Australian Clinical Trials Alliance

Refinement of the standard list of items associated with conducting Clinical Trials in Australia. Draft Final Report –Incorporating the Revised List

The Australian Clinical Trials Alliance (ACTA) welcomes the opportunity to provide feedback to the National Health and Medical Research Council (NHMRC) on the draft final report on revising the list of standard items for clinical trials for the purpose of determining national efficient prices for these items.

About the Australian Clinical Trials Alliance

ACTA was established in 2013 as a national peak body to support high-quality investigator-led clinical trials and clinical quality registries within the Australian healthcare system. ACTA's mission is to promote effective and cost-effective health care in Australia through investigator-initiated clinical trials that generate evidence to support decision-making by health practitioners, policymakers and consumers.

The ACTA community incorporates more than 50 clinical trials networks, clinical trial coordinating centres and clinical quality registries (see Appendix A). Each of these networks comprise up to several hundred senior doctors, nurses, allied health professionals and career researchers, and cover a broad range of disease groups and clinical disciplines. They are among Australia's most productive and high impact researchers - responsible for establishing the effectiveness, and in some cases the harm, associated with new and/or commonly used medical therapies.

Key comments

- ACTA notes the principal purpose of the list and associated table of standard costs "*to provide an authoritative reference point for the negotiations of a trial budget…*" and strongly supports the work of the NHMRC to provide leadership in developing the list as a mechanism to reduce uncertainty and variability around clinical trial costs.
- We believe the revised list and set of guiding principles outlined in the draft final report represent a much improved, streamlined version that has addressed many of the concerns raised previously.
- We believe the most significant development within the revised document is the recognition, as a guiding principle, that trial budgets should be limited to include only those services that are over and above the standard of care that would have been otherwise provided to any patient for his or her condition had they not participated in a clinical trial.

  We recognise and wish to highlight (as was noted in the report), the potential complexity of defining 'standard of care' within a healthcare system in which there is acknowledged variation in care. In this regard we recommend the guiding sub-principle that *for the purposes of costing within a clinical trial budget*, if an intervention is recognised as part of routine practice in any potential trial site in Australia, it is acceptable that it be regarded as an acceptable standard of care at all sites that are willing to participate in the trial.

  Moreover, we believe that the process of applying or 'operationalising' the standard of care principle will be of critical importance and that the document must provide guidance on this accordingly. The only valid and viable method is for determination of what is standard care to be made by individual hospital departments or Medicare Locals or equivalent. *(section III)*
- The guiding principles should recognise the enormous value of investigator-led trials to the health system. As such the costs charged to investigator-led trials, when activity exceeds standard care, should be charged at the marginal rate to the health service. In determining how much is charged, up to the full marginal cost, it is reasonable for health services to consider the potential benefit of the trial to participating patients and broader potential benefits to the institution, healthcare system and future patients. *(section IV)*
- We strongly suggest that the document be amended to outline how sites should apply the list to ensure that the minimum threshold of critical site infrastructure for the site to be capable of conducting trials is factored within trial budgets. *(section V)*

ACTA made a written submission to the Independent Hospital Pricing Authority (IHPA) in response to the initial discussion paper on the development of a table of standard costs for conducting clinical trials in 2013. Box 1 outlines the six key recommendations made by ACTA at that time. We were subsequently invited to provide advice on behalf of the ACTA community during a face-to face interview as part of the most recent consultation round to revise the published list.

Box 1.

ACTA's key recommendations to the Independent Hospital Pricing Authority in 2013.

Recommendation 1. The table of clinical trial costs should be preceded by a section outlining the principles of costing clinical trials and when these costs should be considered (or not considered) a trial cost.

Recommendation 2. The paper should recognise the importance of clinical trials research in ensuring quality health care in Australia and should recommend that there are mechanisms to factor costs of appropriate, high quality clinical trials into the health care system.

Recommendation 3. The costs of undertaking clinical trials should be confined to the additional costs over and above what would be provided as part of a routine or standard care, or any reasonable option for such care.

Recommendation 4. The application of clinical trial costs should differentiate commercial and investigator-led clinical trials aimed at optimising quality health care.

Recommendation 5. Health economic assessment of the value of clinical trials (particularly investigator-led trials) should be factored into future costing and funding models for clinical trials in Australia.

Recommendation 6. Acknowledgement of the important role of the private sector and of private insurance to the clinical trials effort in Australia should be added.

We would like to take this opportunity to acknowledge the work of the NHMRC, IHPA and both the previous and current Commonwealth Governments to strengthen the clinical trials effort in Australia. We believe that the draft final report and revised table submitted by HealthConsult has made substantial progress and addressed a number of the important issues expressed by the clinical trials sector over the last 12 months.

In particular, we applaud the important addition of the guiding principle that;

> 'Although a full suite of clinical services is included on the list, in determining trials budgets it is intended that only those clinical services that are over and above the standard of care that the health services would have provided to any patient for his/her condition if he/she had not been enrolled in the clinical trial are used in the negotiations around setting trial budgets.'

However, we believe that by electing not to differentiate between principles for costing commercial trials and investigator-led trials, the application of the revised list will at best be limited in its application, and at worst, could serve as an impediment to the conduct of important public-good trials in Australia. We strongly suggest that the following critical issues are addressed in the revised document prior to submission to IHPA for re-costing.

I. Who conducts clinical trials?

There are two broad groups that conduct clinical trials: commercial entities and independent academic investigators. However, while the distinctions between these are often entirely clear, there are some clinical trials that involve both a commercial entity and academic investigators. It may be relevant to these guidelines to specify a definition for accurate categorisation of a trial as either commercial or investigator-led. We believe that the critical determinant of whether a trial is investigator-led relates to whether the academic investigators have intellectual and operational independence in relation to the design, conduct, analysis, interpretation, and reporting of a clinical trial. So long as contracts between an investigator group and a commercial entity specify that intellectual and operational independence lie with the investigators, then a trial should be categorised as investigator-led, irrespective of the nature of the sponsor or the provision of resources, either financial or in-kind, by a commercial entity.

II. Who benefits from clinical trials and who pays for clinical trials?

There are three major beneficiaries from clinical trials. Firstly, and most importantly, current and future patients have the potential to benefit. Current patients may have access to treatments that would not otherwise have been available. Future patients benefit from the new knowledge generated by trials to guide their therapy. Secondly, the healthcare sector benefits from new knowledge about the effectiveness and cost-effectiveness of both new and existing therapies/clinical interventions, allowing the sector to make rational decisions that maximise productivity. Thirdly, where trials are conducted by commercial entities, they acquire new knowledge that can be used for licensing, regulatory applications, and marketing. This is an entirely appropriate benefit for the very substantial investment that commercial entities make in developing new treatments and bringing them to market. It needs to be acknowledged that very few if any new drugs or devices can be brought to market for the benefit of patients and the community without engagement of the commercial sector.

There are three major potential sources of funds that pay for the conduct of clinical trials: commercial entities, research funding bodies (both Government and philanthropic), and the healthcare sector. The consideration of the appropriate and optimal source of funding, from among these sources, should take into account a consideration of where benefits from the clinical trials will accrue. If this approach is considered reasonable, there are clear implications for issues around 1) the cost of providing and the process for determining standard of care, 2) marginal versus total cost, and 3) the costing of the minimum infrastructure necessary to undertake clinical trials.

III. Standard of care

ACTA applauds the addition of a guiding principle in the draft final report asserting that it should be accepted that within clinical trials, irrespective of whether they are commercial trials or investigator- led 'public-good' trials, the usual costs of providing healthcare should not be shifted to the trial.
The cost of providing healthcare should, rightly, lie with the healthcare sector and the cost of conducting a trial should be limited to the additional cost, over and above, the provision of healthcare that would have otherwise been provided. This principle should apply to the costing of activities as well as the availability and provision of infrastructure that supports activities.

However, the application of this principle is critically dependent on how it is operationalised and this relates to both the definition of, and the process for, determining what is standard care. This would be straightforward if there was no variation in standard care. Unfortunately, for the vast majority of diseases and corresponding clinical interventions there is substantial variation in standard care. To deal with this complexity we propose that the following definition is added to the document:

> **'The 'standard of care' is an intervention that is recognised broadly within any given institution as routine practice based on the available evidence and is therefore recognised as an acceptable standard of care by all sites that are proposing to participate in the trial.'**

The document should also provide guidance on the process for determination of what is standard care. Given the inherent variability in the nature of standard care, and the locally acceptable range of what is considered acceptable practice, we believe that the only valid and viable method is for determination to be made by relevant hospital departments or Medicare Locals or equivalent (i.e. those institutions or sites that are participating in the trial). It would be appropriate for institutional Research Governance Offices to require departmental sign-off to support assertions of what is standard care, but we do not believe that Research Governance Offices have the clinical knowledge or access to relevant information to make this determination.

The process outlined in the document should also indicate what occurs if, following submission to a Research Governance Office, there is still not agreement as to what constitutes standard care. We propose that ultimate discretion over this decision-making should lie with the hospital or Medicare Local Chief Executive Officer or equivalent. Whilst an alternative might be some form of national or jurisdictional adjudication of what is standard care, we believe this is neither necessary nor desirable as the decision can and should be made at an individual institutional level that is best equipped to understand local clinical practice. This model most closely reflects how decisions are made at present as to what constitutes standard of care outside a clinical trial. If a more central process was required to adjudicate what was appropriate standard of care within a clinical trial it should also be required more broadly - which it is not. Indeed, any attempt to implement a national or even statewide approach is likely to significantly interfere with the timely and efficient conduct of clinical trials.

IV. Marginal Costs

ACTA believes that the guiding principles that accompany the revised list of standard items for clinical trials should recognise and acknowledge the enormous value of investigator-led public- good trials to healthcare. Public-good trials contribute to improving the healthcare system through better outcomes for patients and higher productivity. As such, the healthcare system benefits from public-good trials and has a strong incentive to support the conduct of investigator-led trials.

While it is entirely appropriate that commercial trials should be charged the total cost of trial-related activities and the necessary infrastructure to conduct trials (as per the table of costs), it is neither appropriate nor desirable for investigator-led trials to pay total costs. Rather, the document should include a guiding principle that explicitly states that investigator-led trials should only pay for the marginal cost of trial-related activities or infrastructure. For example, if blood tests are being conducted as part of an investigator-led clinical trial, and such tests can be batched to occupy spots on a clinical test run that would have been otherwise unoccupied, only the marginal cost should be applied to investigator-led trials. The alternative, in which investigator-led trials pay the total cost not only represents a substantial and unnecessary barrier to conducting public-good trials, - trials that benefit patients and the healthcare system overall - but would see Government and philanthropic research funders providing an inappropriate subsidy to the healthcare sector.

Moreover, in determining the costs to be charged to investigator-led trials, institutions should have the discretion to charge less than the marginal cost if they believe that doing so represents a sound investment in providing new knowledge to improve patient outcomes or improve healthcare sector productivity or both. To not allow this, as an explicit option, is to deny institutions the opportunity to meet their broad missions to not only provide patient care but to conduct research and development to improve the quality of healthcare. In allowing institutions to make decisions to charge less than the marginal cost, institutions should be guided by their interpretation of the potential benefit of the trial to participating patients and broader potential benefits to the healthcare system and future patients.

V. Minimum threshold of critical infrastructure

In considering the costs that should be charged to trials it is reasonable to consider both unit costs and costs associated with the provision of the infrastructure that is necessary to be able to conduct the trial at that site. For example, a trial may require a certain number of hours of the time of a Research Coordinator. If there are insufficient resources or promise of income to support employment of a Research Coordinator, above a certain threshold of a full-time equivalent, it is not possible for that site to participate in a trial. Where this human infrastructure already exists, it is entirely reasonable for the site to only charge a trial for the hours utilised for the conduct of that trial. However, where such infrastructure does not already exist it may be reasonable for a trial to be charged a sufficient amount to ensure the presence of the infrastructure necessary to conduct the trial. This would require an 'infrastructure charge' within the table of costs (not an infrastructure percentage) which would vary between zero (if the infrastructure exists) and the amount, specified by that site, that was necessary to provide infrastructure without which the trial could not occur at that site.

If a so-called 'infrastructure charge' principle existed, it would also be appropriate for the actual hours worked on the trial to be applied, without additional charge, against the infrastructure item and to only charge for hours that are additional once the infrastructure charge has been recouped. Trial sponsors would, of course, be in a position to form a judgment as to whether a site was viable for inclusion in the trial given the infrastructure charge being proposed by that site. Where a site already has sufficient infrastructure to be able to undertake a trial it is has a natural incentive to charge an infrastructure cost of zero, so as to attract the income that will be received from participating in the trial.

Summary

1. Trials should not pay for the cost of providing standard care – this is the role of the healthcare system. A trial should only pay for the additional costs of conducting the trial.
2. Standard care should be defined by clinical departments who have local and generalisable knowledge of the local standard of care and the range of acceptable standards of care for that site.
3. Investigator-led trials should only pay for the marginal cost of providing those items that are not part of an accepted standard care.
4. When considering the costs that will be charged for investigator-led trials, healthcare providers should have the option of charging less than the full marginal cost, taking into account the benefit to current and future patients as well as the healthcare system.
5. In determining charges for trials it may be reasonable that such charges take into account the minimum local trial infrastructure necessary for the site to be able to undertake trial activity.

Members of the ACTA Community

1. Australasian Child and Adolescent Obesity Research Network (ACAORN)
2. Australasian Consortium of Centres for Clinical Cognitive Research (AC4R
3. Australasian Gastro-Intestinal Trials Group (AGITG)
4. Australasian Kidney Trials Network (AKTN)
5. Australasian Lung Cancer Trials Group (ALTG)
6. Australasian Radiopharmaceutical Trials Network
7. Australasian Sarcoma Study Group (ASSG)
8. Australasian Sleep Trials Network (ASTN)
9. Australasian Society for Infectious Diseases Clinical Research Network (ASID CRN)
10. Australasian Stroke Trials Network (ASTN)
11. Australia & New Zealand Breast Cancer Trials Group (ANZBCTG)
12. Australia & New Zealand Neonatal Network (ANZNN)
13. Australia & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) National Cardiac Surgery Database
14. Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG)
15. Australian & New Zealand College of Anaesthetists Trials Group (ANZCA Trials Group)
16. Australian & New Zealand Intensive Care Society Centre for Outcomes & Resource Evaluation (ANZICS CORE)
17. Australian & New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)
18. Australian & New Zealand Melanoma Trials Group (ANZMTG)
19. Australian & New Zealand Urogenital & Prostate Cancer Trials Group (ANZUP)
20. Australia New Zealand Gynaecological Oncology Group (ANZGOG)
21. Australia College of Emergency Medicine Trials Group (ACEM Trials Group)
22. Australian Epilepsy Clinical Trials Network (AECTN)
23. Australian Motor Neuron Disease Registry (AMNDR)
24. Australian Musculoskeletal Clinical Trials Group (AUSMUSC)
25. Australian Neuromuscular Network (ANN)
26. Australian Orthopaedic Association National Joint Replacement Register (AOANJRR)
27. Australian Paediatric Research Network (APRN)
28. Australian Primary Care Research Network (APCReN)
29. Australian Research Centre for Health of Women & Babies, Robinson Institute.
30. Bi-national Colorectal Cancer Audit (BCCA)
31. Burns Service of Western Australia
32. Centre for Anaesthesia & Cognitive Function
33. Centre for Biostatistics & Clinical Trials (BaCT)
34. Cooperative Trials Group for Neuro-Oncology (COGNO)
35. Epworth HealthCare Clinical Trials & Research Centre
36. Multiple Sclerosis Research Australia Clinical Trials Network (MSRACTN)
37. Neuroscience Trials Australia (NTA)
38. NHMRC Clinical Trials Centre (NHMRC CTC)
39. NSW Better Treatments 4 Kids (BT4K)
40. Orygen Youth Health Research Centre
41. Paediatric Research in Emergency Departments International Collaborative (PREDICT)
42. Paediatric Trials Network Australia (PTNA)
43. Palliative Care Clinical Studies Collaborative (PaCCSC)
44. Perinatal Society of Australia & New Zealand IMPACT Collaboration
45. Primary Care Collaborative Cancer Clinical Trials Group (PC4)
46. Prostate Cancer Clinical Quality Registry
47. Psycho-oncology Co-operative Research Group (PoCoG)
48. Queensland Centre for Mental Health Research
49. Queensland Clinical Trials & Biostatistics Centre
50. School of Public Health & Preventative Medicine, Monash University
51. South Australian Health & Medical Research Institute (SAHMRI)
52. Spinal Cord Injury Network (SCIN)
53. The ASPREE Study Group
54. The George Institute for Global Health
55. Trans-Tasman Radiation Oncology Group
56. Type 1 Diabetes Clinical Research Network (T1DCRN)
57. Victorian Ambulance Cardiac Arrest Registry
58. Victorian Cardiac Outcomes Registry (VCOR)
59. Victorian Cervical Cytology Registry (VCCR)
60. Victorian State Trauma Outcomes and Monitoring Registry (VSTORM)