Australian Medical Research and Innovation Five Year Strategy

Title: Addressing the challenges of clinical trial access for Australians with rare cancers

Submitted by: CanTeen Australia
Contact information: Peter Orchard (CEO) | E: peter.orchard@canteen.org.au | P: (02) 9007 0201

Improving access to clinical trials for rare or less common cancers will be enhanced by:

- **National coordination, greater efficiencies in trial initiation processes, and strategic investment in workforce development, to ensure capacity to be part of multinational collaborative trials**
- **Establishing data-bases, biobanks and mechanisms for shared access to patient data**
- **Demonstrating capacity to efficiently conduct trials, attracting future funding and international partnerships**
- **Recognition by regulators of broader trial designs as evidence for approval of new treatments**
- **Engagement with multiple stakeholders and funders**

Rare cancers have a collectively high burden

Approximately 130,466 Australians are expected to receive a new cancer diagnoses in 2016 at an average age 66.1 years[1] with a significant proportion being diagnosed with a rare or less common form of cancer. The definition of what constitutes a rare or less common cancer diagnosis varies, but most are characterised by an incidence of less than 12 cases per 100,000 Australians each year[2]. However, given that there are estimated to be more than 200 rare cancer variants, the burden is very high. A recent report from Rare Cancers Australia estimates that more than 42,000 Australians are diagnosed with a rare cancer each year. This constitutes 30% of all cancer diagnoses or approximately 7% of the total Australian burden of disease[2]. Rare cancers disproportionately impact children and young people with Adolescents and Young Adults (AYAs) in particular being diagnosed at a rate of less than 1000 per year, often with a rare or less common form of cancer[3]. Treatments for rare cancers have not advanced at the same pace as treatments for common cancers over the past 20 years. Hence, those diagnosed with a rare cancer are more likely to die from their disease, with these cancers being responsible for 50% of cancer related deaths.

Patients with rare cancers have poor access to clinical trials in Australia

Cancer Australia considers improving national trial capacity and patient access a top priority. Australian patients with rare cancers currently have particularly poor access to world class clinical trials, with pharmaceutical companies reluctant to invest in the complex task of conducting large-scale clinical trials of promising new drugs and devices for a relatively small patient population. Rates of trial enrolment for rare cancer populations are difficult to obtain, partly because such information is not centrally recorded anywhere in Australia, however examination of trial registries suggests that few trials appropriate for these groups are initiated in Australia each year.

Adolescent and Young Adult (AYA) cancer patients, many of whom are diagnosed with rare cancers, are one of very few populations for which such information is available. They have been found to participate in trials at much lower rates than paediatric and older adult patients with only 7% of 16-19 year olds and 4% of 20-24 year olds enrolling in a clinical trial in Australia compared with 45% of younger children[4]. Facilitating trial participation amongst AYAs is particularly challenging as they may be treated in either a paediatric or adult setting. Some patients, typically those between 16 and 18 years of age, will therefore be too old to participate in a trial if treated in a paediatric hospital or too young if treated in an adult setting. There is also evidence that AYA cancer has a distinct biology and responds differently to treatment, requiring clinical trials of specific treatments.

Meeting the challenge of carrying out trials in small populations will become increasingly critical as advances in personalised medicines and development of treatments for specific genetic variations of cancers becomes the norm and populations from which patients can be recruited become narrower.

There are substantial barriers to initiating clinical trials and ensuring rapid recruitment for small and complex populations like those with rare cancers

Clinical trials for rare cancers taking place in other countries are often not available in Australia. Contributing to the poor availability of such trials in Australia are inconsistent regulatory, ethics and governance frameworks and procedures in different states and health districts. Lengthy clinical trial ethics and governance processes persist despite efforts to make them more efficient, with a recent

Pharmaceutical Industry Council survey of 19 companies indicating that slow research study start-up times and unpredictable costs were one of the primary barriers to conducting clinical trials in Australia. This study indicated that in addition to the time to prepare ethics and governance applications and the more than 30 days review time required to obtain ethics approval, governance approvals require an additional 49 days review time per site on average. This far exceeds the best-practice timeframes specified by the Australian Government Clinical Trials Action Group, which recommends that both ethics and governance approval should be achieved within a total of 30 days combined[5].

Workforce preparedness, capacity and willingness to initiate and conduct clinical trials can also be variable and cross-institutional collaboration challenges persist, including barriers to initiating trials across paediatric and adult healthcare settings. These issues can be particularly critical for conducting trials involving patients with rare cancers as trials will typically need to be established in multiple settings in order to recruit sufficient patients within viable timeframes. Variable engagement with rare cancer consumer organisations and with patients themselves in the development, promotion and recruitment stages of clinical trials and inconsistent involvement of general practitioners in clinical trials are also problematic. Taken together, these issues limit the attractiveness of Australian hospitals as sites for internationally conducted clinical trials for rare cancers.

National coordination, greater efficiencies in trial initiation processes and strategic investment in workforce development will improve local capacity to be part of multinational collaborative trials

The establishment of efficient and nationally consistent trial initiation, ethics and governance processes and costs will be critical to attracting industry investment in clinical trials for rare cancer populations and ensuring Australian hospitals are well placed to be involved in international trials. Rapid recruitment, multinational collaboration and cost-saving data sharing initiatives will also be vital to ensure that Australian patients participate in ground breaking, potentially life-saving clinical trials.

Efforts to drive consistent practices and efficient recruitment will require national coordination, led by new or existing services with strong clinical and research networks. Investment in building and maintaining workforce capacity to recruit to and conduct clinical trials in complex rare cancer populations is required in the multiple contexts where such patients are treated. This will include ensuring that staff across paediatric, adult and community health settings are knowledgeable about trials for rare cancer populations and have capacity and confidence to engage in recruitment activities.

Additionally, it will be important to ensure trials are well publicised amongst rare cancer advocacy groups likely to be in contact with patients suitable for, and seeking involvement in, clinical trials. It will also be vital to build networks with multinational trial groups and pharmaceutical industry bodies focussed specifically on rare cancers. This will assist in attracting co-investment by industry and philanthropic organisations, ensuring ongoing sustainable support for rare cancer-focussed clinical trials in Australia.

Establishing data-bases, biobanks and mechanisms for shared access to patient data are essential drivers of progress

A recent position paper from Rare Cancers Europe made a number of recommendations regarding trials of treatments for rare cancers[6]. These included establishing mechanisms for sharing clinical trial databases and data from clinical observational studies, and investment and ongoing support for the establishment of biobanks, prospective clinical databases and illness registries with linkages to patient records. Such efforts will strike an appropriate balance between patient privacy and commercial work-product protections, and expectations of data sharing to foster advancement and collaboration to develop and market new treatments. These initiatives would variously increase the likelihood of discoveries based on secondary analysis of trial data and generate external control population data for use in uncontrolled clinical studies, which may be more appropriate for rare cancer populations where randomised controlled trials can be infeasible.

Demonstrating capacity is critical in attracting future funding and international partnerships

Having addressed regulatory, ethics and governance, workforce capacity and data sharing challenges, it will be necessary to demonstrate local capacity to initiate trials for small and complex patient

populations rapidly and efficiently and to recruit participants in compressed timeframes. This will increase the likelihood that Australian hospitals and community healthcare settings will be included as sites for international collaborative trials. Government funded demonstration trials should ideally be conducted in one or more carefully selected rare cancer sub-populations, with applications assessed utilising existing national research infrastructure such as the Cancer Australia Priority Driven Collaborative Cancer Research Initiative.

AYA cancer patients are a particularly well-placed sub-population to conduct such demonstration trials since they are disproportionately affected by rare forms of cancer. As a group, they experience lower survival gains than children and older adult cancer patients and, as previously mentioned, have extraordinarily low rates of clinical trial participation.

Also in favour of conducting demonstration trials in this group is the existence of the nationally coordinated Youth Cancer Services workforce, which currently reaches 70% of AYA patients requiring in-hospital treatment. This provides a ready research platform that operates across the divide between the paediatric and adult hospital settings and links young cancer patients from across the country with centres of expertise.

Building on its existing AYA research, data and training expertise, funding for workforce development and national coordination, and support for researchers to initiate and carry out trials, will enable rapid and efficient recruitment of patients and provide clear evidence of local capacity to be involved in trials for small and complex populations.

Regulatory bodies need to recognise broader trial designs in approving new treatments

Therapeutic goods administration approval of new drugs typically requires that they have undergone the multiple phases of traditional clinical trial testing. Though some trials may utilise relatively small samples, traditional trials often require hundred or even thousands of patients to be treated in control and active treatment conditions. Many such trials will never be able to be conducted in the rare cancer context due to the small numbers of patients diagnosed each year, diffused across multiple treatment centres across Australia[7]. Thus, to ensure that those with rare cancers are not perpetually disadvantaged, different trial designs may need to be recognised by regulatory bodies[6]. These can include probability-based designs such as Bayesian adaptive trials; externally controlled studies where all patients enrolled in a trial are treated with the drug under study and compared with high quality control patients from observational clinical studies or clinical databases; or trials with surrogate endpoints such as biomarkers or scan data rather than survival outcomes. Appropriate recognition of these trial designs as sufficient evidence for registration and marketing of new treatments will make it more likely that pharmaceutical companies and collaborative trial groups will initiate such trials and hence that new treatments will be available for rare cancer populations.

Engagement with multiple stakeholders and funders will be critical to success

A critical focus of this strategy must be high level engagement with key researchers, clinicians, clinical trial groups and industry and community representatives to develop and implement a consistent national approach to conducting clinical trials in rare cancer populations. This will support not only domestically initiated trials but also inclusion of Australian sites in international trials. Co-investment opportunities with pharmaceutical industry, clinical trial groups and philanthropic partners will also be a priority to ensure the long-term sustainability of supporting access to clinical trials for patients with rare cancers.

References

1. Australian Institute of Health and Welfare. *Cancer in Australia: an overview 2014.* Canberra: AIHW;2014.
2. Rare Cancers Australia. *Just a little more time: Rare cancers update report.* Bowral, Australia: Rare Cancers Australia,; 16/03/2016 2016.
3. Australian Institute of Health and Welfare. *Cancer in adolescents and young adults in Australia. Cancer series No. 62. Cat. No. CAN 59.* 62 ed. Canberra: AIHW; 2011.
4. Mitchell AE, Scarcella, D. L., Rigutto, G. L., Vicky J Thursfield, V. J., Giles, G. G., Sexton, M., Ashley, D. M. Cancer in adolescents and young adults: treatment and outcome in Victoria. *MJA.* 2004;180(19):59-62.
5. Khan OA, Maccarrone C, Jones A, Monk D, Nielsen L. *Survey of Research Governance Timelines in Australia.* Canberra, Australia: Medicines Australia;2013.
6. Casali PG, Bruzzi P, Bogaerts J, Blay J-Y. Rare Cancers Europe (RCE) methodological recommendations for clinical studies in rare cancers: a European consensus position paper. *Annals of Oncology.* February 1, 2015 2015;26(2):300-306.
7. Olver I. Should clinical trials be approached differently for rare cancers? *Future Oncol.* 2016;12(10):1207-1209.