

Human Research Ethics Committees: Standards for Scientific Review of Clinical Trials

Summary The policy sets out minimum standards for the scientific review of clinical trials by NSW Health Human Research Ethics Committees and changes to the use of the Shared Scientific Assessment Scheme.

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HUMAN RESEARCH ETHICS COMMITTEES: STANDARDS FOR SCIENTIFIC REVIEW OF CLINICAL TRIALS

1. Comprehensive scientific review of clinical trials is a fundamental component of ethical approval under the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Human Research (1997)*.
2. To ensure a level of scientific review that protects the interests of research participants and is practicable, sustainable and of a level appropriate to the risks of the research project being reviewed, minimum standards have been developed for the scientific review of clinical trials (attached). All clinical trials must be scientifically reviewed in accordance with these standards before being approved by a NSW Health Human Research Ethics Committee (HREC).
3. Conduct of scientific review must be evidenced by completion of an Assessment Checklist and Certification of Scientific Review. In general, NSW Health HRECs should rely on their own local arrangements to undertake such scientific review.
4. Where a NSW Health HREC is unable to undertake the scientific review and complete the Assessment Checklist and Certification of Scientific Review through its own local arrangements, it has the following options:
 - Refer the scientific review of the clinical trial to another HREC or scientific review body that can meet the requirements;
 - If the study is a clinical drug trial, refer the scientific review to the Shared Scientific Assessment Scheme (SSAS); or
 - Refer the clinical trial to the Therapeutic Goods Administration (TGA) Clinical Trials Exemption (CTX) Scheme, and complete the relevant sections of the Assessment Checklist and the Certification of Scientific Review using the documentation approved by the TGA together with the scientific expertise available to the HREC. If the HREC is unable to assess the documentation provided by the TGA, it should seek the advice of another HREC that is able to do so.
5. It is the responsibility of each NSW Health HREC to determine which, if any, clinical drug trials it will refer to the SSAS. This might be: all clinical drug trials; a pre-determined subset of clinical drug trials; or studies determined by the HREC on an ad hoc basis as raising complex or unusual issues.
6. The Department may from time to time audit an HREC's scientific review process, including completed Assessment Checklists and Certifications of Scientific Review, to ensure compliance with this policy directive.
7. The model for scientific review of clinical trials, including the template Assessment Checklist and Certification of Scientific Validity is attached.
8. HRECs are required to implement these standards for scientific review of clinical trials from **1 July 2007**.
9. As from 1 July 2007, the Shared Scientific Assessment Committee will only accept trials for review that are submitted under this policy directive.

Robert D McGregor AM
A/Director-General

SCIENTIFIC REVIEW OF CLINICAL TRIALS

MAY 2007

PART 1: BACKGROUND

1.1 Introduction

This model provides standards for the scientific review of clinical trials that are to be approved by NSW Health Human Research Ethics Committees (HRECs), including both lead and non-lead HRECs. It also makes changes to the use of the Shared Scientific Assessment Scheme (SSAS). Compliance with this model is mandatory for all NSW Health HRECs.

1.2 Principles

In issuing a model for scientific review of clinical trials, NSW Health considers the following principles to be important.

- Scientific review of clinical trials is necessary for Human Research Ethics Committees (HRECs) to determine whether a research project is scientifically and statistically valid. This is a requirement of ethical approval under the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct In Human Research* (National Statement).
- There is limited expertise within NSW to undertake scientific review.
- The limited resources available should be used efficiently and effectively, to provide a level of scientific review that protects the interests of research participants and is practicable, sustainable, and of a level appropriate to the risks of the research project being reviewed.

1.3 Summary of model of scientific review of clinical trials

The model of scientific review of clinical trials involves the following elements:

- All clinical trials (both single-centre and multi-centre) must be scientifically reviewed in accordance with minimum standards before being approved by a NSW Health HREC.
- The conduct of this review is to be evidenced by the completion of an Assessment Checklist and Certification of Scientific Review.
- HRECs should, where possible, rely on their own local arrangements (that is, their own scientific review, review by a clinical trials committee, local expertise, etc) to undertake the scientific review and complete the Assessment Checklist and Certification of Scientific Review.
- Where the HREC cannot rely on its own local arrangements, it must either refer the trial to the Shared Scientific Assessment Scheme (but only if it is a clinical drug trial) or refer the trial to the Therapeutic

Goods Administration (TGA) Clinical Trial Exemption (CTX) Scheme and use the documentation approved by the TGA together with the scientific expertise available to the HREC to complete the requisite sections of the Assessment Checklist and Certification of Scientific Review.

PART 2: THE SCIENTIFIC REVIEW STANDARDS

2.1 Introduction

- 2.1.1 Scientific review standards have been developed for clinical trials. These standards apply to all trials that are to be approved by NSW Health HRECs.
- 2.1.2 In accordance with the NHMRC National Statement, clinical trials are a form of research designed to find out the effects of an intervention, including a treatment or diagnostic procedure.
- 2.1.3 A clinical drug trial includes testing the formulation, dose form, indications, directions for use, and container for a drug, or combination of drugs.

2.2 Scientific review standards for all clinical trials

- 2.2.1 All clinical trials (both single-centre and multi-centre, including drug trials, and trials of devices and other clinical interventions) are required to have:
- A scientific assessment completed in accordance with the attached Assessment Checklist (**Appendix A**); and
 - A Certification of Scientific Review (**Appendix B**).
- 2.2.2 Where an HREC is unable to rely on its own local arrangements to complete these documents for a clinical trial it has the following options:
- Refer the scientific review of the clinical trial to another HREC or scientific review body that can meet the requirements;
 - If the study is a clinical drug trial (either single-centre or multi-centre), refer the scientific review to the Shared Scientific Assessment Committee (SSAC); or
 - Refer the clinical trial (either clinical drug trial or any other clinical trial) to the CTX Scheme, and complete the relevant sections of the Assessment Checklist and the Certification of Scientific Review using the documentation approved by the TGA together with the scientific expertise available to the HREC. If the HREC is unable to assess the documentation provided by the TGA, it should seek the advice of another HREC that is able to do so (or, for clinical drug trials, refer the scientific review to the SSAC).

The Assessment Checklist

- 2.2.3 The Assessment Checklist sets out standard requirements for the scientific review for all clinical trials.
- 2.2.4 The Assessment Checklist may be completed by:
- The HREC as a whole;
 - A scientific sub-committee or scientific review body utilised by the HREC to undertake scientific review;

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- An individual or group of individuals with the requisite scientific knowledge who provide assistance to the HREC;
 - A combination of any of the above; or
 - The SSAC, for clinical drug studies that have been referred to it
- 2.2.5 The Assessment Checklist may be completed either instead of, or in addition to, an HREC or scientific review body's individual scientific review assessment sheet.
- 2.2.6 An HREC may make additions to the Assessment Checklist to encompass local issues; however, questions may not be deleted from the Assessment Checklist.
- 2.2.7 The completed Assessment Checklist should be maintained by the Executive Officer of the reviewing HREC on the project file. A copy shall be made available to the applicant, on request. The identity of individual reviewers may be removed, if desired.

Certification of Scientific Review

- 2.2.8 The Certification of Scientific Review documents a determination of scientific validity or invalidity of a clinical trial.
- 2.2.9 The Certification of Scientific Review should be completed after consideration of all of the issues going to the scientific validity of the study, including those issues raised in the Assessment Checklist.
- 2.2.10 The Certification of Scientific Review should be completed by the body with overall responsibility for the scientific validity of the study. This could be:
- The HREC as a whole, where that HREC undertook the scientific review of the study (including where the Assessment Checklist was completed by an expert reviewer/s for the purposes of providing advice to the HREC);
 - A scientific subcommittee or scientific review body; or
 - The SSAC, for clinical drug trials referred to it.
- In general, it would not be appropriate for an individual expert reviewer to complete the Certification of Scientific Review.
- 2.2.11 The completed Certification of Scientific Review should be maintained by the Executive Officer of the reviewing HREC on the project file. A copy shall be made available to the applicant, on request.

Audit

- 2.2.12 The Department may from time to time audit an HREC's scientific review process, including completed Assessment Checklists and Certifications of Scientific Review, to ensure compliance with this policy directive.

2.3 Scientific review standards for FTIH clinical trials

- 2.3.1 Additional requirements apply to the scientific review of first time in human (FTIH) clinical trials. These are defined as clinical trials where a proposed investigational product, or route of administration for a proposed investigational product, is being trialed in humans for the first time anywhere in the world. This includes the administration of a combination of treatments, where the combination is being trialed for the first time.
- 2.3.2 FTIH clinical drug trials must be reviewed by a clinical pharmacologist, being a pharmacologist recognised by the Royal Australasian College of Physicians (**Appendix C**).
- 2.3.3 Where an HREC is unable to access a clinical pharmacologist to review a FTIH clinical drug trial it has the following options:
- Refer the scientific review of the FTIH clinical drug trial to another HREC or scientific review body that can meet this requirement; or
 - Refer the scientific review of the FTIH clinical drug trial to the SSAC.
- 2.3.4 An HREC may review a FTIH clinical trial other than a clinical drug trial under the CTN Scheme where it determines that it is able to obtain a completed Assessment Checklist and Certification of Scientific Review for the study relying on its own local scientific review arrangements, or arrangements with another HREC. Where an HREC is unable to complete the Assessment Checklist and Certification of Scientific Review in this way, the study should be referred to the CTX Scheme and the HREC should complete the relevant sections of the Assessment Checklist and the Certification of Scientific Validity using the documentation approved by the TGA together with the scientific expertise available to the HREC. If the HREC is unable to assess the documentation provided by the TGA, it should seek the advice of another HREC that is able to do so.

2.4 Clinical research subject to additional regulatory requirements

- 2.4.1 Specific regulatory requirements apply to clinical trials involving gene therapy and genetically modified organisms.
- 2.4.2 Clinical trials involving human gene therapy must be submitted to the Gene and related Therapies Research Advisory Panel (GTRAP). Clinical trials involving genetically modified organisms must be authorised by the Office of the Gene Technology Regulator (OGTR).
- 2.4.3 Usually, the GTRAP and the OGTR require clinical trials involving human gene therapy or genetically modified organisms to be reviewed under the CTX Scheme. In this situation, the HREC should complete those sections of the Assessment Checklist required for CTX studies generally.

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2.4.4 In limited circumstances, the relevant regulatory authority might approve review of a study under the Clinical Trial Notification (CTN) Scheme. In this situation, the HREC must ensure the completion of the full Assessment Checklist. This may require sourcing additional expertise, for example in molecular biology, manufacturing standards, and/or biosafety.

2.5 An HREC's "Scientific Review Status"

2.5.1 An HREC should determine whether it will:

- Refer all clinical drug trials to the Shared Scientific Assessment Scheme (SSAS); or
- Refer all clinical drug trials of a certain class (for example all First Time in Human trials or all trials of a specific clinical discipline) to the SSAS; or
- Use its discretion on a case by case basis as to whether or not it will refer a particular clinical drug trial to the SSAS.

2.5.2 This information should be publicly available on the HREC's website to facilitate direct submission to the SSAS where required. This information will also be made available on the SSAS website.

2.5.3 See **Part 3** for more information.

Table 1: Procedure for the scientific review of clinical drug trials

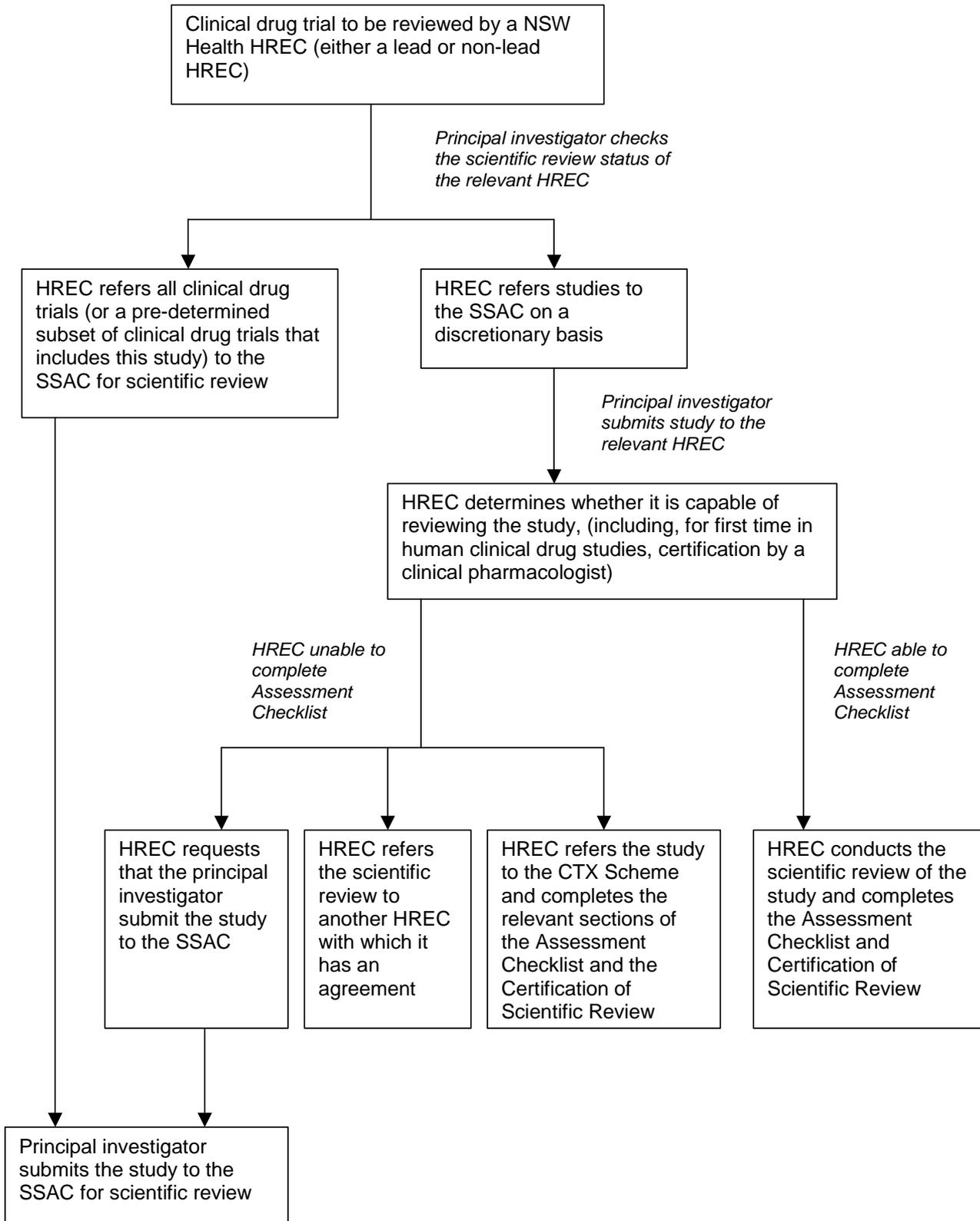
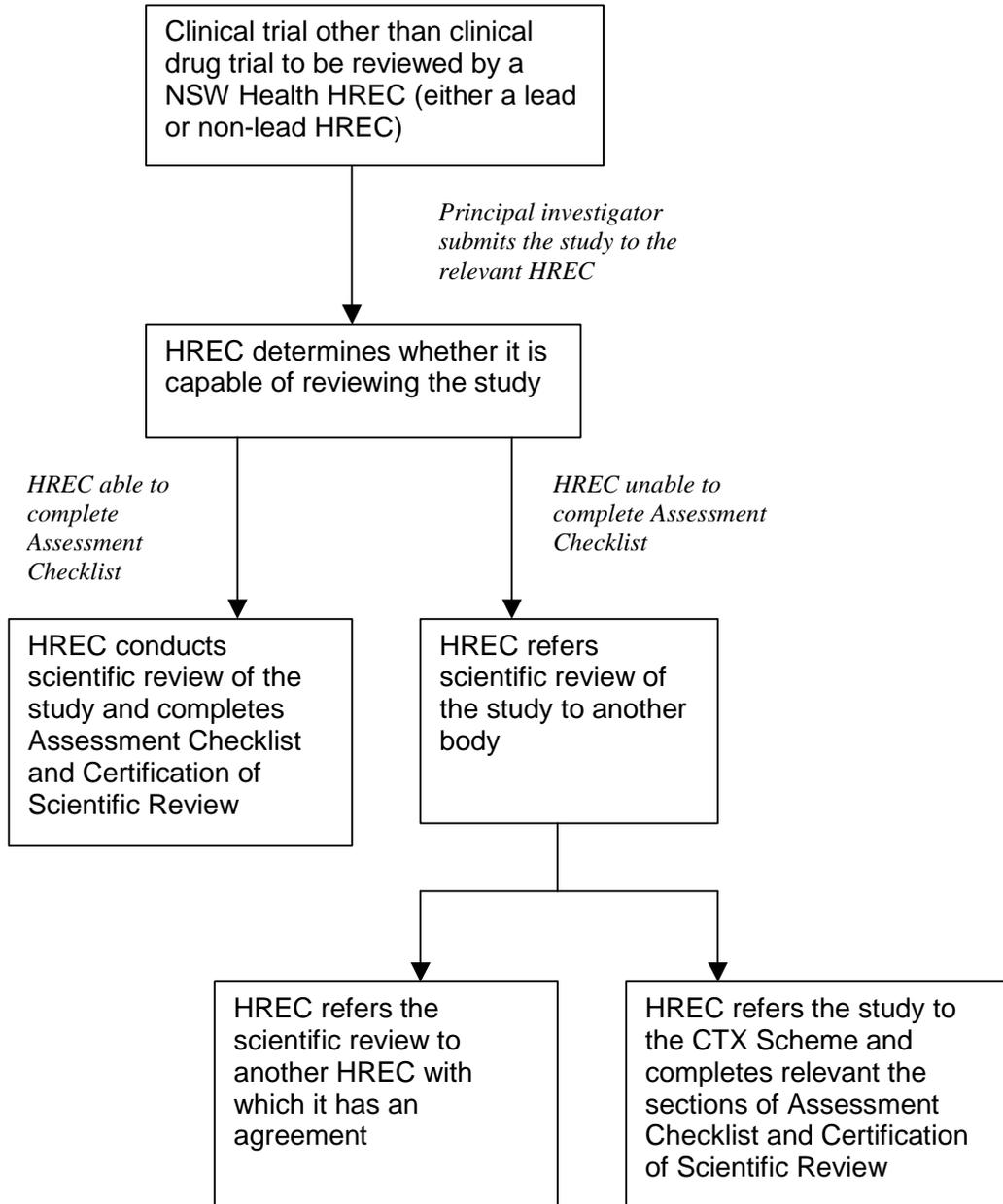


Table 2: Procedure for the scientific review of clinical trials other than clinical drug trials



PART 3: THE SHARED SCIENTIFIC ASSESSMENT COMMITTEE

3.1 Introduction

3.1.1 The Shared Scientific Assessment Committee (SSAC) may review clinical drug trials (both single-centre and multi-centre) for which a NSW Health HREC is unable to obtain a completed Assessment Checklist and Certification of Scientific Review under its own arrangements.

3.1.2 The SSAC will not review clinical trials other than clinical drug trials. Where an HREC is unable to obtain a completed Assessment Checklist and Certification of Scientific Review for a clinical trial other than a clinical drug trial, the HREC should refer the study either to another HREC or scientific review body that has the necessary expertise to review the study or to the CTX Scheme, in accordance with paragraph 2.2.2.

3.2 Submission to the Shared Scientific Assessment Committee

3.2.1 NSW Health HRECs that are unable to obtain a completed Assessment Checklist and Certification of Scientific Review for a clinical drug trial may refer scientific review of the study to the SSAC.

3.2.2 HRECs may refer to the SSAC:

- All clinical drug trials;
- A pre-determined subset of clinical drug trials (for example, first time in human, specific clinical disciplines);
- Clinical drug trials determined by the HREC on an ad hoc basis as raising complex or unusual issues.

3.2.3 It is the responsibility of each HREC to determine which studies will be referred to the SSAC, to provide guidance to applicants about those studies likely to be referred to the SSAC, and to implement timely pathways for such referral.

3.2.4 The SSAC status of each HREC will be publicly available on the Department's website.

3.2.5 Where a principal investigator intends to submit a clinical drug trial to an HREC that refers all clinical drug trials to the SSAC, the principal investigator may submit the study directly to the SSAC.

3.2.6 Where a principal investigator intends to submit a clinical drug trial to an HREC that refers clinical drug trials to the SSAC on an ad hoc or discretionary basis, the principal investigator should contact the HREC prior to submission of the study for advice as to whether referral to the SSAC is required.

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- 3.2.7 Submissions to the SSAC will be accepted on the *National Ethics Application Form* (NEAF), the SSAC application form, or on the application form accepted by the HREC to which the trial is being submitted.
- 3.2.8 Submissions should note the referring HREC.
- 3.2.9 Once a completed application form and all necessary documentation has been received, the SSAC Secretariat will undertake an administrative review of the application to ensure that the application is eligible for the Committee.
- 3.2.10 Eligible applications will be placed on the agenda for the next scheduled SSAC meeting.
- 3.2.11 Notification will be provided to the principal investigator and the referring HREC once a study has been accepted onto the SSAC agenda.
- 3.2.12 NSW Health expects that lead HRECs for the review of clinical research and HRECs situated in major metropolitan hospitals will have sufficient scientific expertise available to them to obtain a completed Assessment Checklist in relation to most clinical trials. NSW Health will periodically review the applications received by the SSAC. If it is of the view that an HREC is overusing the SSAC, the HREC may be required to give additional justification as to why a scientific review cannot be provided for a study.

3.3 Review by the Shared Scientific Assessment Committee

- 3.3.1 The SSAC will operate according to substantially the same Standard Operating Procedures as those outlined in the document '*NSW Health Shared Scientific Assessment Committee (SSAC) Standard Operating Procedures January 2005*'. These will be updated to reflect the amended eligibility requirements for the SSAC.
- 3.3.2 Any interim correspondence from the SSAC will be sent directly to the principal investigator.
- 3.3.3 The SSAC will complete an Assessment Checklist and Certification of Scientific Review for eligible applications referred to it, including review by clinical pharmacologist where required.
- 3.3.4 The completed Assessment Checklist and Certification of Scientific Review will be forwarded to the principal investigator and the referring HREC.
- 3.3.5 The way in which the referring HREC incorporates the review by the SSAC into their overall ethical review of the application remains at the discretion of the HREC.

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3.3.6 The SSAC Secretariat will maintain a database of all clinical drug trials that have been reviewed by the SSAC.

3.3.7 Completed Assessment Checklists and Certifications of Scientific Review for clinical drug trials that have been reviewed by the SSAC will be available to all NSW Health HRECs on request.

3.4 Post-review procedures and responsibilities

3.4.1 The principal investigator should submit all amendments, including the addition of sub-studies to the clinical trial, to the referring HREC. The HREC may refer any amendments that might impact upon the scientific validity of the study to the SSAC for review.

3.4.2 The principal investigator should submit all currently reportable adverse events to the referring HREC in accordance with the usual procedures for that HREC. The referring HREC may notify the SSAC of any events that might warrant review of the scientific validity of the study, including Serious, Unexpected, Suspected Adverse Reactions.

3.4.3 The SSAC will consider those adverse events of which it is notified, and take one of the following courses of action:

- Acknowledge consideration of the adverse event to the referring HREC and recommend that no further action is required;
- Request additional information from the principal investigator;
- Recommend to the referring HREC immediate suspension of ethical approval;
- Recommend to the referring HREC immediate discontinuation of ethical approval; or
- Provide other recommendation to the referring HREC.

3.4.4 Monitoring of trials that have been assessed by the SSAC and subsequently approved by the referring HREC remains the responsibility of that HREC. Copies of progress reports that could warrant review of the scientific validity of the study may be sent to the SSAC for consideration.

3.4.5 The SSAC shall consider such progress reports, and take one of the following courses of action:

- Acknowledge consideration of the progress report to the referring HREC and recommend that no further action is required; or
- Advise the referring HREC that circumstances have arisen such that the trial is no longer scientifically valid.

3.5 Fee for referral of applications to the Shared Scientific Assessment Committee

3.5.1 At this stage, no fee will be charged for scientific review by the SSAC.

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- 3.5.2 After twelve months of operation, this fee structure will be reviewed, in light of the number of applications that have been received by the Committee.

PART 4: ALIGNMENT WITH THE NSW HEALTH MODEL FOR SINGLE ETHICAL AND SCIENTIFIC REVIEW OF MULTI-CENTRE RESEARCH

- 4.1 NSW Health is implementing a model of single ethical and scientific review of multi-centre research. The model involves the accreditation of lead HRECs, which will be responsible for reviewing a multi-centre research project on behalf of the whole NSW public health system. Lead HRECs are required to meet certain accreditation standards, some of which will be directed towards scientific review. These accreditation standards are in addition to the scientific standards outlined in this model.
- 4.2 It is expected that in the vast majority of situations lead HRECs for the review of clinical research will have the requisite expertise to complete the Assessment Checklist for clinical trials submitted to the Committee.
- 4.3 In a small number of situations a lead HREC for the review of clinical research may refer scientific review of a clinical drug trial to the SSAC. The process for referral and review will be the same as outlined under Part 3 of this paper. Similarly, situations may require a lead committee in clinical research to refer a clinical trial to the CTX Scheme.
- 4.4 Where a lead committee refers a study to the SSAC or the CTX Scheme for scientific review, it may result in difficulties in meeting the required 60-day timeframe for HREC review. Considering the infrequent nature of such referrals, NSW Health does not anticipate this to be problematic for lead committees' ongoing compliance with the accreditation standards.

| Investigational product information | | |
|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| <i>This section may be omitted for studies being conducted through the CTX Scheme</i> | | |
| 7 | Have acceptable manufacturing standards been described for the investigational product? | |
| 8 | Have animal/disease models been investigated that are likely to be predictive of effects in humans? | |
| 9 | Is the investigational product thought to be immunogenic? | |
| 10 | (i) Is there evidence suggestive of toxicities that may be clinically significant, including carcinogenesis and teratogenesis? (If so, please specify) | |
| | (ii) Is there a need for contraceptive or barrier precautions? | |
| 11 | (i) Are there sufficient safety data available to justify the proposed usage of the investigational product, including duration of usage? | |
| | (ii) Are there any safety signals that suggest either that it may be unsafe to undertake the study or to justify special safety monitoring? | |
| 12 | Where relevant, is there adequate evidence of potential efficacy? | |
| <i>The following questions 13 to 15 should be answered for <u>clinical drug trials only</u></i> | | |
| 13 | Is the proposed dosing schedule commensurate with the known pharmacokinetics and mechanism of action of the investigational product? | |
| 14 | Have the issues of metabolism and renal clearance been accommodated in the experimental design? | |
| 15 | Are relevant warnings or exclusions in place for drug interactions of likely relevance to the proposed clinical use? | |
| Oversight of the study | | |
| 16 | Is there adequate monitoring for safety and adverse events? | |
| 17 | (i) Is there a Data Safety Monitoring Board? | |
| | (ii) If so, is it independent? | |
| Participant Information Sheet and Consent Form | | |
| 18 | Does the Participant Information Sheet/Consent Form contain appropriate information, including possible side effects, possible drug interactions; administration; dosage and timing; whether the medication may cause drowsiness; what to do if a dose is missed; and important toxicological findings? | |

Recommendations

The scientific methods employed in this study are:

- Sound
- Unsound
- Require review with respect to the following:

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The proposed mechanisms for monitoring the progress and safety of the study are:

- Adequate
- Inadequate
- Require review with respect to the following:

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The potential risks to study participants are:

- Acceptable
- Unacceptable
- Should be minimised through the following:

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Signed by:.....

In the capacity of:

- Chair/Deputy Chair of HREC which undertook a scientific review
- Chair/Deputy Chair of HREC Scientific Sub-committee or scientific advisory body
- Chair/Deputy Chair of Shared Scientific Assessment Committee (SSAC)
- Expert reviewer
- Other (please explain)

Name and Date:

This Assessment Checklist must be completed for all clinical trials reviewed by NSW Health Human Research Ethics Committees. Components of the Assessment Checklist may be completed by a number of different individuals and/or groups of individuals (including Human Research Ethics Committees and scientific sub-committees or scientific review bodies). However, all relevant sections of the Assessment Checklist must be addressed prior to completion of a Certification of Scientific Review. For all First Time In Human clinical drug trials, a Review by Clinical Pharmacologist must also be completed.

Appendix B

Certification of Scientific Review

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
| Clinical Trial Name | |
| Protocol Reference <i>[including version number and date]</i> | |
| Investigator's Brochure <i>[including version number and date]</i> <i>*Where product information other than an Investigator's Brochure has been provided, please specify</i> | |
| Patient Information Sheet <i>[including version number and date]</i> | |

In accordance with the completed Assessment Checklist and (for First Time in Human Clinical Drug Trials only) the Review by Clinical Pharmacologist, including all follow-up on issues raised, this study is:

- Recommended as scientifically sound
- Recommended as scientifically sound, subject to the following:

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- Not recommended as scientifically sound, for the following reasons:

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Signed by:.....

In the capacity of:

- Chair/Deputy Chair of HREC which undertook a scientific review
- Chair/Deputy Chair of HREC Scientific Sub-committee or scientific advisory body
- Chair/Deputy Chair of Shared Scientific Assessment Committee
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Name and Date:

