

Standard Operating Procedure
Section 1: AKTN operating Principles
AKTN SOP 1.11: AKTN Trial Endorsement

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Policy Statement:

The mission of Australasian Kidney Trials Network (AKTN) is to deliver high quality clinical trials to improve the health and wellbeing of people with kidney disease. To achieve this end, the AKTN can be engaged to coordinate, facilitate or endorse kidney disease-related clinical trials in the region. All trials under these arrangements require a rigorous review process, but as Endorsed trials do not have the same level of AKTN involvement or control once the Endorsement approval has been granted, these trials must adhere to the procedures contained within this policy document.

An AKTN Endorsed trial is one that has been identified by the Australasian Kidney Trials Network as addressing a research area of importance, and having sound scientific and statistical merit, but that is not being coordinated by the Network.

Scope:

All clinical trials submitted to the AKTN for review under an *Endorsed* arrangement should adhere to the procedures contained within this policy document.

Applicability/Responsibility:

It is the responsibility of the AKTN Project Manager to ensure this policy document is circulated to all Investigators who propose a trial for AKTN Endorsement, as part of the review process. These Investigators should read this policy prior to submitting a trial protocol for review, to ensure their expectations are in line with those of the AKTN Operations Secretariat.

Procedure:

Advantages to AKTN Endorsement

Requires discussion: what are the advantages to AKTN endorsement?

1. Scientific & statistical review by opinion leaders/experts, making for a more robust protocol
2. Promotion of the trial through AKTN activities may help with recruitment of sites to the trial, and have the trial known through the ANZ Nephrological community
3. Facilitation of leveraging funding from government, non-government organisation (NGO) and industry sources

Endorsement Activities of the Network

Endorsement of a trial by the AKTN may encompass any of these activities, and Investigators/trial proposers should nominate on the submission form (Appendix A) which activities they would like the AKTN assistance with. These requests will form part of the review process.

Scientific Review

This is mandatory; all trials requesting Endorsement require scientific review to ensure the scientific merit of all trials associated with the AKTN is high. The procedure for this approvals process involves 2 nephrologists (or other speciality if appropriate for the trial) to review the trial and provide feedback, and the Scientific Committee to then discuss and vote on whether to approve the trial for Endorsement. This process is summarised in Appendix B.

Statistical review

This is mandatory; all trials requesting Endorsement require statistical review to ensure the power of the trials is sufficient. The procedure for this approvals process involves a Biostatistician to review the trial and provide feedback to the Scientific Committee to inform their discussions.

Funding applications

If Endorsement is approved, the Investigator can use the AKTN name on funding applications, indicating that the trial was identified as being one of importance, and with high scientific merit, by the AKTN.

Use of name/logo

If Endorsement is approved, the Investigator can use the AKTN name on presentations, indicating that the trial was identified as being one of importance, and with high scientific merit, by the AKTN.

Statistical consulting

If endorsement is approved, a service that can be requested is for statistical consulting to advise on all matters relating to trial design, statistical analysis plans (SAP), sample size/power calculations, preparation of reports for Data and Safety Monitoring analyses, interim analyses and full data analysis. This service is subject to AKTN statistician availability and is offered at a cost-recovery rate.

Promotion

If Endorsement is approved, the Investigator can request that the AKTN promote the trial at relevant AKTN-promotional opportunities, such as conferences, presentations, and on the AKTN website. This will rely on update reports being provided to the AKTN so the information can be disseminated.

Data and Safety Monitoring Board

The Investigator can request AKTN assistance with running an independent Data and Safety Monitoring Board (DSMB) for the trial. A trial DSMB is an International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirement. This service will be subject to AKTN workload capacity, and could involve members from the AKTN Operations Secretariat/Scientific Committee sitting on the DSMB, and/or the AKTN Operations Secretariat coordinating the activities (eg meetings, reports) of the Board. The provision of this service may be offered at a cost to the trial proposers, at a cost- recovery rate.

Site monitoring/ auditing

Another service that may be offered to AKTN-Endorsed trials is monitoring and/or auditing of trial sites to ensure compliance with ICH GCP guidelines and other regulatory requirements. The provision of this service is subject to AKTN staff capacity at the time of the request, and may be offered at a cost to the trial proposers at a cost- recovery rate.

The submission and review process

The Investigator should contact the AKTN Project Manager (currently Alicia Morrish on a.morrish@uq.edu.au) for a copy of the Trial Proposal form (Appendix A) and the submission guidelines. The Project Manager will then liaise with the Investigator and the AKTN Operations staff (including statistician, nephrologists and clinical trialist) to prepare the proposal for distribution to independent reviewers.

At least 2 Nephrologist (or other speciality as appropriate) reviews and one Statistician review will be obtained and de-identified (using Appendix C). These comments will then be sent to the trial proposer for the opportunity to respond or clarify, then the proposal, the reviews, the proposer's response and the protocol (if appropriate) will be distributed to the AKTN Scientific Committee. After the Committee's discussion of the trial via teleconference or face-to-face meeting and a subsequent

vote (if appropriate), the Investigator will receive a letter advising of the Scientific Committee's decision, or a request for clarification or alteration of aspects of the protocol to proceed.

The timelines for this process depend on the timing of the Scientific Committee meetings; meetings are held quarterly, and the proposal needs to be ready for review at least 6 weeks prior to the meeting date to allow time for the review process to occur.

Requirements of the AKTN

The AKTN offers most of the endorsement support free of charge as a service to the Nephrological community, with the exception of statistical consulting and monitoring/auditing, as outlined above. To ensure the AKTN obtains appropriate benefit for this support, the following requirements of the AKTN must be met in order for Endorsement to continue.

Trial conduct

The trial should be conducted according to the NHMRC National Statement on Ethical Conduct in Research Involving Humans (The "National Statement")¹, as well as the ICH GCP guideline, with annotated TGA comments². This includes obtaining informed, voluntary consent from all participants; having the protocol, participant information & consent form, and all other relevant trial documentation reviewed by a Human Research Ethics Committee, and conducting regular trial monitoring to ensure the trial is being conducted correctly.

Reports

The AKTN has reporting responsibilities to its external stakeholders, including the National Health and Medical Research Council, the Australian and New Zealand Society of Nephrology (ANZSN), the Scientific Committee, the Advisory Board and the Qld Health research foundation. As such, progress reports on the AKTN-endorsed trials are required to be supplied to the AKTN quarterly.

In addition, an information poster is to be submitted to the AKTN by the end of August each year if the trial proposers wish the AKTN to promote the trial at the annual ANZSN conference booth.

If a significant trial milestone occurs, and the trial proposers want this to be included on the AKTN website, this information can be supplied to the AKTN on an ad-hoc basis.

Notifications

If an AKTN-endorsed trial is terminated early for any reason, the trial proposer/Chief Investigator must inform the AKTN immediately, with the reason for trial termination. Similarly, if an external audit uncovers any significant findings, these must be reported to the AKTN.

Publication

The AKTN should be acknowledged in the primary trial publication in terms of contribution towards critical appraisal of the concept, design and methodology of the research trial. If the AKTN facilitates or forms part of the DSMB, if significant statistical, scientific, or logistical input is obtained from the AKTN, or if assistance with grant writing is rendered, these inputs should also be appropriately acknowledged in the primary trial publication. Acknowledgments and publication expectations are to be negotiated prior to the provisions of endorsement services.

References:

1. National Health and Medical Research Council, *The National Statement on Ethical Conduct in Research Involving Humans* 2007. Australian Government, E35. Accessed.
2. Therapeutic Goods Administration of Australia. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Annotated with TGA comments. *Australian Government, Department of Health and Ageing*, 2007.July 2000, (Accessed 24 October, 2010, at <http://www.tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf>.)

Definitions:

AKTN Coordinated Trial

A trial that is being coordinated by the AKTN, including assistance with scientific content, protocol, all ethical and regulatory documentation, Trial Management Committee, and formation of Data and Safety Monitoring Board (DSMB).

AKTN Endorsed Trial

A clinical trial that has the support of the AKTN and for which the AKTN assumes a limited number of duties, eg assistance with scientific content of protocol development, promotional activities, and occasionally formation of Data and Safety Monitoring Board (DSMB). Daily coordination of an Endorsed trial is not handled by the AKTN.

AKTN Facilitated Trial

A trial for which the AKTN assumes responsibility for a limited number of coordination tasks on behalf of an International or other external Collaborative Research Group, eg local/regional site recruitment, coordination of regional sites, Sponsorship responsibilities (including Clinical Trials Agreements and indemnity as appropriate), and occasionally grant/budgetary responsibility. Usually a facilitated trial will not require AKTN involvement in protocol development, statistical analysis and the Data and Safety Monitoring Board (DSMB).

AKTN Project Manager (PM)

The staff member of the AKTN responsible for facilitating set up of the trial at the AKTN, and a back-up contact at the coordinating centre.

Audit

The evaluation of a person, organisation, system, process, enterprise, project or product for the purpose of assessing and ensuring quality.

Chief Principal Investigator

Physician or other Investigator who, in collaboration with the Trial Management Committee, designed the protocol. Often the Chief PI is also the trial proposer and/or the Chair of the Trial Management Committee.

Clinical Trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or pharmacodynamic effects of an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Data and Safety Monitoring Board (DSMB)

An independent board of physicians, epidemiologists, clinical trialists and statisticians (as required) responsible for monitoring each trial at pre-determined intervals to ensure ongoing participant safety.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of participants are protected.

Human Research Ethics Committee (HREC)

An independent body which reviews research proposals involving human participants to ensure that they are ethically acceptable, and in compliance with relevant standards and guidelines. The National Statement requires that all research proposals involving human participants be reviewed and approved by an HREC and sets out the requirements for the composition of an HREC.

International Conference on Harmonisation (ICH)

International Conference on Harmonisation of Technical requirements for Registration of Pharmaceuticals for human Use is a joint initiative involving both regulators and research-based industry focusing on the technical requirements for medicinal products containing new drugs.

Monitoring Visit

On-site visits conducted by the AKTN Project Officer, or delegate, to ensure the trial is being conducted according to the protocol, and to verify the data captured by the site in the case report forms can be verified from the source, eg medical records, lab reports etc.

National Health and Medical Research Council (NHMRC)

The National Health and Medical research Council (NHMRC) is Australia's leading expert body promoting the development and maintenance of public and individual health standards.

Operations Secretariat (OS)

Key members of the AKTN including a Chair, Deputy Chair, Scientific Committee Chair, Scientific Committee Deputy Chair, Business Development Manager, Project Manager, and other staff as required. The Operations Secretariat meets at least monthly to discuss and monitor the daily running of the Network.

Participant

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Participant Information Sheet and Informed Consent (PISCF)

The information sheet describes the all aspects of the trial that are relevant to the subject's decision to participate in a clinical trial. It also documents the patient's willingness to participate by means of a written, signed and dated informed consent form.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually includes the background and rationale for the trial, but these could be provided in other protocol referenced documents.

Scientific Committee (SC)

An independent committee comprising members including clinical researchers, study coordinators, and other members as necessary, that monitors the scientific direction of the AKTN trials, and ensures the scientific rigour of the protocols accepted at the AKTN.

Standard Operating Procedure (SOP)

Detailed, written instructions to achieve uniformity of the performance of a specific function

Trial Proposer

A physician or other Investigator who has developed an idea for a clinical trial that they want Coordinated, Facilitated or Endorsed by the AKTN.

Appendices:

Appendix A: Trial Endorsement Submission form

Australasian Kidney Trials Network

TRIAL CONCEPT SUBMISSION FORM

It is not required that all fields in this form are filled out. Assistance will be given if required. If there are any questions please contact the Operations Secretariat.

Clinical Trial Synopsis	
Title:	
Objective:	
Population:	
Primary Hypothesis:	
Intervention:	
Control:	
Primary Outcome:	
Main inclusion criteria:	
Main exclusion criteria:	
Treatment plan & timing:	
Brief background/rationale (250-300 words)	
Outcome measures & timing:	
Sample size:	
Estimated accrual time:	
Proposed start date:	
Principal investigator:	
Current & proposed funding:	
Are you proposing this trial to be coordinated/facilitated by the AKTN, or are you applying for AKTN endorsement: <input type="checkbox"/> AKTN Coordinated Trial (AKTN to coordinate whole trial) <input type="checkbox"/> AKTN facilitated trial (AKTN to run trial at Aus/NZ sites for an existing overseas trial) <input type="checkbox"/> AKTN Endorsed Trial	

If the proposal is for a **coordinated** trial, is it your intention to lead the trial?

Yes

No

If the proposal is for a **facilitated** trial, please indicate how the AKTN could assist in the management of this trial:

- Trial comes with sufficient funding
- OR AKTN will require own funding
- Statistical management
- Data Management
- Site Monitoring/auditing
- Responsibilities of Trial Sponsor in ANZ region

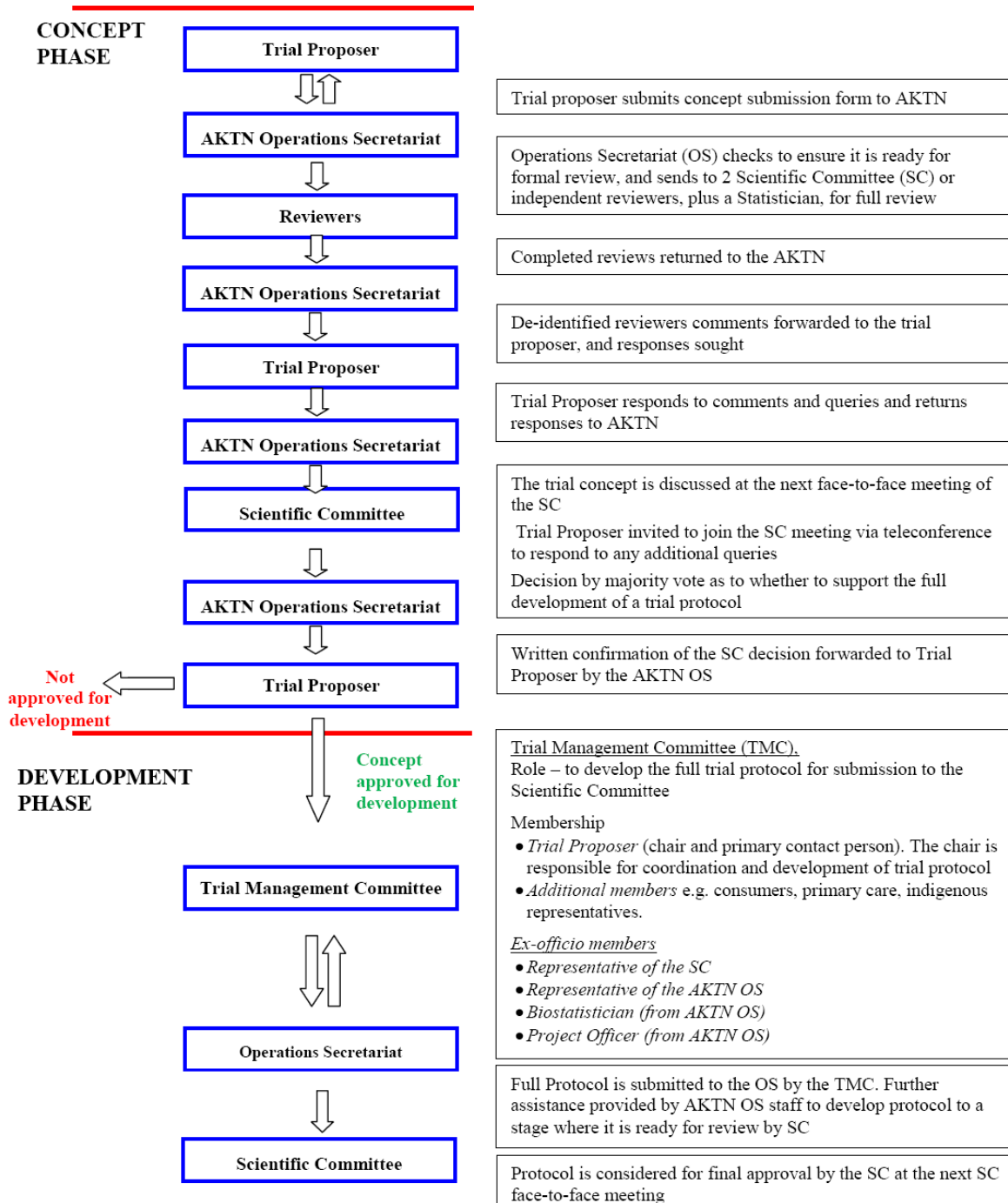
If the proposal is for an **endorsed** trial, please indicate how the AKTN could assist in the development and completion of this trial:

- Scientific Review of protocol (required)
- Statistical Review of protocol (required)
- Assistance with funding applications
- Trial use of AKTN name/logo in public fora
- Statistical consulting (paid service)
- Promotion of the trial in public fora on behalf of Proposer/s
- Data and Safety Monitoring Board (DSMB) (paid service)
- Site Monitoring/auditing (paid service)
- Other (please specify):

Please email the completed form to the AKTN Project Manager Alicia Morrish a.morrish@uq.edu.au

Appendix B: Trial Endorsement review process

AKTN Trial Approval Process



Please note: for trials seeking endorsement of Trial Concept only, and for facilitated trials with existing Full Protocols, only one approvals round is required.

Appendix C: Endorsed trial Concept Review report

Australasian Kidney Trials Network

Trial Concept – Review Form for Endorsement

The trial proposer(s) have requested endorsement of this trial. This means the trial will not be coordinated by the AKTN, but the following services have been requested of the AKTN during the trial. Please consider this when making your final recommendation

- Scientific Review of protocol
- Statistical Review of protocol
- Assistance with funding applications
- Trial use of AKTN name/logo in public fora
- Statistical consulting (paid service)
- Promotion of the trial in public fora on behalf of Proposer/s
- Data and Safety Monitoring Board (DSMB) (paid service)
- Site Monitoring/auditing (paid service)

Title of trial: **xxxx**

Objectives		Yes	No	Not clear
1 .	Are the trial objectives and/or research question clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 .	Has the need for this trial been sufficiently well demonstrated (e.g. by systematic review)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Suggestions for alternatives or improvements (including requests for information e.g. systematic review):</i>				
<i>Other Comments:</i>				
Patients		Yes	No	Not clear
3.	Is the study population (ie inclusion/ exclusion criteria):			
	a. clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	b. appropriate?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Suggestions for alternatives or improvements:</i>				
<i>Other Comments:</i>				

Intervention	Yes	No	Not clear
4. Is the intervention			
a. clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. appropriate?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Suggestions for alternatives or improvements:</i>			
 <i>Other Comments:</i>			
Comparator	Yes	No	Not clear
5. Is the comparator (ie the control group)			
a. clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. clinically relevant?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c. considered the standard treatment for the condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Suggestions for alternatives or improvements:</i>			
 <i>Other Comments:</i>			
Trial Design	Yes	No	Not clear
6. Is this the appropriate trial design	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If not, what alternatives or improvements should be considered?			

Outcomes	Yes	No	Not clear
7. Are the outcomes			
a. clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b. clinically relevant?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Are the primary outcomes an accepted measure of the effectiveness of treatment?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Is the primary outcome measure reliable & valid?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Is the proposed detectable treatment difference realistic?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Is the proposed detectable treatment difference clinically worthwhile?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Suggestions for alternatives or improvements:</i>			
<i>Other Comments:</i>			
Further Information	Yes	No	
12. Do you require any further information to finish this assessment (eg literature search, specific questions of proposer etc)?	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If so, what information would you request:</i>			

Rating				
<i>Please rate each of the following:</i>				
A. Scientific importance / interest and novelty of the research question				
1	2	3	4	5
Very uninteresting	Uninteresting	Indifferent	Reasonably interesting	Very interesting
Enter rating here (1-5)				
B. Potential value and relevance to clinical practice				
1	2	3	4	5
Very poor	Poor	Fair	Good	Excellent
Enter rating here (1-5)				
C. Appropriateness of design				
1	2	3	4	5
Very poor	Poor	Fair	Good	Excellent
Enter rating here (1-5)				
D. Ability to answer question				
1	2	3	4	5
Very poor	Poor	Fair	Good	Excellent
Enter rating here (1-5)				
E. How well do you believe this trial fits with the priorities of the network				
1	2	3	4	5
Very poor	Poor	Fair	Good	Excellent
Enter rating here (1-5)				
F. Overall trial merit				
1	2	3	4	5
Very poor	Poor	Fair	Good	Excellent
Enter rating here (1-5)				
Recommendation				
<input type="checkbox"/> Proceed with endorsement of trial (taking into consideration my comments)				
<input type="checkbox"/> Revise outline as per comments and then re-submit				
<input type="checkbox"/> Do not endorse				
General comments:				