescribers to use licensed (evaluated) products.

665. The various mechanisms for supply of an unlicensed product are intended to be temporary measures pending general marketing approval (licensing) of the product. Unfettered access would remove any incentive for a sponsor to seek evaluation and formal marketing approval of the unlicensed product or for other sponsors to seek evaluation and licensing of alternative products.

666. With these principles in mind, in the opinion of the review the current New Zealand situation, whereby practitioners have unfettered access to unapproved products through mechanisms other than clinical trials and are individually responsible for making an assessment of the safety, quality and efficacy of an unlicensed product, may not meet the requirements of the principle of ensuring that products used in the community are of appropriate safety quality or efficacy. The review therefore does not support the Joint Agency adopting the current New Zealand approach.

667. The Review noted comments from members of New Zealand's Medsafe, that during the consultation with stakeholders regarding the proposed Joint Agency, there were no objections to the adoption of the Australian Special Access and Authorised Prescriber Schemes. Thus, the Review is of the opinion that key elements of the SAS and Authorised Prescriber system should be adopted for the Joint Agency. Currently, these systems work well, however, this does not preclude the need for the Joint Agency to examine whether administrative procedures could be streamlined for greater efficiency.

668. In relation to the regulation of clinical trials, throughout the Australian and New Zealand consultations, there was general recognition that the primary aim of regulation is the protection of individual safety and public health.

669. It was also recognised that it is important to foster and develop quality therapeutics research to advance technology and clinical practice locally, and to contribute data to global medical knowledge as well as applications for marketing of therapeutic products.

670. In order for these goals to be met, there needs to be rigorous scientific and ethical evaluation and approval of all trials prior to their commencement. Also, clinical trials

must be regulated to an internationally accepted standard. All first line international therapeutic regulatory agencies have active roles in both the pre-trial approval process and subsequent review and monitoring activity.

671. Based on its comparison of international practices in the areas of monitoring and inspection of clinical trials, the Review is of the opinion that the Joint Agency should, at least, have a formal program to address these responsibilities in order to be operating on a par with comparable regulatory agencies.

672. The Joint Agency should have some role in the scientific approval of trials and should undertake random inspections of clinical trial sites, in addition to inspecting sites where concerns have been raised about the protection of participant's rights, well-being and safety. Although the TGA has adopted international standards of Good Clinical Practice in clinical trials, it is the opinion of the Review that greater emphasis should be focussed on ensuring compliance with these standards via inspection of clinical trial sites, to complement the undertakings for compliance given by trial stakeholders when CTN and CTX forms are completed. The review sees this as an opportunity for TGA staff to play a more active educative role, as well as fulfil obligations for promoting credibility of data and public safety.

673. The Review team recognises that the advent of the CTN Scheme triggered a dramatic increase in the level of clinical research carried out in Australia. Submissions to the Review from all stakeholders have supported the value of a notification scheme, and have not identified any problems or loss of confidence in clinical research. This research climate is something to be preserved, while maintaining the balance of adequately protecting public health and safety. It is the opinion of the Review that a formal program of monitoring and inspection of clinical trials would achieve an appropriate balance of these requirements.

674. A key issue is whether or not the Joint Agency should retain a role in the evaluation of scientific data with respect to clinical trial proposals. Throughout the consultations, there were clear arguments in favour of the agency having such a role in some form. The Agency was seen as possessing considerable scientific and evaluation expertise, (the comment was in fact made that the TGA has not made this expertise widely available) particularly in the areas of toxicology and development of new vaccines.

675. The issues around which trials should undergo evaluation by the regulatory agency have been canvassed in Chapter Five. The concept of having detailed scientific reviews undertaken by Scientific Assessment Panels (SAPs) was also introduced in Chapter Seven. Bringing all these concepts together and based on submissions put before it, the Review believes specific types of trials and trials using particular therapies should be required to undergo scientific assessment either via the Joint Agency or an accredited "Scientific Assessment Panel". These requirements should be stipulated as 'rules' within the legislation. The advantage of having rules is:

- the immediate ability to deal with products incorporating new technologies;
- straightforward application; and
- increased transparency, accountability and consistency in the regulation of clinical trials such that they are subject to a level of scrutiny commensurate with their risks to individual and public health.

676. This issue is explored further below under the Review's proposed model for clinical trial regulation by the Joint Agency.

A Proposal for a Trans-Tasman Clinical Trial Model.

677. The Joint Agency will regulate all clinical trials of separate and distinct therapeutic products that do not have a product licence.

Avenues for Trial Scrutiny

678. It is proposed that some trials could, via rules in the legislation, be mandated to proceed via scientific review carried out by either the Joint Agency or a Scientific Assessment Panel. It is not envisaged that Scientific Assessment Panels be of limited number and created from scratch, but rather that many existing institutional ethics committees could receive some form of "accreditation" or endorsement, recognising their membership's expertise to carry out detailed scientific assessment. In this way, institutions would be made aware of the required expertise to "qualify" as a SAP, and those who wished to, where necessary, could take steps to augment their committee's membership in order to have this status. In New Zealand, the SCOTT committee would obviously perform the functions of a SAP. To set up such panels independently from current Australian ethics committees or the New Zealand SCOTT committee is unnecessary, does not recognise the enormous human resource of current committees, and would likely encounter problems recruiting the required expert membership outside public institutions. Furthermore, this would involve significant costs that would have to be recovered, and numbers of such SAPs would not approach those of current major institutional ethics committees, raising the possibility of a bottleneck in approvals for clinical trial proposals.

679. Such endorsement could be received after committees conformed to a membership considered satisfactory for such status. This could be determined via guidelines compiled by the NHMRC in consultation with the Joint Agency, which would foster a more uniform standard of scientific review. Such trials that may be required to proceed via this route **could** include:

- The first application from a sponsor/researcher for a clinical trial exemption to introduce an active ingredient or new device (i.e. not listed in the database of approved therapeutic products) for human use in Australia or NZ (Joint Agency or SAP).The first application from a sponsor/researcher for a clinical trial exemption to introduce an active ingredient or new technology into individual specific patient group in Australia or NZ (Joint Agency or SAP). Though it is recognised this group ranges from the lowest risk trial to the highest depending on the substance being studied.
- The first application from a sponsor/researcher for a clinical trial exemption to introduce an active ingredient or new device into heterogeneous patient populations i.e. phase III type pharmaceutical studies. (Joint Agency or SAP). Again this does not equate to a high risk population of trials.
- The first application from a sponsor/researcher for a clinical trial exemption to introduce an active ingredient for use in a novel (unrelated) therapeutic area i.e. for treatment of medical conditions unrelated to the current approved indications

(Phase II and III). (Joint Agency or SAP). Again this does not equate to a high risk trial by definition.

- Gene therapy and related therapy trials (Joint Agency and Joint Specialist gene technology/biotechnology SAP)
- Trials utilising xenotransplantation or somatic cell lines (Joint Agency and Joint Specialist gene technology/biotechnology SAP).

680. Clearly, these definitions need further explanation in the area of what would define a product as "first" use. Distinct guidelines on the trials considered to fall into these categories would need to be agreed on by the Joint Agency in consultation with stakeholders.

681. All other trials would require scientific review, undertaken at the discretion of the institution(s) at which the trial is being conducted. The institution(s) may approve the trial based on the views of its own scientific and ethical reviews, or require further scientific assessment by the Joint Agency or a Scientific Assessment Panel before making a final decision. However, those trials described above are a guide for those trials requiring SAP or Joint Agency review of scientific content. In Australia, a SAP would provide ethical review as well as scientific for a given trial proposal.

682. Consideration should also be given to requiring Joint Agency or SAP review of the first phase III study for an intended indication. This is desirable to capture situations where the proposed new trial indication for use is substantially different from earlier trials eg. an antidepressant is suddenly investigated as a weight loss drug. However, it is also recognised that this imposes an additional burden for potentially little gain.

Operational aspects of the model

683. The sponsor of the clinical trial would be responsible for applying the rules and for determining and justifying the evaluation route.

684. It is the intention that application may be made in parallel for ethical and scientific review. Clearly, in Australia, the same ethics committee or SAP will likely give ethical approval in most instances.

685. Documentation required for review by the Joint Agency (or SAP) and HRECs would be set out in guidelines published by the Agency. It is not foreseen that such documentation would differ significantly, if at all, with the documentation currently submitted for review in relation to the Australian CTX system or the New Zealand SCOTT committee's requirements.

686. To ensure evaluation timeframes are kept as short as reasonably possible, the Joint Agency will have timeframes for initial consideration of an application and for amendments and review of supplementary data. The timeframe could be legislated in relation to Joint Agency review, but this should be accompanied by a fee for cost recovery of such review. It is recommended the timeframe be 20 working days. Amendments and review of supplementary data will have a further 20 working days for approval.

687. The data reviewed by the Joint Agency or SAP will, generally, be in keeping with that required by the ICH/EU/CPMP guidance documents or other international standards.

688. There should be a requirement for SAPs to be constituted according to Joint Agency/NHMRC guidelines and to use standard operating procedures and proforma for evaluating scientific data. In this way the SAP would operate within set requirements and endeavour to meet similar agreed timeframes.

Monitoring

689. The Joint Agency shall have in place a system of clinical trial inspection as well as monitoring of adverse events.

Comparison between the old and the new

690. A comparison of the current Australian system of CTN/CTX, the current New Zealand system and the proposed model is shown below.

	Regulatory System			
	CTN	CTX	NZ	Proposed CTS
Scope	Medicines and medical devices	Medicines and medical devices *gene therapy and related therapies	Medicines	All therapeutic products
Who decides route?	Sponsor, HREC	Sponsor, HREC	Legislation	Legislation stipulates rules trying to identify risk. Rules to be applied by sponsor & HREC.
Scientific r/v	Institution - all	TGA - all	SCOTT committee - NCE, and new formulations only	*Agency* - Gene therapy and xenotransplantation; *Agency or SAP* – High risk trials. *Institution* - All others
Ethical r/v	Institutional HREC	Institutional HREC	Regional HREC	*Single centre trials* Institution HREC or SAP in Australia and Regional HREC in NZ *Multicentre trials*; NAHREC in Australia or several SAPs/Institutional HRECs as currently occurs, regional HRECs in NZ
Agency role	Receives notification Monitors adverse events Inspects trial sites	Evaluates summary scientific data and approves usage guidelines Receives notification of all trials Monitors adverse events Inspects trial sites	Receives notification and approves exemption on basis of advice from SCOTT Monitors adverse events	Evaluates summary scientific data for trials mandated by legislation Receives notification of all trials Monitors adverse events Inspects trial sites

*although not mandated in legislation, current NHMRC guidelines require CTX route for all gene therapy and related therapies unless GTRAP advises CTN is acceptable.

Recommendations

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 articulated 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 the Joint Agency or an accredited "Scientific Assessment Panel".

R43. With reference to scientific assessment of non-mandated trials and their documentation for evaluation, ethics committees should have a range of review avenues including the TGA, Scientific Assessment Panels, and expertise within their own institution(s), 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.

Appendix 1: Written Submissions Received

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 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

Appendix 2: Oral 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 Hospital, Commercial Road, Prahran.	1 July 2003
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	30 July 2003

Kangan Drive, Berwick, Victoria.	
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 Oncology, Peter MacCallum Cancer Institute, Melbourne.	31 July 2003
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,	14 July 2003

Hobart, and National President of the Cancer Council of Australia.	
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

Appendix 3: Workshops on Significant Issues

1. The following section is an account of the Clinical Trial Review workshops conducted on Tuesday 11 November, 2003 (in Sydney) and on Thursday 13 November, 2003 (in Melbourne). The statements DO NOT represent the conclusions of the Review. Some comments of the Review team appear in parentheses [ ] to correct some issues of significant misunderstanding.

Human Research Ethics Committees

2. Discussion during the Workshops highlighted:

- HRECs as a good way to administer research;
- HRECs as essential to research;
- The importance of improving the administrative process; and
- The strong support of the Pharmaceutical industry for HRECs.

3. The Workshops considered a number of proposals raised at earlier stages of the Review, including a proposal to enable institutional HRECs more effectively to fulfil their responsibilities by:

(a) Ensuring that, through Institutional HRECs, local issues are dealt with locally.

Workshop Response: That local issues be dealt with locally is important, but discretion needs to be exercised. This is not as big an issue in Australia as it is in New Zealand, and there would be problems with any attempt at trans-Tasman legislation. Attempts should be made to get clarity in relation to local issues before making changes.

(b) Achieving consistency in approach and standards under the leadership of the Australian Health Ethics Committee (AHEC), and adopting as prescriptive the NHMRC *National Statement on Ethical Conduct in Research Involving Humans* ***[259]***.

Workshop Response: There **was** support for HRECs adopting a national approach. However, the consensus view was that more leadership from the NHMRC and AHEC is required.

(c) Eliminating duplication of effort.

Workshop Response: Eliminating duplication of effort was fully supported.

(d) Better provision of resources (including fees for sponsored trials and Australian/State Government and institutional contributions).

Workshop Response: In relation to the sources of the resources for HRECs, there was a view that HRECs are not adequately resourced to do the job they were set up to do, and that institutions set fees for pharmaceutical company sponsored trials at a higher rate than for others conducting research. It was agreed that the starting point

should be the policy issues associated with HRECs and clinical trials, including the large number of potential beneficiaries and the perception that the public sector carries the bulk of the responsibility.

(e) Ensuring consumer representation on all HRECs.

Workshop Response: The Workshop tried to clarify the meaning of "*consumer representation*", with some stakeholders interpreting this as requiring an additional person who had at some time been a trial participant. Ethics committees may need to be alert to when they need to recruit additional expertise. It was noted that the NHMRC's National Statement requires two 'lay people' to be part of every HREC, but this proposal differs from the current arrangement and from the meaning of "lay person".

(f) Holding regular, frequent meetings, and paying sitting fees and time-based remuneration to Members.

Workshop Response: Participants should be paid for their time and responsibility, although this might not include reading time. It was noted that the Australian Institute of Health and Welfare HREC members are paid for their participation. The key question associated with this issue was "who pays?" It was suggested that payment come from the Department of Health and Ageing and from drug trials, but there needed to be transparency regarding the source of funding.

(g) National mandatory use of a standardised application form developed by AHEC in full consultation with stakeholders utilising an optimal data set.

Workshop Response: There was support for the use of standardised forms. This raised the question of how to enlist the support of the RACGP and private hospitals in the use of standardised forms.

(h) National mandatory use of standardised patient consent forms developed by AHEC in full consultation with stakeholders taking into account both legal and ethical viewpoints.

Workshop Response: There was support for standardising the information in patient consent forms, to include common definitions for terms such as indemnity and randomisation. Much of the language provided by pharmaceutical headquarters could be standardised. It was agreed that this would probably require a two-stage process, i.e. a standardised glossary of terms, followed by a standardised form.

(i) Providing under legislation that the Government indemnifies non-sponsored, properly approved CTN trials (including investigator-driven trials and collaborative group trials).

Workshop Response: This was acknowledged as a very real problem due to the inability to obtain indemnity insurance for non-sponsored trials. However, if Government was to underwrite the risk, would it want more control? This issue was not resolved.

(j) Requiring Phase IV studies, especially where they are post-approval, marketing-related studies, to obtain HREC approval.

Workshop Response: Stakeholders expressed confusion over which studies are considered Phase IV, and that there is a need to define what is a clinical trial and what is not. At present the wording is considered too broad which leads to a loose interpretation.

Coordinating Human Research Ethics Committees (CHRECs).

4. The Workshops examined a proposal to establish a limited number of CHRECs by:
(a) Establishing where appropriate either geographically-based (eg State-wide) and/or specialty-based (eg oncology) CHRECs.
(b) Making CHRECs Mandatory where any trial is to be undertaken at two or more sites.
(c) Providing that, for multi-centre trials where the host institution is a national centre, only the host institution needs to be registered by the appropriate CHRECs while the sites where patients are seen but that participate in but do not run trials are to be recorded.
(d) Providing mutual recognition of the decisions of CHRECs by all other HRECs.
(e) Ensuring that CHRECs relate appropriately to and communicate effectively with HRECs, with CHRECs mandating conditions for trials and with HRECs providing institutional sign-off.
(f) Providing for the establishment of a CHREC review for national collaborative group trials, with HRECs receiving/accepting that approval.
(g) The provision of resources (including fees for sponsored trials and Australian Government contributions through AHEC).

Workshop Response: The establishment of a limited number of CHRECs was discussed. A clear view was expressed that duplication was to be avoided and that the CHRECs should focus on multi-centre trials. It was agreed that specialty-based CHRECs would improve the quality of clinical research. Uncertainty over the best model, i.e. national versus state-based CHRECs, was not resolved at the Workshops. The barriers were identified as financial, indemnity, and state-based differences. In addition, accountability and insurance were highlighted as important issues associated with the CHREC proposal that will need to be resolved.

Scientific Assessment Panels (SAP)

5. It was proposed that each CHREC establish or have access to a Scientific Assessment Panel (SAP):
(a) SAPs to be formed along the lines of the Shared Scientific Assessment Scheme (NSW).
(b) SAPs to provide CHRECs and HRECs with access to scientific expertise and assessment.

Workshop Response: Discussion concentrated on whether scientific assessment should occur separately from ethics approval. There was support for the separation of science and ethics functions on the basis that no single CHREC could have the scientific knowledge required for the range of research work put forward for approval. The question of how to get the breadth of advice that is required was raised. While some stakeholders felt that the science in large multi-centre trials is generally good, the smaller trials can cause concern. In addition, the lack of availability of experts in

toxicology is an issue in Australia. The consensus view was that an expert scientific assessment panel is very useful, particularly for rural HRECs, and for early phase trials where issues over the quality of the product need to be addressed.

Data and Safety Monitoring Boards (DSMB)

6. It was proposed that Serious Adverse Events (including adverse drug reaction) monitoring should be undertaken using the Data and Safety Monitoring Boards (DSMB) approach.
(a) DSMBs separate from HRECs/CHRECs to be established by AHEC/NHMRC, and to be responsible for monitoring all aspects of drug safety, including receipt of reports of adverse reactions, the placing of all such reactions in an appropriate epidemiological context, assessment and reporting on such reactions.
(b) DSMBs to be responsible for reporting their findings and recommendations to HRECs/CHRECs, to TGA, and to NHMRC (AHEC).
(c) TGA to establish a working group to develop the Good Clinical Practice Guidelines to ensure clarity in the process for reporting and evaluating events.

Workshop Response: Currently drug event monitoring is undertaken through the TGA Experimental Drugs Section. For those trials being undertaken under a CTN, adverse events must be reported to the pharmaceutical company. The volume of serious adverse events and drug reactions are quite different. There is a question as to how the information is being evaluated. The volume of these reports means that investigators are not examining all the data although they are obliged to advise the HREC in a situation where the Study Chair has decided the report is of concern. An optimal outcome to reduce the volume of SAE reports is to develop a minimum data set that has international validity.

Australian Health Ethics Committee (AHEC).

7. A strengthened role was proposed for the AHEC to enable it to:
(a) Set mandatory standards and operational guidelines governing the establishment, membership, processes, procedures and standards of HRECs and CHRECs, using as a model the European Union *Directive of the European Parliament and of the Council on …the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*.
(b) Assist HRECs and CHRECs to avoid perceived conflicts of interest in acting on behalf of patient participants as well as on behalf of the participating institutions in regard to resources and medico-legal issues.
(c) Accredit all HRECs and CHRECs.
(d) Undertake audits of HRECs and CHRECs to identify problems of compliance.
(e) Ensure the provision of appropriate training and education to HREC and CHREC members.
(f) Mandate time limits for HRECs and CHRECs, with a 60-day maximum between application and approval.
(g) Work in close cooperation with State Governments.

Workshop Response: The role of AHEC has been to provide guidelines and advice, although it has no statutory power. It cannot audit or obtain information from any organisation; only the TGA can do this. It uses its influence to achieve change and improvements. [The Review notes that the NHMRC does possess the power to

withdraw funds from organisations not compliant with the National Statement – the National Statement has been given authority via amendments in 2000 to the Therapeutic Goods Act 1989].

It was noted that the National Statement[32] is due for review next year (2004). Some concerns were expressed regarding responsibility for the guidelines and the review. Raising the standards, regulations and mandatory requirements were not considered to be a substitute for efficiency, but the need for standards, operational guidelines and standardised forms was not discounted. The seemingly slow speed of progress and changes made by AHEC were of concern to stakeholders.

Currently AHEC meets four times per year and has a small secretariat. [The Review notes that much of AHEC's work is achieved through teleconferences and workgroups]. Its members are part-time. It was suggested that industry might finance AHEC to improve its processes. [The Review notes this would create a huge conflict of interest]. AHEC is moving towards a more effective way of training and education using CD-ROM technology. [The Review notes, from consultation with the AHEC, that a CD ROM program might eventuate from a new round of training workshops underway at the time of the Review, but the intention is that they would not replace face-to-face training]. The American system of having to complete an on-line researcher program prior to membership on any ethics committee was suggested in this context. [The Review understands the US on-line system is a means of ensuring researchers gain an understanding of the US ethics committee system and it is NOT used to train members of IRBs] It was suggested that perhaps the maximum time between application and approval could be less than 60 days.

Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) Arrangements

8. Notification under CTN and CTX is currently required for clinical investigational use of:
(a) Any medicine or device not entered in the Australian Register of Therapeutic Goods (ARTG), including any new formulation of an existing product or any new route of administration; or
(b) A marketed medicine or device beyond the conditions of its marketing approval, including new indications extending the use of the product to a new patient group and the extension of does or duration of treatments outside the approved range.

9. The Workshops considered a proposal that, while the current CTN/CTX arrangements should, by and large, be retained, CTX should be used more widely than at present for Phase I trial approval applications, with TGA to issue a clear definitional statement:
(a) To aid researchers and sponsors determine whether their proposed trial falls into the CTX or CTN category;
(b) To improve clarity about the CTN scheme and its appropriateness for phase I and II trials;
(c) To clarify the level of overseas review; and
(d) To specify the appropriate arrangements for trials of approved drugs and for Phase I and II non-sponsored trials.

Workshop Response: There has been a lack of clarity for HRECs about when to use CTN versus CTX processes. This is particularly relevant to Phase 1 and 2 trials where there is no guarantee that the science is good. Decisions in relation to Phase 1

trials have been dependent upon where the trial originates. As a result the decision has generally been left to the researcher. The CTN process has been used by industry to promote Australia as a place to do research, and is considered very positively. Phase 1 trials take place very quickly under CTN and the industry stakeholders believe that if CTX were mandated for Phase 1, they would no longer be conducted in Australia. The cost of registering trials and conducting them needs to be contained in order to make Australia attractive to industry.

10. Similarly, it was proposed that the current CTN arrangements should be improved by:
(a) Maintaining comparability of costs and time lines with the rest of the world.
(b) The inclusion of formal benchmarking performance indicators.
(c) Introduction by the TGA of 'on-line' applications/approvals to reduce delay, and the consequent abolition by the TGA of the current requirement to wait seven days for notification.
(d) A tightening up of the requirements for Australian sponsorship to introduce additional accountability.
(e) Significant upgrading of the TGA's IT and database capacity.
(f) Introduction of a single CTN application fee for cooperative trial group listing of multiple centres, with TGA confirming batch submissions with a single fee.

Workshop Response: TGA has a database of all CTN approvals. It was acknowledged that the website needs to be improved, particularly in relation to regulatory advice. The American FDA website was highlighted as a great source of information that could be used as a model for the TGA.

There was a call for clarification of the role of overseas companies in relation to sponsorship arrangements. Details relating to "sponsor" are already contained in the TGA legislation. Small Australian CROs are not able to compete with larger overseas companies. As a result they act as an agent for the larger overseas companies, but the cost of indemnity is very high.

A large volume of clinical trials is undertaken through general practitioners, and investigator stakeholders expressed reluctance at having to pay for each clinic that may be enrolled in a trial.

Special Access Scheme (SAS) and Authorised Prescriber Scheme

11. The SAS is an arrangement that provides for the import and/or supply of an unapproved therapeutic good for a single patient, on a case-by-case basis. These arrangements are either:
(a) Category A patients – under Section 18 and Regulation 12A, medical practitioners can supply unapproved goods to some very seriously ill patients without the approval of the TGA but the TGA must be notified.
(b) Category B patients – under subsections 19(1) to 19(4), approval is given by a delegate in the TGA or a delegate outside the TGA (known as an external delegate).

12. The Workshops considered a proposal that the SAS and the authorized prescriber scheme, under which patients are able to access the drugs they need, should be retained in its current form, but be improved by:
(a) The current somewhat time consuming process to be simplified, including the use of 'on-line' application and approval, and approval of patient, not of prescriber.

(b) Untested drugs to be made subject to a more intense scrutiny, with additional guidelines (particularly for multiple and longer term usage), but with easier 'fast-track' access to drugs with proven efficacy overseas and registered in other countries.
(c) Ongoing use of SAS for multiple patients to require an approved treatment protocol and patient consent.
(d) Category differentiation to be used as intended, with 'very seriously ill' being the sole criterion.

13. It was also proposed that a link be established between the end of Phase IV, licensing, and PBAC listing by earlier involvement by TGA to take into account likely PBAC implications.

14. Further, recognizing that many SAS and authorized prescriber arrangements are 'clinical trials' with poor data collection and unclear end points (despite protocols), it was proposed that access before licence (including to orphan drugs) be tied to monitoring and routine clinical evaluation with clinician and patient to agree to more formal data collection for assessment.

15. It was also suggested that the current prohibition of the promotion of orphan drugs be relaxed to permit advice to physicians and pharmacies as to the availability of such drugs, perhaps by way of a national register of available drugs.

Workshop Response: This was general discussion on the issue, and on the changes made in 2000 to the legislation and to the Special Access Scheme. It was recognized that there should always be appropriate balance between rights of access and level of regulation.

Clinical Trials Register

16. The Workshops considered a proposal that a clinical trials register be established:
(a) To document all trials to eliminate bias in reporting (especially regarding early cessation or negative results).
(b) To prevent duplication of trial design.
(c) To assist planners, to provide patients with information on access to clinical trials, to provide clinicians with a mechanism to offer trials, and to offer researchers with a means to identify trials.
(d) To provide patients with an assurance that the research they are participating in leads to something.

17. Under the proposal:
(a) The TGA database of all trial notifications would be expanded as the basis for the establishment of the database, together with concentration on the development of an oncology trials register.
(b) Trials not registered by TGA (including non-drug/device trials and surgical or psycho-oncology trials), but which require HREC approval would be listed on the register.
(c) The Register would be managed and developed by the NHMRC and the TGA.
(d) Access to the Register would be as wide as possible, with entries as complete as possible and in plain English, to include publication details, and to be searchable by postcode and by disease. There should be no HREC trial approval or funding (including NHMRC panel decisions and grants/fellowships) without registration.

(e) To maintain the necessary degree of confidentiality regarding pharmaceutical company sponsored trials, commercial-in-confidence material would be kept confidential.

Workshop Response: This proposal is based on both the investigators' and patients' "need to know" what trials are being conducted or have been conducted, their scope, access, content, and outcomes (if completed/closed). There was agreement with the importance of this information and the development of a register, but the issue of commercial-in-confidence information was flagged to be addressed in the development of this type of database.

In the EU only regulatory authorities have access to the information held on such a register. However, in the Australian and New Zealand context, the level of access to information would vary according to the inquirer's status (eg. medical practitioner, consumer, etc).

Some preliminary comments in relation to the development of such a database included:

- The information available should be simple to start with;
- A cost/benefit analysis of providing this sort of information should be conducted;
- Tracking of HREC approval should be part of the database; and
- The status of the application should be included.

It was suggested that any such register should be publicly funded, particularly as it would account for all trials undertaken, including those that were abandoned and the reasons for discontinuation.

Funding of Clinical Research

18. The Workshops considered a proposal that infrastructure for trial management to underpin Australia's collaborative clinical research trial activity should be funded at an appropriate level by way of a special earmarked additional grant to be administered by the NHMRC.

19. It was also suggested that PBS, Medicare, and the health insurance industry should be encouraged to fund audits/evaluations of the use of approved drugs, and to spend a set percentage of their turnover on research and development in the drug and procedure trials area.

Workshop Response: The proposals were supported as an initiative. It was agreed that it is in the best longer-term interest of the PBS, Medicare and the health insurance industry to ensure that the monies spent are on useful drugs and devices and not on continuing to invest in older and outdated products. It was suggested that Government should support infrastructure costs, and that a percentage of State government expenditure on health be directed to support clinical research.

Complementary and Alternative Medicines/Therapies and Unapproved Therapeutic Goods

20. The Workshops considered a proposal that all complementary and alternative medicines/therapies and unapproved medical products should be subject to a thorough

and scientifically based testing system equivalent to that applied to prescription drugs, together with properly controlled clinical trials in humans, to determine the purity of the compound, the exact composition, the dose, the efficacy, and the lack of harm.

Workshop Response: There was full support for the proposal that complementary and alternative medicines be subject to a scientific testing system equivalent to that applied to prescription medicines. This process would be difficult to implement and monitor, but the proposal should not be discarded on this basis.

Appendix 4: Extracts From The "National Statement On Ethical Conduct In Research Involving Humans", Issued by the National Health and Medical Research Council (NHMRC) in accordance with the *NHMRC Act*, 1992 (Cth).

2. Human Research Ethics Committees

Research proposals involving human participants must be reviewed and approved by a Human Research Ethics Committee (HREC) which is established by and advises an institution or organisation regarding ethical approval for research projects. Requirements are set out for:

- institutions or organisations in establishing HRECs;
- researchers in submitting research proposals to HRECs; and
- HRECs in considering and reaching decisions regarding those proposals and in monitoring the conduct of approved research.

2.1 Institutions and organisations in which research involving humans is undertaken must individually or jointly establish, adequately resource, and maintain an HREC composed and functioning in accordance with this Statement.

2.2 The institution or organisation must, when establishing an HREC, set out its terms of reference including the scope of its responsibilities, relationship to non-affiliated researchers, accountability, mechanisms of reporting, and remuneration, if any, for members.

2.3 The institution or organisation (individually or jointly) must accept legal responsibility for decisions and advice received from the HREC and indemnify its members.

2.4 Researchers without affiliation to an institution or organisation with an HREC must ensure that the project is approved by an established HREC. There should be an agreement between the institution or organisation and researchers that defines the approval, conduct and monitoring of research, and who carries legal responsibility for it.

2.5 The primary role of an HREC is to protect the welfare and the rights of participants in research and the primary responsibility of each member is to decide, independently, whether, in his or her opinion, the conduct of each research proposal submitted to the HREC will so protect participants.

Composition

2.6 The minimum membership of an HREC is seven members, being men and women, comprising:

(a) a chairperson;

(b) at least two members who are lay people, one man and one woman, who have no affiliation with the institution or organisation, are not currently involved in medical, scientific, or legal work, and who are preferably from the community in which the institution or organisation is located;

(c) at least one member with knowledge of, and current experience in, the areas of research that are regularly considered by the HREC (eg. health, medical, social, psychological, epidemiological, as appropriate);

(d) at least one member with knowledge of, and current experience in, the professional care, counselling or treatment of people (eg. medical practitioner, clinical psychologist, social worker, nurse, as appropriate);

(e) at least one member who is a minister of religion, or a person who performs a similar role in a community such as an Aboriginal elder; and

(f) at least one member who is a lawyer.

2.7 The institution or organisation must ensure that the membership will equip the HREC to address all relevant considerations arising from the categories of research likely to be submitted to the HREC. For example, an experienced medical practitioner should be included if the HREC considers research protocols which involve any physically invasive procedures or medical interventions, (eg. surgical, pharmacological, physiological, technological, or nutritional intervention).

2.8 An HREC must ensure that it is sufficiently informed on all aspects of a research protocol, including its scientific and statistical validity, that are relevant to deciding whether the protocol is both acceptable on ethical grounds and conforms with this Statement. This may necessitate appointment of additional members with specific expertise.

2.9 If an institution or organisation appoints additional members it should ensure that the membership continues to reflect both the diversity of the categories of members listed in paragraph 2.6, including gender, and the relative proportion of institutional to non-institutional members.

Appointment of Members

2.10 The institution or organisation may recruit members for an HREC in such a manner and shall appoint them for such a period and on such terms and conditions as it determines.

2.11 Members are to be appointed for their expertise and not in a representative capacity.

2.12 Members must receive a formal notice of appointment and assurances that the institution or organisation will provide legal protection in respect of liabilities that may arise in the course of bona fide conduct of their duties as committee members.

Procedures

2.13 Institutions and organisations and their HRECs must establish working procedures concerning:

- frequency of meetings;
- preparation of agendas and minutes;
- distribution of papers prior to meetings;
- presentation of research protocols;
- timely consideration and review of research protocols;
- methods of decision making;
- prompt notification of decisions;
- reporting of adverse occurrences;
- appropriate monitoring;
- receiving complaints;
- advising institution(s) or organisation(s) to discontinue a research project;
- fees, if any, to be charged; and
- confidentiality of the content of protocols and of committee proceedings.

2.14 An HREC may approve, require amendment of, or reject a research proposal on ethical grounds. The HREC must record decisions in writing and should include reasons for rejection.

2.15 Meetings of an HREC must be so arranged as to allow, wherever possible, all members to be fully informed by receipt of all relevant papers and the opportunity to attend.

2.16 Where there is less than full attendance at a meeting, the Chairperson must be satisfied, before a decision is reached, that the minimum membership listed in paragraph 2.6 have received all papers and have had an opportunity to contribute their views and that these have been recorded and considered.

2.17 An HREC should endeavour to reach decisions by general agreement. This need not involve unanimity, but failure to agree may require an extension of time to reconsider the research protocol and its possible amendment, especially when any member is not satisfied that the welfare and rights of participants are protected.

2.18 An HREC may invite the researcher(s) to be present for discussions of the research and may request amendments to the research protocol.

2.19 An HREC may seek advice and assistance from experts to assist with consideration of a research protocol, but must be satisfied that such experts have no conflicts of interest in relation to the research project under consideration arising from any personal involvement or participation in the research, any financial interest in the outcome or any involvement in competing research.

2.20 An HREC shall ensure that no member of the committee adjudicates on research in which that member has any conflict of interest including any personal involvement or participation in the research, any financial interest in the outcome or any involvement in competing research.

2.21 A researcher must disclose to the HREC the amount and sources or potential sources of funding for the research and must declare any affiliation or financial interest when proposing and when reporting the research. The HREC must consider the extent to which it should disclose that information about funding sources.

2.22 A researcher must include, in the research proposal, a statement of the ethical considerations involved in the proposed research and an HREC must be satisfied that the research protocol gives adequate consideration to participants' welfare, rights, beliefs, perceptions, customs and cultural heritage both individual and collective.

2.23 An HREC should not communicate directly with a research sponsor on matters relating to the protocol or ethics of a project, but the institution or organisation and the sponsor may have direct communication on matters relating to administration, indemnity and insurance.

2.24 All documents and other material used to inform potential research participants should be approved by the HREC including plain language information sheets, consent forms, questionnaires, advertisements and letters of invitation.

Advocates and interpreters

Advocates

2.25 An HREC must consider whether an advocate for any participant or group of participants should be invited to the HREC meeting to ensure informed decision making and understanding by these participants.

Interpreters

2.26 Where research involves the participation of persons unfamiliar with the English language (or the language in which the research is to be conducted), an HREC must ensure that:

(a) the participant information statement has been translated into the participant's language; and

(b) an interpreter is present during discussions with the participants about the project. Normally the interpreter should be independent, but when the research proposed is of minimal risk, an English-speaking relative or friend may be acceptable.

Expedited Review for Minimal Risk Research

2.27 An HREC may establish procedures for expedited review of research involving minimal risks to participants and in so doing may depart from the requirements of paragraphs 2.15, 2.16 and 2.17 and if so, must determine:

(a) the class or classes of research to which an expedited review procedure is to apply;

(b) the scope of the Chairperson's authority;

(c) the delegation of tasks to sub-committees;

(d) the relationship between the Chairperson of the full Committee, and the Chairpersons of such sub-committees; and

(e) the method of reporting and ratification of decisions by the full Committee.

2.28 Research with potential for physical or psychological harm should generally not be considered for expedited review. This includes drug trials, research involving invasive physical procedures and research exploring sensitive personal or cultural issues.

2.29 Where the Chairperson of an HREC considers that research may involve a departure from any of the ethical principles in this Statement, the protocol must be considered by the full Committee and cannot be dealt with by expedited review.

Recording of Decisions

2.30 An HREC shall maintain a record of all research protocols received and reviewed including:

- name of responsible institution or organisation;
- project identification number(s);
- principal researcher(s);
- title of project;
- ethical approval or non-approval with date;
- approval or non-approval of any changes to the protocol;
- the terms and conditions, if any, of approval of any protocol;
- whether approval was by expedited review;
- whether the opinion of another HREC was considered;
- action taken by the HREC to monitor the conduct of the research; and
- the relevance, if any, of the Guidelines for the Protection of Privacy in the Conduct of Medical Research.

2.31 For multi-centre research proposals the HREC shall also record, from information provided from the researcher (see paragraph 3.7):

- details of other centres involved;

- the approval status of the study at each centre; and
- details of any amendments required at other centres.

2.32 An HREC shall retain on file a copy of each research protocol and application for HREC approval, including any information sheets, consent forms or relevant correspondence, in the form in which they are approved.

Monitoring

2.33 An institution or organisation and its HREC have the responsibility to ensure that the conduct of all research approved by the HREC is monitored by procedures and/or by utilising existing mechanisms within the institution or organisation which will ensure the achievement of the goals for monitoring as determined by the institution or organisation and the HREC.

2.34 The frequency and type of monitoring determined by an HREC should reflect the degree of risk to participants in the research project.

2.35 As a minimum an HREC must require at regular periods, at least annually, reports from principal researchers on matters including:

(a) (a) progress to date or outcome in the case of completed research;

(b) maintenance and security of records;

(c) compliance with the approved protocol; and

(d) compliance with any conditions of approval.

2.36 An HREC may recommend and/or adopt any additional appropriate mechanism for monitoring including random inspections of research sites, data and signed consent forms, and/or interview, with their prior consent, of research participants.

2.37 An HREC shall, as a condition of approval of each protocol, require that researchers immediately report anything which might warrant review of ethical approval of the protocol, including:

(a) serious or unexpected adverse effects on participants;

(b) proposed changes in the protocol; and

(c) unforeseen events that might affect continued ethical acceptability of the project.

2.38 An HREC shall, as a condition of approval of the research proposal, require researchers to inform the HREC, giving reasons, if the research project is discontinued before the expected date of completion.

Complaints

2.39 An institution or organisation with an HREC shall establish mechanisms for receiving and promptly handling complaints or concerns about the conduct of an approved research project.

2.40 An HREC must nominate a person to whom complaints from research participants, researchers, or other interested persons may be made in the first instance. This person or the HREC shall attempt to resolve these complaints.

2.41 Where a complaint made under paragraph 2.40 cannot be resolved, the HREC must refer the matter to a person nominated by the institution or organisation to handle and resolve such complaints.

2.42 When information on the research is first provided to participants, the name or position and contact details of the person nominated by the HREC to receive complaints must be included together with the procedures for raising concerns or obtaining additional information on the research.

2.43 An institution or organisation shall also establish procedures for receiving and promptly handling concerns or complaints from researchers about the consideration of their research protocol by an HREC.

Suspension or Discontinuation of Research

2.44 Where an HREC is satisfied that circumstances have arisen such that a research project is not being or cannot be conducted in accordance with the approved protocol and that, as a result, the welfare and rights of participants are not or will not be protected, the HREC may withdraw approval, inform the researcher(s) and the institution(s) or organisation(s) of such withdrawal, and recommend to the institution(s) or organisation(s) that the research project be discontinued, suspended, or that other necessary steps be taken.

2.45 A researcher must not continue the research if ethical approval has been withdrawn and must comply with any special conditions required by the HREC.

Compliance Reports to the National Health and Medical Research Council

2.46 The National Health and Medical Research Council (NHMRC), through the AHEC, will audit the activities of HRECs to ensure compliance with this Statement.

2.47 An institution or organisation and its HREC shall provide information from its records to the NHMRC on request.

2.48 An institution or organisation and its HREC shall report annually to the NHMRC information relevant to its procedures including:

- membership/membership changes;
- number of meetings;
- confirmation of participation by required categories of members;

- the number of protocols presented, the number approved, and the number rejected;
- monitoring procedures in place and any problems encountered; and
- complaints procedures and number of complaints handled.

12. CLINICAL TRIALS

A clinical trial is a study involving humans to find out whether an intervention, including treatments or diagnostic procedures, which it is believed may improve a person's health, actually does so. A clinical trial can involve testing a drug, a surgical or other therapeutic or preventive procedure, or a therapeutic, preventive or diagnostic device or service. Any intervention, including so-called "natural" therapies and other forms of complementary medicine, can be tested in this way. Other related disciplines also conduct research which involves similar ethical considerations to those raised in clinical trials.
In pharmaceutical and medical device trials there are established codes of good clinical research practice which define clearly what is meant by a clinical trial for those purposes.

2.49 *Clinical Trials* has principal application in the context of biomedical clinical trials but should also apply to any other intervention claiming therapeutic benefit, wherever provided or conducted.

12.1. The *aims* of every trial must be precisely stated in a protocol presented to and approved by an HREC and every trial must be conducted by researchers with suitable experience, qualifications and competence and, where applicable, adequate training in relevant procedures including the use of any device being investigated.

12.2. An HREC must consider all aspects of the design of a clinical trial and be satisfied that:

(a) the trial is directed to answering a specific question or questions;

(b) there is a scientifically valid hypothesis being tested which offers a realistic possibility that the interventions being studied will be at least as effective as standard treatment;

(c) where the research is therapeutic, and is therefore intended and likely to be of direct benefit to participants, there is an acceptable balance between the risks and benefits of the trial;

(d) the methodology provides:

i) a rationale for the selection of appropriate participants;

ii) an appropriate method of recruitment;

iii) adequate, understandable information for the purpose of obtaining participant consent;

iv) a clear description of the intervention and observation to be conducted; and

v) a sample size adequate to demonstrate clinically and statistically significant effects;

(e) it has access to adequate expertise or advice to consider the safety of the drugs, medical devices or other intervention under investigation; and requirements of the TGA in relation to unregistered drugs and devices, particularly the Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) schemes, where relevant.

12.3. An HREC, before granting approval to a clinical trial, must be satisfied that the protocol conforms to:

(a) this Statement;

(b) the World Medical Association *Declaration of Helsinki*;

(c) where relevant, the CPMP/ICH *Note for Guidance on Good Clinical Practice* (CPMP/ICH-135/95) and the ISO 14155 *Clinical Investigation of Medical Devices* and the requirements of the TGA; and

(d) any requirements of relevant Commonwealth or State/Territory laws.

12.4. The use of a placebo alone or the incorporation of a non-treatment control group is ethically unacceptable in a controlled trial where:

(a) other available treatment has already been clearly shown to be effective; and

(b) there is risk of significant harm in the absence of treatment. If there is genuine uncertainty about the net clinical benefit of treatment, a placebo controlled trial or a trial with a no-treatment arm may be considered.

12.5. A researcher must inform an HREC of any business or other similar association which may exist between a researcher and the supplier of a drug or surgical or other device to be used in the trial.

12.6. An HREC must examine those aspects of the budgets of clinical trials which raise ethical issues, including capitation fees, payments to researchers, institutions or organisations involved in the research, current and consequential institutional or organisational costs and costs which may be incurred by participants. It should be satisfied that:

(a) payment in money or kind would not cause researchers to apply pressure to individuals so as to obtain their consent to participate;

(b) payment in money or kind could not influence the findings of the research;

(c) there will be disclosure to the research participants of relevant aspects of those budgets; and

(d) funding is sufficient to conduct and complete the trial so that participants are not disadvantaged by premature cessation.

12.7. An HREC must be satisfied, before approving a clinical trial, that arrangements exist to ensure adequate compensation to participants for any injury suffered as a result of participation in the trial.

12.8. An institution or organisation and its HREC must require the researcher:

(a) to conduct the trial in compliance with the approved protocol;

(b) to provide reports of the progress of the trial to the HREC at a frequency directed by the HREC that is related to the degree of risk to participants, but at least annually;

(c) to inform the HREC of, and seek its approval of, amendments to the protocol including any:

i) proposed or undertaken in order to eliminate immediate hazards to participants;

ii) that may increase the risks to participants; or

iii) that significantly affect the conduct of the trial;

(d) to inform the HREC and the TGA of all serious or unexpected adverse events that occur during the trial and may affect the conduct of the trial or the safety of the participants or their willingness to continue participation in the trial;

(e) to inform the HREC as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the trial or which may indicate the need for amendments to the trial protocol;

(f) to inform the HREC, giving reasons, if the trial is discontinued before the expected date of completion; and

(g) in relation to trials with implantable medical devices, to confirm the existence of or establish a system for tracking the participant, with consent, for the lifetime of the device, and to report any device incidents to the TGA.

12.9. The institution or organisation and its HREC must determine the type and frequency of review appropriate to the drug or device being investigated and to the degree of risk to participants provided that the review occurs at least once a year.

12.10. It may be unethical for a researcher to continue a trial if:

(a) there are or have been substantial deviations from the trial protocol;

(b) side effects of unexpected type, severity, or frequency are encountered; or

(c) as the trial progresses, one of several treatments or procedures being compared proves to be so much better, or worse, than other(s) that continuation of the trial would disadvantage some of the participants.

12.11. In a clinical trial, data must be accurately recorded in a durable and appropriately referenced form and:

(a) data management should comply with relevant privacy requirements, including the Standards Australia *Personal Privacy Protection in Health Care Information Systems* (AS4400-1995);

(b) if data are of a confidential nature, confidentiality must be observed;

(c) data and records must be preserved for such periods and in such manner as prescribed by laws of the Commonwealth, the relevant State or Territory or national policies or guidelines; and

(d) where materials of biological origin are being used in a trial, records should be preserved for such periods as will enable participants to be traced in the event that evidence of late or long-term effects emerge.

12.12. In trials of therapeutic goods, including pharmaceuticals and biological substances the HREC must follow the requirements of the TGA and the *CPMP/ICH Note for Guidance on Good Clinical Practice* (CPMP/ICH-135/ 95).

12.13. In medical device trials, the HREC and the researcher must follow the requirements of the TGA (*Australian Device Requirement Version 4, DR4, May 1998*) and the *ISO 14155 Clinical Investigation of Medical Devices on Human Subjects*.

Appendix 5: RELEVANT AUSTRALIAN AND NEW ZEALAND LEGISLATION

Australia:

Legislation Extract No. 1: Therapeutic Goods Act 1989 - Section 18:

THERAPEUTIC GOODS ACT 1989 - SECTION 18:

Exempt goods
(1) The regulations may, subject to such conditions (if any) as are specified in the regulations, exempt:
(a) all therapeutic goods, except those included in a class of goods prescribed for the purposes of this paragraph; or
(b) specified therapeutic goods; or
(c) a specified class of therapeutic goods;
from the operation of this Part (except section 31A and sections 31C to 31F).
(2) An exemption in terms of paragraph (1)(a) has effect only in relation to such classes of persons as are prescribed for the purposes of this subsection.
(3) Where the regulations revoke an exemption, the revocation takes effect on the day, not being earlier than 28 days after the day on which the regulations are made, specified in the regulations.

Legislation Extract No. 2: Therapeutic Goods Act 1989 - Section 19:

THERAPEUTIC GOODS ACT 1989 - SECTION 19:

Exemptions for special and experimental uses
(1) The Secretary may, by notice in writing, grant an approval to a person for the importation into, or the exportation from, Australia or the supply in Australia of specified therapeutic goods that are not registered goods, listed goods or exempt goods:
(a) for use in the treatment of another person; or
(b) for use solely for experimental purposes in humans;
and such an approval may be given subject to such conditions as are specified in the notice of approval.
…
(5) The Secretary may, in writing, authorise a specified medical practitioner to supply:
(a) specified therapeutic goods for use in the treatment of humans; or
(b) a specified class of such goods;
to the class or classes of recipients specified in the authority.
(5A) An authority may be given subject to the conditions (if any) specified in the authority.
(5B) The Secretary may impose conditions (or further conditions) on an authority given to a person under subsection (5) by giving to the person written notice of the conditions (or further conditions).
(6) An authority under subsection (5) may only be given:

(a) to a medical practitioner included in a class of medical practitioners prescribed by the regulations for the purposes of this paragraph; and

(aa) to a medical practitioner who has the approval of an ethics committee to supply the specified therapeutic goods or the specified class of such goods; and

(b) in relation to a class or classes of recipients prescribed by the regulations for the purposes of this paragraph.

Paragraph (aa) does not apply in the exceptional circumstances (if any) prescribed by the regulations for the purposes of this subsection.

(7) The regulations may prescribe the circumstances in which therapeutic goods may be supplied under an authority under subsection (5).

(8) The giving of an authority under subsection (5) does not render the Commonwealth, the Secretary or a delegate of the Secretary liable to a person in respect of loss, damage or injury of any kind suffered by the person as a result of, or arising out of, the use of therapeutic goods by that person or another person.

(9) In this section, *medical practitioner* means a person who is registered, in a State or internal Territory, as a medical practitioner.

Legislation Extract No. 3: Therapeutic Goods Act 1989 - Section 31A:

THERAPEUTIC GOODS ACT 1989 - SECTION 31A(1):

Secretary may require information etc. about goods exempt under section 18 Exempt goods for use for experimental purposes in humans

(1) If therapeutic goods are exempt under subsection 18(1) from the operation of this Part (except this section and sections 31C to 31F) to allow for their use for experimental purposes in humans, the Secretary may give the sponsor of the goods a written notice requiring the sponsor to give to the Secretary specified information or documents relating to one or more of the following:

(a) the supply of the goods;

(b) the handling of the goods;

(c) the monitoring of the supply of the goods;

(d) the results of the supply of the goods;

(e) any other matter prescribed by the regulations for the purposes of this paragraph in relation to goods of that kind.

Statement by medical practitioner about medicine

(2) If a medicine is exempt under subsection 18(1) from the operation of this Part (except this section and sections 31C to 31F) because a medical practitioner has signed a statement in accordance with regulation 12A of the *Therapeutic Goods Regulations 1990*, the Secretary may give the medical practitioner a written notice requiring the medical practitioner to give to the Secretary specified information or documents relating to one or more of the following:

(a) the condition of the person to whom the medicine is to be given or is given;

(b) the supply of the medicine;

(c) the handling of the medicine;

(d) the monitoring of the supply of the medicine;

(e) the results of the supply of the medicine;

(f) any other matter prescribed by the regulations for the purposes of this paragraph in relation to medicines of that kind.

Legislation Extract No. 4: Therapeutic Goods Act 1989 - Section 31B:

THERAPEUTIC ***GOODS ACT 1989 - SECTION 31B:***

Secretary may require information relating to approvals and authorities under section 19

(1) The Secretary may give to a person who is granted an approval under subsection 19(1) in relation to specified therapeutic goods a written notice requiring the person to give to the Secretary specified information or documents relating to one or more of the following:

(a) the supply of the goods;

(b) the handling of the goods;

(c) the monitoring of the supply of the goods;

(d) the results of the supply of the goods;

(e) any other matter prescribed by the regulations for the purposes of this paragraph in relation to goods of that kind.

Approval under subsection 19(1)—use by another person

(2) The Secretary may give to a person using specified therapeutic goods that are the subject of an approval granted to someone else under paragraph 19(1)(b) a written notice requiring the person to give to the Secretary specified information or documents relating to either of both of the following:

(a) the use of the goods;

(b) any other matter prescribed by the regulations for the purposes of this paragraph in relation to goods of that kind.

Authority under subsection 19(5)

(3) The Secretary may give to a person who is granted an authority under subsection 19(5) in relation to specified therapeutic goods, or a specified class of therapeutic goods, a written notice requiring the person to give to the Secretary specified information or documents relating to one or more of the following:

(a) the supply of the goods;

(b) the handling of the goods;

(c) the monitoring of the supply of the goods;

(d) the results of the supply of the goods;

(e) any other matter prescribed by the regulations for the purposes of this paragraph in relation to goods of that kind.

Legislation Extract No. 5: Therapeutic Goods Regulations 1990 - Regulation 12:

THERAPEUTIC GOODS REGULATIONS 1990 - REGULATION 12:

Exempt goods
(1) For the purposes of subsection 18 (1) of the Act, the therapeutic goods or classes of therapeutic goods specified in Schedule 5 are exempt from the operation of Part 3-2 of the Act (except sections 30EA, 31A and 31C to 31F).

Legislation Extract No. 6: Therapeutic Goods Regulations 1990 - Regulation 12A:

THERAPEUTIC GOODS REGULATIONS 1990 - REGULATION 12A:

Unapproved medicines - exemption in life-threatening cases
(1) For the purposes of subsection 18 (1) of the Act, all medicines, other than medicines of a class or kind listed in the 9th Schedule to the Poisons Standard, as in force from time to time, are exempted, subject to subregulation (2), from the operation of Part 3-2 of the Act (except section 31A and sections 31C to 31F).
(2) The exemption of a medicine is subject to the following conditions:
(a) the medicine is to be given to a person who satisfies the following criteria:
(i) the person is a Category A patient (as defined in subregulation (5)); and
(ii) the person, or the guardian of the person, has given informed consent (as defined in subregulation (5)) to the medicine being given to the person; and
(iii) the medical practitioner by whom, or at whose direction, the medicine is to be given to the person has signed a statement in relation to the person in the form approved by the Secretary for the purposes of this paragraph; and
(b) the medicine is dispensed on the prescription of a medical practitioner who has prescribed the medicine in accordance with good medical practice.
(3) A person who signs a statement referred to in subparagraph (2) (a) (iii) must send a copy of the statement to the Secretary within 4 weeks of signing it.
Penalty: 10 penalty units.
(3A) An offence under subregulation (3) is an offence of strict liability.
Note For *strict liability*, see section 6.1 of the *Criminal Code*.
(4) This regulation does not affect the operation of regulation 12.
(5) In this regulation:
Category A patient means a person who is seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.
informed consent, in relation to treatment or proposed treatment, means consent freely given by a person on the basis of information concerning the potential risks and benefits of the treatment that was sufficient information to allow the person to make an informed decision whether to consent to the treatment.

Legislation Extract No. 7: Therapeutic Goods Regulations 1990 - Regulation 12B:

THERAPEUTIC GOODS REGULATIONS 1990 - REGULATION 12B:

Exemptions for special and experimental uses
(1) For the purposes of paragraph 19 (6) (a) of the Act, in relation to medicines, medical practitioners engaged in clinical practice in or outside a hospital are a prescribed class of medical practitioners.
(1A) For the purposes of subsection 19 (6) of the Act, in relation to medicines, paragraph 19 (6) (aa) does not apply to a medical practitioner engaged in clinical practice outside a hospital if the medical practitioner:
(a) has demonstrated that, in relation to the proposed supply of the medicines, the medical practitioner does not have access to an ethics committee that could approve the supply; and
(b) has received an endorsement, from a specialist college with established expertise relevant to the use of the medicines, to supply the medicines.
(2) The class of recipients prescribed for the purposes of paragraph 19 (6) (b) of the Act is the class of recipients consisting of persons each of whom is suffering from a life-threatening, or otherwise serious, illness or condition.
(3) For the purposes of subsection 19 (7) of the Act, the prescribed circumstances in which a medicine, or a class of medicines, may be supplied in accordance with an authority under subsection 19 (5) of the Act are that the supplier of the medicine or class of medicines complies with the treatment directions (if any) mentioned in the authority for the medicine or class of medicine.
(4) For the purposes of subsection 19 (7) of the Act, the prescribed circumstances in which a therapeutic device, or a class of therapeutic devices, may be supplied in accordance with an authority under subsection 19 (5) of the Act are:
(a) that, in each case, the medical practitioner authorised under subsection 19 (5) of the Act:
(i) is a specialist engaged in clinical practice at a hospital; and
(ii) is endorsed by the relevant ethics committee of the hospital; and
(b) that the authority states the particular therapeutic intervention, or class of therapeutic intervention, for which the medical practitioner may supply the therapeutic device or class of therapeutic devices.

Legislation Extract No. 8: Therapeutic Goods Regulations 1990 - Regulation 12AA – 12AD:

THERAPEUTIC ***GOODS REGULATIONS 1990 - REGULATION 12AA:***

Applications for special and experimental uses
Without limiting the information that may be required by the Secretary under subsection 19 (2) of the Act, that information may include, in relation to therapeutic goods the subject of an application under subsection 19 (1) of the Act for a use described in paragraph 19 (1) (b) of the Act:
(a) the names of the members of the ethics committee that has given approval for each proposed clinical trial of the goods and that will have responsibility for monitoring the conduct of each trial; and

(b) the name of, and the contact details for, the principal investigator for each trial; and
(c) the name of the person who will be in charge of the trial site (or each trial site, if the trial is to be conducted at more than 1 site), unless that person is the principal investigator; and
(d) information about whether or not any conditions specified by the committee have been met.

THERAPEUTIC GOODS REGULATIONS 1990 - REGULATION 12AB:

Goods imported etc for experimental uses
(1) For subsection 19 (1A) of the Act, this regulation specifies conditions attaching to an approval for the importation or supply of therapeutic goods for use solely for experimental purposes in humans.
(2) Before any clinical trials proposed to be undertaken in relation to the goods are started, the National Manager, Therapeutic Goods Administration, must receive from the person to whom the approval is granted, and the principal investigator for each trial site:
(a) a written assurance that clinical trials will be conducted in accordance with the Guidelines for Good Clinical Practice (the *Practice Guidelines*), as in force from time to time, published jointly by the International Conference on Harmonisation on Technical Requirements for Registration of Pharmaceuticals for Human Use and the Committee for Medicinal Products; and
(b) a written undertaking:
(i) to comply with requests by an authorised officer, whether made before or after the start of the trial, to give information about the conduct of the trial; and
(ii) allow an authorised officer to do the things mentioned in regulation 12AC.

THERAPEUTIC GOODS REGULATIONS 1990 - REGULATION 12AC

Powers of authorised officers in relation to goods imported etc for experimental uses
(1) An authorised officer may, in relation to a clinical trial mentioned in regulation 12AB:
(a) enter the site of the trial; and
(b) search the site and any thing on the site; and
(c) inspect, examine, take measurements of, or conduct tests on (including by the taking of samples), any thing on the site that relates to the trial; and
(d) take photographs, make video recordings or make sketches of the site or any thing on the site; and
(e) inspect any book, record or document on the site that relates to the trial; and
(f) request the principal investigator to:
(i) answer any questions put by the authorised officer; and
(ii) produce any book, record or document requested by the authorised officer.
(2) An authorised officer is not entitled to do a thing mentioned in subregulation (1) if:

(a) the principal investigator, or any other person present at the site concerned and in apparent control, requests the authorised officer to produce his or her identity card for inspection; and

(b) the authorised officer fails to comply with the request.

Note For identity cards, see section 52 of the Act.

(3) The principal investigator, or any other person present at the site and in apparent control, is entitled to observe a search conducted under paragraph (1) (b), but must not impede the search.

(4) Subregulation (3) does not prevent 2 or more areas of the site being searched at the same time.

THERAPEUTIC GOODS REGULATIONS 1990 - REGULATION 12AD:

Use of goods for experimental purposes — specified conditions

For subsection 19 (4A) of the Act, the following conditions are specified:

(a) the use of therapeutic goods in a clinical trial must be in accordance with the Practice Guidelines;

(b) the use must comply with a procedural protocol approved by the ethics committee that has the function of monitoring the conduct of the trial at each trial site;

(c) the use must be in accordance with the ethical standards set out in the National Statement on Ethical Conduct in Research Involving Humans, as in force from time to time, published by the National Health and Medical Research Council;

(d) the use must cease if the ethics committee mentioned in paragraph (b) informs the principal investigator that the use is inconsistent with:

(i) the protocol mentioned in paragraph (b); or

(ii) any condition subject to which approval for the use was given.

Legislation Extract No. 9: Therapeutic Goods Regulations 1990 - Schedule 5:

THERAPEUTIC GOODS REGULATIONS 1990 - SCHEDULE 5:

Therapeutic goods exempt from the operation of Part 3-2 of the Act (subregulation 12 (1))

therapeutic goods that are imported for use in the treatment of the importer or the importer's immediate family where:

(a) the goods do not contain a substance the importation of which is prohibited under the *Customs Act 1901*; and

(b) in the case of injections that contain material of human or animal origin - the goods are the subject of an approval under section 19 of the Act, or are insulin preparations; and

(c) in the case of other medicines:

(i) the quantity imported in one importation is not more than 3 months' supply at the maximum dose recommended by the manufacturer; and

(ii) the total quantity of the medicine imported for use in the treatment of the importer or the importer's immediate family in the period of 12 months ending on the day on which the latest importation occurs does not exceed 15 months' supply of the medicine at the maximum dose recommended by the manufacturer; or the medicines have been approved, or are included in a class of medicines that has

been approved, under regulation 5 of the Customs (Prohibited Imports) Regulations for importation into Australia; and

(d) if the goods are subject to Schedule 4 or Schedule 8 to the Poisons Standard — the goods are the subject of a written authority issued by a medical practitioner registered under a law of a State or Territory, except where the goods are carried by the importer as a passenger on a ship or aeroplane

Legislation Extract No. 10: Therapeutic Goods Regulations 1990 - Schedule 5A (Paragraph 3):

THERAPEUTIC GOODS REGULATIONS 1990 - SCHEDULE 5A (Paragraph 3)

Therapeutic goods exempt from the operation of Part 3-2 of the Act subject to conditions (sub-regulation 12 (1A))

3 Therapeutic goods used solely for experimental purposes in humans

(a) before starting to use the goods, the sponsor must notify the Secretary:

(i) in a form approved by the Secretary; and

(ii) in accordance with the requirements (if any) determined by the Secretary for the form of notification;

that the sponsor intends to sponsor a clinical trial using specified goods; and

(b) the notification must be accompanied by the relevant notification fee referred to in paragraph 14 or 14A of Schedule 9; and

(c) the approval of the goods for this purpose must be given by the sponsor (if the sponsor is conducting the trial), or by the body or organisation conducting the trial for the sponsor, having regard to the advice of the ethics committee that has, or will assume, responsibility for monitoring the conduct of the trial; and

(d) the terms of the approval by the sponsor, body or organisation referred to in paragraph (c) must be no less restrictive than the terms advised by the ethics committee; and

(e) the Secretary must not, at any time:

(i) have become aware that to conduct or continue the trial would be contrary to the public interest; and

(ii) have directed that the trial not be conducted, or be stopped; and

(f) the sponsor (if the sponsor is conducting the trial), or the body or organisation conducting the trial for the sponsor, must not receive, or have received, advice from the ethics committee that is inconsistent with the continuation of the trial; and

(g) the conditions set out in regulation 12AD must be complied with, as if that regulation applied to a person using therapeutic goods under this item

New Zealand:

Legislation Extract No. 11: Medicines Act 1981 – Section 29:

MEDICINES ACT 1981 - SECTION 29

Exemption for medicine required by medical practitioner

(1) Neither section 20 nor section 24 of this Act shall prevent—

(a) The supply by any person to any medical practitioner, on the medical practitioner's request, of any medicine required by that medical practitioner for the treatment of a particular patient currently under that medical practitioner's care; or

(b) The administration by any medical practitioner of any such medicine to any such patient.

(2) Every person who, for the purposes of subsection (1) of this section, sells or supplies to any practitioner any medicine that is a new medicine by virtue of paragraph (a) of the definition of the term ``new medicine'' in section 3(3) of this Act before the consent of the Minister to the distribution of that medicine has been notified in the *Gazette* shall, as soon as practicable after the end of every month in which he has so sold or supplied any such medicine, report that sale or supply to the Director-General in writing, naming the practitioner and patient, describing the medicine, and identifying the occasion when and the place where the medicine was so sold or supplied.

(3) Without limiting section 48 of this Act, if any person fails to comply with subsection (2) of this section, the Minister may, in the manner prescribed in that section but without complying with subsection (2) of that section, prohibit that person from selling and supplying any new medicine to which subsection (2) of this section applies before the consent of the Minister to the distribution of that medicine has been notified in the *Gazette*.

Legislation Extract No. 12: Medicines Act 1981 - Section 30:

MEDICINES ACT 1981 - SECTION 30

Exemption for clinical trial

(1) Notwithstanding section 20 or section 24 of this Act, but subject to the succeeding provisions of this section, the importer or manufacturer in New Zealand of any medicine may distribute it for the sole purpose of obtaining clinical and scientific information with respect to its safety and efficacy, if the clinical trial, and the persons (in this section called the investigators) who will conduct the trial, have been approved by the Director-General on the recommendation of the Health Research Council of New Zealand.

(2) An application for the approval of the Director-General in respect of this section shall be made by the importer, manufacturer, or packer, or the intending manufacturer, packer, seller, or supplier, in New Zealand of the medicine, and shall

(a) Be made in the prescribed manner (if any); and

(b) Be addressed to the Director-General; and

(c) Set out the true name of the applicant; and

(ca) Be accompanied by the prescribed fee; and

(d) State, or be accompanied by a statement of, the particulars set out in subsection (3) of this section.

(3) The particulars required by subsection (2)(d) of this section are the following:

(a) The nature of the medicine, its identifying name or mark, and its chemical formula:

(b) The purpose of the trial:

(c) The names and qualifications of the investigators who will conduct the trial, and their curricula vitae:

(d) A written consent to nomination from each of the investigators:

(e) A copy of the information supplied to the investigators, particularly in relation to the safe use of the medicine:

(f) A protocol of the trial, setting out

(i) The number of patients to be involved; and

(ii) The form that the trial is to take, and the nature of the records to be kept; and

(iii) The persons or classes of persons (if any) who are to be specially excluded from the trial; and

(iv) Any special measures proposed to be taken to ensure the safety of the patients:

(g) The names and addresses of the institutions or laboratories where the medicines will be used by approved persons, and a description of the facilities that will be available to those persons.

(4) The Director-General shall determine every application for his approval under this section within 45 days after the receipt of the application, and shall notify the applicant of his decision and (where he declines the application) the reasons for his decision.

(5) At any time after a clinical trial has been approved by the Director-General, the applicant may apply to the Director-General for the approval of an investigator, notwithstanding that the name of that person did not appear in the application for approval of the clinical trial; and paragraphs (a) to (c) of subsection (2), and paragraphs (c), (d), and (g) of subsection (3), of this section shall apply in respect of every such application.

(6) The Director-General may at any time, by notice in writing given to an applicant, require the applicant to supply such further information and particulars as he thinks fit relating to a clinical trial or to the identity and qualifications of an investigator.

(7) The distribution of any medicine under this section shall be subject to the following conditions:

(a) The Director-General shall be informed, before the medicine is so distributed, of the identifying name or mark by which it may be recognised:

(b) Every label on every package or container of the medicine shall bear the words ``To be used by qualified investigators only'':

(c) The importer or manufacturer shall, before so distributing the medicine, take all reasonable steps to ensure that every person to whom it is supplied is approved under this section as a person qualified to carry out, and has available the necessary facilities for, the trial to be conducted by him, and the medicine shall be used solely by that person or under his direction for the purposes of the trial:

(d) The importer or manufacturer shall

(i) Keep complete and accurate records of all quantities of the medicine supplied under this section:

(ii) Keep the Director-General informed of the progress of the trial by six-monthly reports:

(iii) Supply to the Director-General a copy of the results of the trial on its completion.

(8) The Director-General may at any time, by notice in writing to the applicant, revoke or suspend his approval of a clinical trial.

Appendix 6: Reference List

1. *where this includes medicines and medical devices*
2. *See Legislation Extract No. 1 in Appendix 5.*
3. *See Legislation Extract No. 3 in Appendix 5.*
4. *See Legislation Extract No. 5 in Appendix 5.*
5. *See Legislation Extract No. 10 in Appendix 5.*
6. *See Legislation Extract No. 2 in Appendix 5.*
7. *See Legislation Extract No. 4 in Appendix 5.*
8. *See Legislation Extract No. 8 in Appendix 5.*
9. *See Appendix 4: Extract from the "National Statement On Ethical Conduct In Research Involving Humans".*
10. *or 30 working days for Phase I*
11. *(n = 14 of top 20 international companies)*
12. *See Legislation Extract No. 1 in Appendix 5.*
13. *See Legislation Extract No. 3 in Appendix 5.*
14. *See Legislation Extract No. 6 in Appendix 5.*
15. *See Legislation Extract No. 2 in Appendix 5.*
16. *See Legislation Extract No. 4 in Appendix 5.*
17. *See Legislation Extract No. 2 in Appendix 5.*
18. *See Legislation Extract No. 4 in Appendix 5.*
19. *See Legislation Extract No. 7 in Appendix 5.*
20. *See Legislation Extract No. 1 in Appendix 5.*
21. *See Legislation Extract No. 5 in Appendix 5.*
22. *See Legislation Extract No. 9 in Appendix 5.*
23. *Access to Unapproved Therapeutic Goods – the Special Access Scheme (SAS) May 2001*
24. *See Appendix 4: Extract from the "National Statement On Ethical Conduct In Research Involving Humans".*
25. *See Legislation Extract No. 12 in Appendix 5.*
26. *See Legislation Extract No. 11 in Appendix 5.*
27. *The UK Regulatory Agency, the MHRA was formed by the merger of the two previously existing agencies: the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA).*
28. *In the UK and EU regulations "medicinal product" is the term used for medicines and does not include medical devices.*
29. *Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.17.*
30. *Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.17.*
31. *Submission: Deborah Monk, Medicines Australia.*
32. *Submission: Deborah Monk, Medicines Australia.*
33. *Submission: Deborah Monk, Medicines Australia.*
34. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
35. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
36. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
37. *Submission: Martyn Goddard, Australian Consumers' Association.*
38. *Ryle G. Playing patients in the fast lane. Sydney Morning Herald, 13/02/2001*

39. *Therapeutic Goods Administration. Medicines regulation and the TGA. Department of Health & Aged Care, Canberra, December 1999..*
40. *Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.*
41. *Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.*
42. *Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.*
43. *Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.*
44. *Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.*
45. *Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.*
46. *Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.*
47. *Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.*
48. *Submission: Christopher Reid, Baker Heart Research Institute.*
49. *Submission: Christopher Reid, Baker Heart Research Institute.*
50. *Submission: Christopher Reid, Baker Heart Research Institute.*
51. *Submission: Christopher Reid, Baker Heart Research Institute.*
52. *Submission: Christopher Reid, Baker Heart Research Institute.*
53. *Submission: Christopher Reid, Baker Heart Research Institute.*
54. *Submission: Christopher Reid, Baker Heart Research Institute.*
55. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
56. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
57. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
58. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
59. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
60. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
61. *Submission: Dr Mark Nelson et al, Department of Epidemiology and Preventive Medicine, Monash University.*
62. *Submission: Dr Mark Nelson et al, Department of Epidemiology and Preventive Medicine, Monash University.*
63. *Submission: Dr Mark Nelson et al, Department of Epidemiology and Preventive Medicine, Monash University.*
64. *Submission: Dr Mark Nelson et al, Department of Epidemiology and Preventive Medicine, Monash University.*
65. *Submission: Dr Mark Nelson et al, Department of Epidemiology and Preventive Medicine, Monash University.*
66. *See Appendix 4: Extracts from the "National Statement On Ethical Conduct In Research Involving Humans".*
67. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
68. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
69. *See Appendix 4: Extracts from the "National Statement On Ethical Conduct In Research Involving Humans".*
70. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
71. *See Appendix 4: Extracts from the "National Statement On Ethical Conduct In Research Involving Humans", paragraph 12.9.*
72. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*

73. *Appendix 4: Extracts from the "National Statement On Ethical Conduct In Research Involving Humans", paragraph 12.8d*
74. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
75. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
76. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
77. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
78. *Submission: Quintiles Pty Ltd.*
79. *Submission: Deborah Monk, Medicines Australia.*
80. *Submission: Quintiles Pty Ltd.*
81. *Submission: Quintiles Pty Ltd.*
82. *Submission: Quintiles Pty Ltd.*
83. *Submission: Felicity Cassidy Powell: Novo Nordisk Pharmaceuticals Pty Ltd.*
84. *Submission: Felicity Cassidy Powell: Novo Nordisk Pharmaceuticals Pty Ltd.*
85. *Submission: Felicity Cassidy Powell: Novo Nordisk Pharmaceuticals Pty Ltd.*
86. *Submission: Dr Winston Liauw: Clinical Trials Centre, St Vincent's Hospital.*
87. *Submission: Dr Winston Liauw: Clinical Trials Centre, St Vincent's Hospital.*
88. *Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.*
89. *Report of the review of the role and functioning of Institutional Ethics Committees. Report to the Minister for Health and Family Services. Canberra: AGPS, 1996. P. 25.*
90. *Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.17.*
91. *Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.17.*
92. *Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.17.*
93. *Submission: GlaxoSmithKline Australia Pty Ltd.*
94. *Submission: GlaxoSmithKline Australia Pty Ltd.*
95. *Submission: GlaxoSmithKline Australia Pty Ltd.*
96. *Submission: GlaxoSmithKline Australia Pty Ltd.*
97. *Submission: GlaxoSmithKline Australia Pty Ltd.*
98. *Submission: GlaxoSmithKline Australia Pty Ltd.*
99. *Submission: GlaxoSmithKline Australia Pty Ltd.*
100. *Submission: GlaxoSmithKline Australia Pty Ltd.*
101. *Submission: GlaxoSmithKline Australia Pty Ltd.*
102. *Submission: GlaxoSmithKline Australia Pty Ltd.*
103. *Submission: GlaxoSmithKline Australia Pty Ltd.*
104. *Submission: GlaxoSmithKline Australia Pty Ltd.*
105. *Submission: GlaxoSmithKline Australia Pty Ltd.*
106. *Submission: GlaxoSmithKline Australia Pty Ltd.*
107. *Submission: GlaxoSmithKline Australia Pty Ltd.*
108. *Submission: GlaxoSmithKline Australia Pty Ltd.*
109. *Submission: GlaxoSmithKline Australia Pty Ltd.*
110. *Submission: GlaxoSmithKline Australia Pty Ltd.*
111. *Submission: GlaxoSmithKline Australia Pty Ltd.*
112. *Submission: Deborah Monk, Medicines Australia.*
113. *Submission: Deborah Monk, Medicines Australia.*
114. *Submission: Deborah Monk, Medicines Australia.*
115. *Submission: Deborah Monk, Medicines Australia.*
116. *Submission: Deborah Monk, Medicines Australia.*
117. *Submission: Deborah Monk, Medicines Australia.*

118. Submission: Deborah Monk, Medicines Australia.
119. Roberts et al MJA 2004; 180 (3): 139.
120. Taken from Roberts et al MJA 2004; 180 (3): 139.
121. Number appears to be an error, as it does not match narrative in full letter.
122. Submission: Quintiles Pty Ltd.
123. Submission: Quintiles Pty Ltd.
124. Submission: Quintiles Pty Ltd.
125. Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.
126. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
127. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
128. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
129. Submission: Dr Christopher Reid, Baker Heart Research Institute.
130. Submission: Dr Christopher Reid, Baker Heart Research Institute.
131. Submission: Dr Christopher Reid, Baker Heart Research Institute.
132. Submission: Martyn Goddard, Australian Consumers' Association.
133. Submission: Martyn Goddard, Australian Consumers' Association.
134. Submission: Martyn Goddard, Australian Consumers' Association.
135. Submission: Martyn Goddard, Australian Consumers' Association.
136. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
137. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
138. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
139. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
140. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
141. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
142. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
143. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
144. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
145. Submission: Jean-Luc Picker, Servier Laboratories (Australia) Pty Ltd.
146. Submission: Jean-Luc Picker, Servier Laboratories (Australia) Pty Ltd.
147. Submission: Jean-Luc Picker, Servier Laboratories (Australia) Pty Ltd.
148. Submission: Jean-Luc Picker, Servier Laboratories (Australia) Pty Ltd.
149. Submission: Dr Mark Nelson et al, Department of Epidemiology and Preventive Medicine, Monash University.
150. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
151. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
152. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
153. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.

154. Submission: Paris Brooke, AusBiotech Ltd.
155. Submission: Paris Brooke, AusBiotech Ltd.
156. Submission: Paris Brooke, AusBiotech Ltd.
157. Submission: Paris Brooke, AusBiotech Ltd.
158. Submission: Paris Brooke, AusBiotech Ltd.
159. Submission: Prof Garry Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
160. Submission: Quintiles Pty Ltd.
161. Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.
162. Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.
163. Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.
164. Report of the Review of the Role and Functioning of Institutional Ethics Committees. Report to the Minister for Health and Family Services. Canberra: AGPS, 1996. P. 29.
165. Submission: Deborah Monk, Medicines Australia.
166. Submission: Kay Hynes, Society of Hospital Pharmacists of Australia.
167. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
168. Report of the Review of the Role and Functioning of Institutional Ethics Committees. Report to the Minister for Health and Family Services. Canberra: AGPS, 1996. P. 29.
169. Report of the Review of the Role and Functioning of Institutional Ethics Committees. Report to the Minister for Health and Family Services. Canberra: AGPS, 1996. P. 29.
170. Report of the Review of the Role and Functioning of Institutional Ethics Committees to the Minister for Health and Family Services. Canberra: AGPS, 1996.
171. Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.
172. Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.
173. Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.
174. Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.
175. Submission: Kay Hynes, Society of Hospital Pharmacists of Australia.
176. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
177. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
178. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
179. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
180. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
181. Facilitated Workshops conducted on Tuesday 11 November 2003 (in Sydney) and on Thursday 13 November 2003 (in Melbourne). See Chapter 2.
182. Submission: Carmel Edwards, Health Ethics Branch, NSW Department of Health.
183. Submission: Kay Hynes, Society of Hospital Pharmacists of Australia.
184. Submission: Quintiles Pty Ltd.
185. Submission: Quintiles Pty Ltd.
186. Submission: Martyn Goddard, Australian Consumers' Association.
187. Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.
188. Submission: Felicity Cassidy Powell, Novo Nordisk Pharmaceuticals Pty Ltd.
189. Submission: Dr Winston Liauw, Clinical Trials Centre, St Vincent's Hospital.
190. Submission: Deborah Monk, Medicines Australia.
191. Submission: Deborah Monk, Medicines Australia.
192. Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.
193. Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.
194. Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.
195. Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.

196. *Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.*
197. *Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.*
198. *Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.*
199. *Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.*
200. *Letter: Dr John Simes to Mr Terry Slater, 23 December 2002.*
201. *Contribution: Health Research Council of New Zealand Te Kaunihera Rangahau Hauora o Aotearoa*
202. *Contribution: Health Research Council of New Zealand Te Kaunihera Rangahau Hauora o Aotearoa*
203. *Contribution: Health Research Council of New Zealand Te Kaunihera Rangahau Hauora o Aotearoa*
204. *Submission: GlaxoSmithKline Australia Pty Ltd.*
205. *Submission: Christopher Reid, Baker Heart Research Institute.*
206. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
207. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
208. *Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.*
209. *Submission: National Association of People Living with HIV/AIDS (NAPWA).*
210. *Submission: National Association of People Living with HIV/AIDS (NAPWA).*
211. *Submission: National Association of People Living with HIV/AIDS (NAPWA).*
212. *Submission: National Association of People Living with HIV/AIDS (NAPWA).*
213. *Submission: National Association of People Living with HIV/AIDS (NAPWA).*
214. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
215. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
216. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
217. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
218. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
219. *Five of the seven cancer cooperative groups are incorporated bodies.*
220. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
221. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
222. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
223. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
224. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
225. *Co-operative Clinical Trials in Cancer – the Need for Increased Capacity: Oceania Health Consulting, January 2002.*
226. *Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).*

227. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
228. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
229. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
230. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
231. Private Paper made available to the Review: Co-operative Clinical Trials in Cancer, Prof. John Zalcberg, President of the Oncological Society of Australia.
232. Private Paper made available to the Review: Co-operative Clinical Trials in Cancer, Prof. John Zalcberg, President of the Oncological Society of Australia.
233. Private Paper made available to the Review: Co-operative Clinical Trials in Cancer, Prof. John Zalcberg, President of the Oncological Society of Australia.
234. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
235. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
236. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
237. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
238. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
239. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
240. Minutes of Discussion, Victorian Cooperative Oncology Group (VCOG) Forum, 29 July 2003.
241. Submission: Paris Brooke, AusBiotech Ltd.
242. Submission: Paris Brooke, AusBiotech Ltd.
243. Submission: Paris Brooke, AusBiotech Ltd.
244. Submission: Jeremy Kenner, Peter MacCallum Cancer Institute.
245. Submission: Jeremy Kenner, Peter MacCallum Cancer Institute.
246. Submission: Jeremy Kenner, Peter MacCallum Cancer Institute.
247. Submission: Jeremy Kenner, Peter MacCallum Cancer Institute.
248. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
249. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
250. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
251. Submission: Cancer Trials Australia (formerly the Centre for Developmental Cancer Therapeutics Inc).
252. Submission: Prof Gary Jennings, Centre for Clinical Studies, Baker Heart Research Institute.
253. Submission: Dr Jacqueline Waterkeyn et al, Clinical Trials Victoria.
254. Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.18.
255. Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.18.

256. Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.18.
257. Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.18.
258. Anita Kamat (GlaxoSmithKline NZ): Article: "Living in Harmony", Good Clinical Practice Journal, May 2003, p.18.
259. *"National Statement On Ethical Conduct In Research Involving Humans"*. National Health and Medical Research Council. Commonwealth Department of Health and Ageing. Canberra, Australia.
260. *Submission: Deborah Monk, Director, Scientific and Technical Affairs, Medicines Australia. July 2004.*