Research Australia
An alliance for discoveries in health

Productivity Commission – Public support for science and innovation in Australia
Research Australia – Supplementary submission

Attention: M. Binder

Thank you for the opportunity to provide further details on ethical approval issues that impact on the progress of clinical trials.

Research Australia recognises the importance of ethical approval for both clinical trials and epidemiological studies, and raised this as an important issue in our submission to the Productivity Commission (Attachment 1).

In response to your request for additional information with specific examples of difficulties associated with ethics approvals processes, Research Australia invited members to respond. Over 15 responses were received from members located in industry, hospitals, medical research institutes and universities. A number of issues have been identified; most commonly the difficulties faced in conducting multicentre trials. Solutions for some barriers have been found such as the Mutual Acceptance program (See response from Professor Mark Rosenthal). In addition, several responses described difficulties in obtaining insurance for clinical trials.

Responses

A list of responses, either in full or part, is provided.

Professor Peter Hartmann
University of Western Australia

Requirement for multiple ethics approvals. There does not appear to be any agreement that approval by one Australian ethics committee is recognised by all other (eg university versus hospital) yet they are all supposed to be following the same guidelines. In some cases I have had to obtain three separate approvals.

It would also be efficient to recognise North American and EEC ethic committee approvals. I recently received samples to assay from a collaborative study with an American university and I was required to get Australian ethics approval at UWA although I had the details of the USA IRB approvals. This delayed analysis and forced us to rush the analysis to meet deadlines.

Serving on an ethics committee is an onerous task. It would seem to me that as the volume of work increases the quality of assessment decreases. It would be more efficient for committees to be able to make executive decisions for applications that conform to certain low risk criteria. This may be happening with some committees already. National guidelines for ethics committees would be useful.

Confidential submission

Thank you for informing us that following Research Australia's submission to the Productivity Commission's Review of Public Support for Science and Innovation, Research Australia has been given an opportunity to provide information regarding ethical approval processes that are hampering clinical trials. In this regard, we suggest that our experience per the following is typical of the sort of thing that is faced:

- A site in one of our projects required the IEC application to be presented at the hospital level at least one month prior to submission to the IEC. For example, the IEC meeting scheduled for 28Nov05 had a submission deadline of 08Nov05 but the reality was that one had to get the IEC application to the site by 11Oct05. Responses are generally issued up to one month following the meeting date so by the time the application had concluded the 1st round of consideration, almost 3 months had already passed. This is significant when you consider that few projects are approved without 2nd round submissions.

- Another site had multiple committees that made up the IEC approval process - Radiology, Drug and IEC. Approval needed to be obtained from all three committees but their meetings and responses were not streamlined which caused unnecessary delays. The IEC application was submitted on 13Oct05 for the Drug meeting 27Oct05; changes were requested on 02Nov05 and were allowed to be incorporated into the submission to the IEC. The IEC tabled the submission on 16Dec05 and changes were requested on 22Dec05, including that the Radiology Committee review the project. Following a break over Christmas, the Radiology Committee tabled the submission on 07Feb06 and had no comments. The overall IEC approval was subsequently granted on 15Feb06, considering the Drug and Radiology Committees' satisfaction. However on 09Feb06, the Radiology Committee amended their response and requested additional changes. They re-tabled the submission on 27Feb06. There was then a need to resubmit the project to the IEC. Final approval from all sub-committees was not granted until 27Apr06 (i.e. six months after the original submission).

Professor Ken Ho
Garvan Institute of Medical Research

I very much welcome your timely call for comments on the issue of indemnity for the conduct of clinical trials in NSW where current Government policy threatens the viability of clinical research. I write as a physician scientist with dual appointments, one as a staff specialist to a University Teaching Hospital and as a Head of a Research Group in a medical research institute.

The reasons are as follows:

- The NSW health policy does not indemnify the conduct of clinical research by staff specialists. This situation I believe is different in other States in Australia.
- Most medical indemnity organisations do not provide cover for the conduct of research in patients
- The current system does not provide cover for the conduct of research in normal volunteers
- Only drug trials sponsored by industry provide indemnity cover for clinical researchers
- A large component of human research is investigative in nature and does not involve the administration of a therapeutic substance.

At a personal level, I hold a NHMRC Project Grant which entails undertaking investigations in normal volunteers and patients with endocrine disease. This project cannot proceed until the issue of indemnity is resolved. This is a matter which has created an untenable future for clinical research in NSW. It requires a clear solution ie the state government indemnify clinical research undertaken by staff specialists for research approved by the Hospital Research Ethics Committee.

Report on Six Sigma Project: Reducing Ethics Committee Cycle Time in Australian Clinical Trials
Sponsored by Merck Sharp & Dohme (Australia) Pty Limited (MSDA)

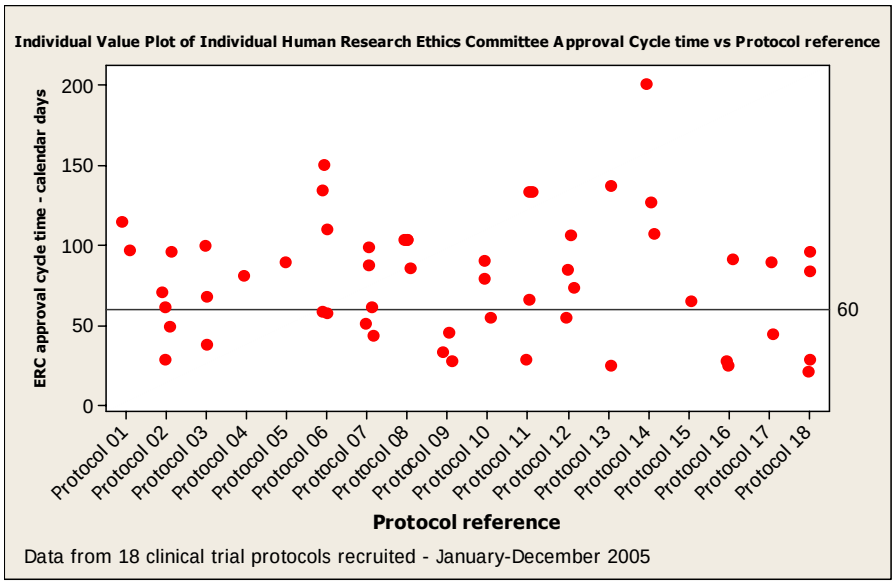
Macro Statement of Problem: The longest delay in clinical trial cycle time in Australia is the ethical review approval process which reduces the available time to screen and fully recruit for a

clinical study. The average cycle time is 78 days. The comparison mean ethics approval cycle time in New Zealand is 44 days.

(Australian data based on the review of 18 protocols recruited from January-December 2005).

Extent of issue: Multi-centre research in Australia requires individual submission to institutional Human Research Ethics Committees at the respective investigational centre. The timeliness, requirements and specifications of these committees vary across Australian states and territories with no consistency in performance. Schedules for submissions vary from one month to two months, with no flexibility to accept protocols if schedules are full.

One identical study protocol, patient information and consent form, (and supporting materials), submitted to four different Research Ethics Committees in Australia can vary in research ethics approval cycle time from 30 days to 100 days (see reference to protocol 2 below).

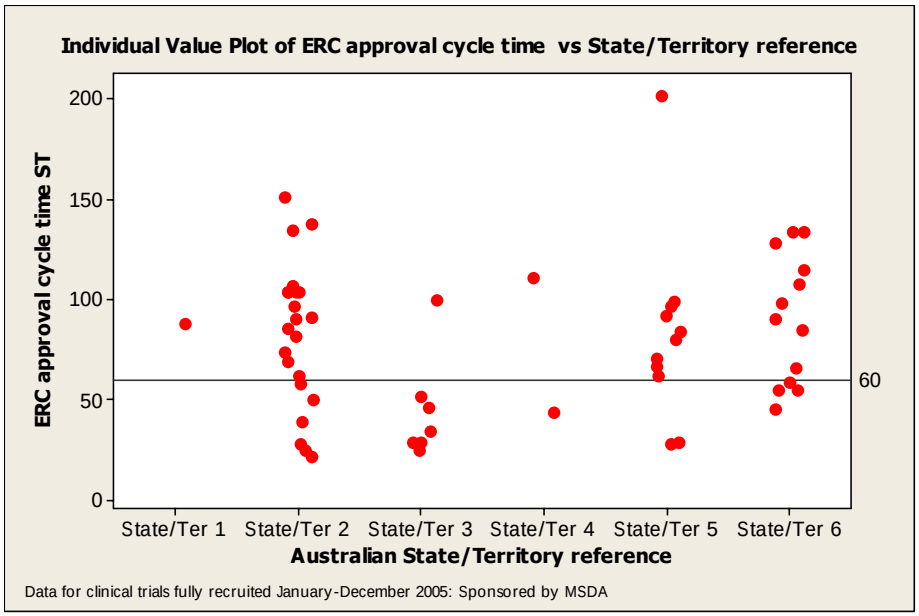


In the experience of MSDA, less than 10% of Research Ethics Committees, during the period January-December 2005, fully approved a clinical trial protocol at the first committee meeting.

The most common issue affecting first time approvals are comments on the content of the patient information and consent form. These issues relate to patient compensation, privacy and risk. Efforts have been made by MSDA to ensure there issues are proactively resolved prior to the committee meeting, invariably the same comments arise.

Concerted efforts are in place to produce a single ethical review structure in Australia; however the progress of these efforts is slow with an expected implementation date not feasible until late 2007.

There is further evidence of lack of consistency in performance by the states and territories: (see below human research clinical trials sponsored by MSDA only).



A target of 60 days has been set as a goal for the proposed national approach to central Human Research Ethics Review. As shown above, the majority of committees across states and territories in Australia presently struggle with a target of a 60 day review.

MSDA does recognise the constraints such as available resources placed on individual Human Research Ethics Committees in processing applications in a timely fashion are real and understandable.

Summary of difficulties affecting Research Ethics Approval:

- There is no central Research Ethics Approval system in Australia, similar as we understand it, to the systems in New Zealand, the USA and European countries. Individual submissions significantly hamper our ability to competitively recruit for patients in worldwide clinical trials and encourage further competitive investment in Australia.

- Progress towards the proposed national system has been slow to progress with the NSW pilot planned for 3Q 2006 now delayed until 2Q 2007.

- Current experience with Human Research Ethics Committees regarding issues which affect timely approvals is inconsistent with no standardisation across committees in the states and territories, differing ethics submission schedules and a lack of expected performance targets.

Dr Carlo Maccarrone
GlaxoSmithKline

Streamlining the multicenter ethical review process has been highlighted by the work of the Pharmaceutical Action Agenda.

The current ethical review process for multicentre trials can be slow, resource intensive (both internally and externally), inefficient and also costly. There is a wide range of variance in speed (and quality) of review of clinical trials by ethics committees. The duplication of effort (wastage) is also considerable. Administrative issues and resourcing is often the reason for delays; and not questions related to the scientific and ethical appropriateness of mutli-centre trials.

Some recent examples :

- One study with a diabetes drug took over eight months to gain approval at one centre in contrast to best practice of two months.
- One study in a hospital took six months to be cleared by the hospital's legal advisors (which had nothing to do with the science or ethics of the clinical trial).
- An Alzhiemer's disease study at a hospital will be delayed by a further two/three months due to relocation of the ethics committee office.
- A study in overactive bladder disease in women is still awaiting approval after eight months.

This is not the most productive use of GSK's internal resources and of resources of research centres (time and money). It also means a loss of opportunity of research and development activity and patients do not get the opportunity to participate in trials with new medicines.

Adrian Bootes
Roche Products Pty Limited
ACN 000 132 865; ABN 70 000 132 865

With regards to your request to furnish examples of "complex ethical approvals processes hampering clinical trials", we can give you some recent examples from our department, which runs phase I-IV clinical studies in Australian sites.

The first example is for a phase III trial with a new chemical entity envisaged for a major teaching hospital. The experience was that the ethics committee (EC) approval was delayed due to a number of factors, and that the time for submission to approval was increased to approximately 4 months. The underlying issues causing this delay were:

- slow EC administrative processes;
- a reliance on busy site study coordinators to follow-up multiple sign-offs, questions and submissions;
- cumbersome and lengthy ethics submission forms; and
- the required sign-off of the study from other departments such as Pathology and Pharmacy, for the submission to be considered and approved.

The substantial impact was that patients were no longer available to be recruited for this study, primarily as patients who were known to the study team and were in pain and discomfort were not content to await the initial study start, and that further recruitment of newly referred patient was negated due to changes in the PBS availability of alternative products. Unfortunately, this last factor could not have been foreseen when the process of site selection and EC submission was started. The consequence for the study and the institution was that the study site had to be closed prematurely as they had not entered any patients into the study.

The second and third examples are also for phase III trials run at two other major teaching hospitals. Both of these institutions require radiology and therapeutics committee approvals prior to EC review and approval, making an unnecessarily complex sequential process, which then hampers both the start-up timelines and the window of opportunity to recruit with fast-evolving alternative treatment algorithms.

To compound the issue for the second example, preferred institution-specific statements have to be included (and improved internally by our international affiliate staff), to minimise time taken for the subsequent submission, delaying the start of the submission process.

For the third example, the institution was slowed by the time-consuming nature of the Victorian application paperwork, to be completed by study staff before the submission may begin. This is

compounded by their institution not having good tracking systems in place for these many submission documents, which have been misplaced. In addition, extraneous information (which is readily available in the public domain) has also to be compiled and submitted such as Product Information monographs from MIMS for comparators in the study, though these are usually standardised treatments.

Furthermore, we have a general point that the final approval for many other institutions is delayed by the Ethics Chairperson, who has been slow in delivering the approval letter and associated paperwork once all EC questions have been addressed.

In recent years, an additional step inserted in the clinical trial submission and approval process has been that ethics committees are now referring contracts and indemnity agreements to individual lawyers, who unfortunately have little or no experience in clinical research issues. This has resulted in multiple requests to make small changes in wording in even standard agreements like the Medicines Australia Indemnity or standard product liability (investigator studies where only drug is supplied).

Although often minor - these word changes must be communicated from the lawyer to ethics to investigator to sponsor and back causing significant delay. Of more concern however, is that changing words based on an individual lawyers preference usually has unanticipated ramifications based on possible interpretations of the new words versus the standard wording accepted for many years. This starts a long negotiation of multiple versions of proposed wording without actually changing the agreed principles or coverage of indemnity.

Lastly, it is apparent that certain institutions have embarked upon a legal review of all of their contracts with pharmaceutical companies for clinical trials and have now put forward mandatory institution-specific contract documentation. Some institutions will not issue clinical trial approval documentation until these contracts are agreed and signed. Whilst the intention of the individual institutions is understandable, our company works with many hundreds of clinical trial centres in Australia. If this individual institution trend continues, we face a slowing of clinical trial negotiations, submissions and approvals based on the need to adopt each contract to the needs of the study and then obtain a legal review. To meet the needs of both parties, it would be of benefit if we had a common state-based generic contract document that we could utilise and thereby minimise review and submission timelines and costs.

Paul Davies
George Institute

Long term evaluation of glucosamine sulphate study (The LEGS study)
Participants are required to have annual knee X-rays. I have noted time-consuming inconsistencies in gaining ethics approval for our clinical trial from one NSW Health area to the next. In some cases even within the same health area, each radiology department where our participants knee X-rays are to be performed has a different requirement for the patients informed consent for the same trial and protocol. We have a variety of consent forms for the same trials and exactly the same procedure. Surely there should be uniformity across the various centres?

Associate Professor Jonathan Shaw
International Diabetes Institute

Our main issue with ethics approvals relates to the need to submit a multi-site study to multiple ethics committees. This includes clinical trials, which are run at a number of different centres and epidemiological studies. As an example of the latter, in our own national AusDiab study, we want to obtain hospital medical records on a number of our participants. This involves many hospitals. Despite the fact that the study has been approved by our ethics committee, and all individuals have consented to access to their records, it is likely that many of the hospitals will require us to submit to their ethics committees as well. We will have to go through this laborious process many times.

Professor Geoffrey Donnan
National Stroke Research Institute

There are enormous difficulties with clinical trials and epidemiological studies related to ethics.

Problems are:

1. For multi-centre trials too many ethics submissions.
2. Often minor and eccentric modifications required for each ethics committee.
3. This is the same for epidemiological studies.
4. Costs mount up for each submission.

Professor Malcolm Horne
Howard Florey Institute

The following clinical studies have been performed recently. These were all investigator driven studies without issues of TGA coverage or use of a therapeutic.

Genetic analysis of Parkinson's disease
Original approval was obtained through the Howard Florey Institute human ethics committee. Separate and full applications were made to St Vincents and to the Austin. Each further application was further amended and modified. Most of these were trivial and minor.

Analyses of blood for abnormalities in alpha synuclein in Parkinson's disease
Original approval was gained through St Vincent's human ethics committee. Two reapplications were required for changes in syntax or patient information and took three months. The Austin required a full and separate application.

Gait analyses in Parkinson's disease
Original approval was gained through St Vincent's human ethics committee. The Austin required a separate and full application. Each institution required several minor modifications relating to syntax. Both institutions charged a fee of $250 for reviewing the application. One patient decided to opt out of the study because they were uncomfortable being "off" medications. We were requested to submit a major adverse event form and the project went under further review. This demonstrates a lack of understanding and perspective as to what constitutes a severe or adverse event.

In summary, ethics applications are:

- Bureaucratic requiring multiple applications and amendments.
- Demonstrate lack of perspective – detail on form and legalise rather on substantive ethical issues.
- Demonstrate lack of expertise in understanding real medical or ethical issues.

The small snapshot of the experience with culture of ethics committees leads me to the view that they are no longer custodians of the patients interests or interested in supporting science.

Confidential submission

Mutual recognition

There is very limited mutual recognition of evaluation protocols for multicentre trials. At one time, a pilot group existed to examine mutual recognition. There was an overarching lack of trust between institutions and highly variable standards of competence within institutions to review clinical trial proposals. It seems now that some mutual recognition is available in one small group of institutions although seems limited to a very specific therapeutic area.

Another consideration in the mutual recognition process has been insurance and legal jurisdiction. That is, institutions have maintained they cannot accept review of another Institutional Ethics Committee's (IEC) decision due to insurance considerations. The public hospitals operate within the boundaries of their area health service or similar requirements of these groups have precedence.

Harmonisation of documentation

Some public hospitals in some states have harmonised documentation to some degree. Mostly this is not the case and of course the private hospitals have their own requirements. Industry provides harmonised indemnity documentation. However clinical trials agreements (CTA) usually are bespoke and much time wasting is involved in achieving acceptable CTAs.

Harmonisation of evaluation

Some IECs stand alone in their institutions and evaluate the scientific and ethical considerations of individual protocols. Others have both scientific ("drug") committees and IECs to share the load. Other groups have attempted "shared scientific assessment" without much success.

Informal systems

At least some attempt is in progress to provide "one stop shopping" for multicentre clinical trial proposals. However, confounding this initiative is the requirement to provide what may be referred to as a "Mini-CTX" approach. That is, the sponsor is required to provide independent toxicological and manufacturing reports for CTN (Clinical Trial Notification Scheme) applications in one group. This means that the institution appears to require greater regulation than is required by the Regulatory Authority, the TGA, and is hedging its bets by attempting a short-form CTX approach while reviewing a CTN.

Another impediment is the matter of "additional advice" sought by the IECs. Such advice does not need to involve the sponsor, does not need to inform the sponsor of the advice sought and may take as long as the IEC requires without any recourse by the sponsor.

Professor Mark Rosenthal
Royal Melbourne Hospital

Clinical trials opened at Cancer Trials Australia (CTA) sites (Austin Health, Peter MacCallum Cancer Centre, Western Hospital and Melbourne Health) and are approved through our Mutual Acceptance (MA) Program. This has taken five years to set up and we have published papers on the process. Effectively, there is a standard primary site review which is mutually accepted (expeditiously) by the Human Research Ethics Committee (HREC) of the other sites.

The process of MA is available to any other HREC according to the NHMRC guidelines but I don't think anyone has taken up the opportunity.

Unquestionably, the problems with HREC processes is a major hindrance in attracting studies from overseas.

Publications

Sarson-Lawrence M, Alt C, Mok M, Dodds M and Rosenthal MA. Trust and confidence: towards mutual acceptance of ethics committee approval of multicentre studies. Internal Medicine Journal 2004; 34: 598-603.

Rosenthal MA et al. Ethics Committee Reviews and Mutual Acceptance: A pilot study. Internal Medicine Journal 2005; 35: 650-4.

Dr Andrew Roberts
Walter and Eliza Hall Institute

The Centre for Developmental Cancer Therapeutics (CDCT) and subsequently CTA has led moves to streamline ethical approval for multi-site clinical trials and this has been successful at least in part for early phase studies (ie Phase I and II with which CTA specialises). CTA has also been working with Melbourne Health and perhaps other ethics committees to facilitate approval for first-in-man Phase I studies.

However, there remain distinct issues about large Phase III studies with as many as 50 different sites (versus 2-4 for CTA studies).

Michael James
Royal Adelaide Hospital

Research ethics committees face massive inconsistencies in the requirements of sponsors, many of which could be resolved if there was a willingness for a dialogue between pharma and ethics committees.

Yvonne Lungershausen
Centre for Pharmaceutical Research
University of South Australia

Personally I have not ever had any problems with ethics approvals for multicentre trials, receiving approvals at all sites within 6-8 weeks. I do think it is very dependent on the experience of the committee and the quality and complexity of the protocol and submission package. Further, it is extremely important to liaise with the sites and their respective ethics committees upfront as much as possible prior to protocol submission if there is any reason to assume there may be contentious issues.

Professor Susan Kippax
National Centre in HIV Social Research

In my limited experience of ethics committees, there is often uncritical and inappropriate imposition of NHMRC medical guidelines to social research.

As per Attachment 2 (Professor Kippax's submission to Professor Mark Israel in a report entitled "Ethics and the Governance of Criminological research in Australia" published by the NSW Bureau of Crime Statistics and Research (2004) and in a submission made to the NHMRC and its the Review of the "National Statement on Ethical Conduct of Research involving Humans (1999)" in March 2005) the following recommendations were made.

A set of regulations and a separate human ethics committee specific to the social sciences should be developed.

Recommendation 1

1. Provide separate ethics committees for the assessment of research applications one for biomedical research another for social research and 2) allow social researchers to develop their own guidelines OR
2. Ensure there an adequate (about equal numbers of) biomedical and social researchers on university ethics committees.

The requirement of signed and witnessed consent

Recommendation 2

In research in which research participants are interviewed/take part in conversations/tell their stories/describe their experiences and so on (as is the case with much sociological, historical and anthropological research), informed consent should be provided but in such a way that signatures, witnessed or otherwise, are not required. For example, informed consent may be obtained on an audio tape.

This will ensure anonymity and improve recruitment success. This will offer better protection for research participants and thus enhance the ethical standing of the research project.

Access to archived data

Recommendation 3

Bona fide researchers should be able to access "derived" data, that is, data that is de-identified and anonymised where such access does not breach anonymity and confidentiality agreements and can have no foreseeable impact on individual subjects. Such access would only be granted under certain conditions, that is, with the permission of the principal investigators and the research participants.

Professor Ken Hillman
Critical Care Services
Sydney South West Area Health Service

It is difficult to conduct research in Australia on the critically ill, an increasing proportion of the hospital population. They are not able to give immediate consent for trials as they are etiher too ill and/or unconscious. Under existing legislation, we can deliver any care, including drugs and interventions that may be remotely appropriate but we cannot determine whether these interventions, many of which are very expensive, are effective or not.

Professor Donald Chisholm
Garvan Institute of Medical Research

Ethical approval processes hampering clinical trials is a major issue particularly in NSW. Gaining ethical approval from multiple institutions has been helped by the establishment of a NSW shared scientific assessment scheme but individual institutional ethics committees may have concerns related to the following:

- In NSW public hospitals, medical indemnity of staff specialist appointees for clinical trial research and perhaps some other research is not covered by their indemnity as public hospital employees (whereas staff specialists do have such coverage in at least some other states).
- Some medical indemnity organisations have now declared that medical practitioners undertaking clinical research are not covered for this activity under their medical indemnity policies.

These issues create a very major problem for clinical research activity, especially in NSW and the level of activity will clearly suffer dramatically unless steps are taken to overcome the difficulties. For example, State Department of Health indemnity for activities related to clinical research approved by public hospital institutional ethics committees.

Tim Dugan
Victor Chang Cardiac Research Institute

We have had issues with getting insurance coverage for the institute where it is collaborating on a trial with a hospital where the hospital is the sponsor. We have been told that some vicarious risk may still exist for the Institute in these cases as it is contributing to the trial scientifically and financially, however, we have not been able to get insurance for this risk from the insurance industry.

The alternative is for the Institute to sponsor trials directly however this would involve significant trial insurance costs and would not reflect the reality of the trials. In addition we are also unable to get cover under NSW Government arrangements (the Tertiary Managed Fund) in cases where we would sponsor a trial so are caught between the two electing to get hospitals to sponsor trials as this is a lower risk but as mentioned above not risk free.

I know that many other research institutes are in the same position and are thus reticent to sponsor trials as it would give great insurance expense.

Professor Jonathan Golledge
Faculty of Medicine Health and Molecular Sciences
James Cook University

The dilemma of clinical research, industry, government funding and the insurance agencies.

Clinical researchers identify neglected areas of clinical need that they believe requires new therapeutic development and push for well designed studies to identify effective and safe treatments. A particular example is the problem of aortic aneurysm which presently has no effective drug therapy with only 1 trial of over 100 patients having been performed to date.

Industry (such as a drug company) is interested in the marketing of greatly utilised medications with potential for return. Decisions on research and development are usually made centrally in the USA or UK. Studies are usually funded by drug companies if they believe that the results will be generally applicable to large parts of the population rather than clinical conditions limited to a smaller part of the population (such as aortic aneurysm, which still affects 5% of men over 60 years). Involvement with industry by clinical researchers can be extremely time-consuming and frustrating. In order to develop appropriate studies a researcher may approach a company with basic science data suggesting a value of a medication. The following process of assessment of “investigator-initiated” studies usually takes 6-12 months or longer. If the company becomes interested they may only provide very limited funding (e.g. for drug) but not for indemnity or funding for the running of the study. The researcher if keen will seek to develop such a trial by obtaining funding from government funding bodies.

Government funding bodies in most countries fund very few randomised controlled trials since in order to have sufficient power such studies require large numbers and long follow-up. Thus such studies are very expensive usually in excess of 1 million dollars to run (often more than 5 million). If such a study involves a drug the funding body may well expect a substantial input from industry, however, for the reasons listed above this is often not forth-coming. The problem is particularly acute in smaller countries such as Australia where investigators are removed from the central decision makers in industry.

Most academic centres and hospitals have experienced difficulty over the last few years in obtaining insurance cover for clinical studies. This has been particularly the case with clinical trials where there is believed to be an extra risk by the insurance company. The company may have no way of adequately assessing the risk but will be frightened by past experiences of large drug related suits. Establishments such as universities or hospitals may be particularly concerned if they

have no insurance cover and fail to allow randomised trials for this reason rather because of scientific excellence.

Randomised clinical trials are the cornerstone to the scientific testing of new therapies. For a trial to occur a researcher involvement may be limited to industry led trials which may not be designed to answer some of the most important clinical questions which need answering. The road to an investigator initiated trial is an increasingly difficult one.

Reference

1. Rothwell PM. Funding for practise-orientated clinical research. Lancet 2006;368:262-6.