

Co-operative Clinical Trials in Cancer –
the need for increased capacity

The Executive Summary,
Recommendations and Budget
from the report by
Oceania Health Consulting

January 2002

Executive summary

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 majority of advances in cancer care are made through clinical trials conducted by cooperative groups. This has long been recognised by the US Government, and more recently the UK Government. Both see that cancer clinical trials are a vital priority in improving patient outcomes and that there is a need for greater numbers of cooperative clinical trials in cancer. Both have further increased the funding for cooperative cancer trial groups.

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.

This project was commissioned to assess the current capacity of Australian cooperative groups to conduct clinical cancer research trials in Australia. Consultations were conducted with cooperative group chairs and members, other cancer researchers, cancer councils and consumers, and the relevant literature was reviewed.

Current status

The gold standard for clinical research is the randomised controlled trial (RCT). However, they 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 an multicentre 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. In children for example, leukaemia now has 75% long term survival (from 0% in 1970). Similarly, outcomes for patients with limited stage breast and bowel cancer have substantially improved as a result of large scale trials in these diseases. Australian groups have been an important part of this world-wide effort.

Relative to the costs of health care, the costs of clinical trials research are value for money, as they provide a highly cost-effective means of ensuring more effective and cost-effective cancer care for patients. This has been recognised overseas, where increased funding in other countries to enhance the capacity of cancer cooperative groups is helping them forge ahead while Australian trials groups continue to struggle to conduct high-quality research. There is a risk that we will lose the ability to conduct large local trials or participate in international trials, thereby losing the numerous benefits that arise from the conduct of such studies.

Benefits of clinical trials

Clinical trials are important for the benefits they provide. Benefits may be 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.

Conduct of national cancer trials and participation in international cancer trials necessitates formation of national cooperative groups with substantial expertise and capacity. Australian groups treat around 2000 new cases in clinical trials in a year but could treat many more if there was funding to do so. Fewer than 3% of the new adult cases each year enter a clinical trial. This is in line with historical levels here and in many similar overseas countries but it is less than optimal. At least twice as many adult cancer sufferers that would benefit from trial entry are denied the opportunity.

Australia's cooperative groups

Australia is fortunate in having seven national cancer cooperative groups¹ all of which are conducting world class research, despite severe financial constraints. The groups 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.

The number of new cancer therapies is growing rapidly, based on advances in molecular biology and pharmacology. This

¹ Five of the seven cancer cooperative groups are incorporated bodies.

growth presents a great opportunity to improve cancer care, but all of the new therapies have to undergo trials to demonstrate their correct place in treating cancer. The objective of the cooperative groups, finding the correct place, differs fundamentally from that of industry trials. 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.

Gaps in capacity

This review has identified gaps that are developing as a result of the funding crisis. There is a risk that as the gaps continue to widen, the limited number of major Australian research centres will drop out of Australian trials groups and focus on participation in international trials or industry-sponsored trials that provide funding to meet costs. This would mean that in future even major regional centres and possibly the smaller capital cities will have no access to clinical trials and the modern treatment options to which they provide early access. Large sectors of the community will then miss out on the benefits of such access. Finally, this will greatly weaken the existing cooperative group structure in Australia, resulting in the potential loss of a valuable asset.

Gaps in capacity have been identified as:

1. 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. A fixed annual payment (the same for each group) is proposed to assist in these fundamental requirements.

2. Local data management;

The ability to manage data and other aspects of the trial locally is key to trial recruitment and quality. Oncologists need trial nurses/data managers on hand if they are to be able to recruit subjects efficiently. Nearly all State cancer councils provide some support in this way, mostly in metropolitan teaching hospitals. Additional support for local data management is required if increased recruitment is to occur. It could also be targetted on sectors that have not been involved in trials before, e.g. the private and rural sectors.

3. Central trial coordination, management and analysis of trials;

The 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.

Funding arrangements should reflect the actual cost of each of these activities by providing a cooperative group with a lump sum at activation of the protocol (around \$100,000 for a national phase III trial with lesser amounts for phase II and international phase III trials) and a modest amount per case (\$500) thereafter. A large payment per case as the sole funding mechanism does not reflect expenditure patterns or actual cash flow.

4. Audit and quality assurance of trials.

Triennial on-site audits of at least 10% of records is the de facto international standard. That is met by some groups in Australia but is unaffordable for others. All cooperative group trials need to be part of

an audit/monitoring scheme that meets certain minimum standards. Data audits are one universal aspect of quality. Quality assessment of radiation, chemotherapy, surgery, pathology, etc. also needs consideration. Agreed minimum audit and quality standards for Australia need to be defined. An amount per trial site should be allocated for audit programs.

In addition to funding the four areas discussed above, consideration needs to be given to funding for coordination of the program, promotion of clinical trial enrolment to the public and health providers, establishment of a clinical trials register and program evaluation.

Funding mechanism

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, and there is no indication that disease-specific funding will be supported, although in other respects the NHMRC (Chalmers) Review of Clinical Research in Australia and this proposal are consistent and complementary.

Governance

It is assumed that the funder (the Commonwealth) would establish an oversighting committee possibly under the aegis of an existing organisation such as COSA. The Chair should have a good understanding of clinical research and preferably no affiliation with any of the cooperative groups. This committee would implement the program in line with the funder's objectives and guidelines. Funding in the first instance should be for a three year period.

List of Recommendations

1. That the Commonwealth enhance the capacity of Australian cancer cooperative groups by providing Department of Health and Ageing funding for a period of three years, with ongoing assessment and final review in the third year.
2. That the funding be applied to:
 - a) develop and enhance the existing cooperative groups' organisational capacity, trial design/protocol preparation, local and central trial coordination, data management and analysis, and quality and audit programs, so that Australia retains its capacity to conduct world-class clinical cancer research;
 - b) develop cooperative groups for common cancers where no such groups are established;
 - c) provide for cancers that are too small to warrant a dedicated cooperative group in Australia.
3. That performance be continuously assessed, including measures of:
 - a) the number of clinical trial protocols facilitated, and the quality, relevance and health priority of each;
 - b) the number of positions funded, and the organisations supported through the funding;
 - c) evidence of improved quality assurance activities including the establishment of uniform standards across groups and increase in audit activities undertaken;
 - d) leverage of funding from other sources;
 - e) other appropriate longer term measures.
4. That the review in the third year consider whether any future funding should remain with the Department of Health and Ageing or be rolled into NHMRC funding processes.
5. That the Department of Health and Ageing fund a consumer awareness campaign as to the availability of, and benefits from participation in cancer clinical trials.
6. That funding be conditional on appropriate consumer involvement in the operations of the cooperative groups.
7. That a Cooperative Cancer Clinical Trials Committee be established to oversee the implementation and management of any funding program that is provided.
8. That the Cooperative Cancer Clinical Trials Committee have the power to form an Executive Committee for day-to-day management, as well as such subcommittees as are necessary to its efficient and effective functioning.
9. That the Cooperative Cancer Clinical Trials Committee be provided with the resources to access the services of an Executive Officer, and other financial resources as are necessary for its efficient operation.
10. That the Cooperative Cancer Clinical Trials Committee be able to require such data as are necessary to assess the outcomes of the cooperative group trials program, but that the Committee be mindful of the administrative burden on the cooperative groups in setting the reporting requirements.
11. That assessment and review of the program be funded as part of the program, the review commencing not later than nine months before the end of the initial funding period.
12. That funding be provided to establish of a Clinical Trials Register for cancer trials in Australia.

Recommended Budget

An estimate of the required budget for capacity development of the cancer cooperative group trials (all amounts in \$000)

	Year 1	Year 2	Year 3
1. Operational support funding			
– current 7 groups +1 new group (lung, assumes germ cell → urology group) \$85K/yr each	680	680	680
2. Protocol development and central trial management			
– Assume 8 then 10 then 12 national Phase III trials activated per year @ \$100,000; & 12 international Phase III trials year @ \$50,000 ea.	1,400	1,600	1,800
– Assume eight phase 2 trials activated per year @ \$40,000 each	320	320	320
– Per case funding for all trials – assume 2,000 people in year 1 increasing by 500 per year @ \$500 each	1,000	1,250	1,500
3. Local data management capacity			
– Funding of cancer councils or coop groups for data managers (not for industry trials)	500	550	600
– targeted funding for rural, private etc, say	200	250	300
4. On-site auditing	250	250	250
5. Program coordination	350	200	200
6. Promotional activity	200	200	200
7. Review and evaluation	75	75	150
7. Clinical Trials Register	200	100	100
Totals	5,175	5,475	6,100