

# Trials and tribulations: improving outcomes for adolescents and young adults with rare and low survival cancers

Coordinated national action is needed to develop an evidence base and standards of care for young Australians with rare and low survival cancers

In November 2016, the Australian Senate established a select committee to explore the impact of funding models on rare and low survival cancer research.

CanTeen Australia presented a submission to this inquiry which highlighted the impact of these cancers on adolescents and young adults (AYAs) and the systemic barriers to improving outcomes for patients with rare and low survival cancers. Drawing from that submission, we present the argument for a strategic national approach, including a national trial network, to facilitate cross-sectoral coordination and investment to improve outcomes for AYA patients with cancer and the broader Australian population affected by rare and low survival cancers.

## Disproportionate burden of rare and low survival cancers in adolescents and young adults

Five-year (all cancers) survival is high for AYAs (88%); however, this masks their poorer outcomes for certain central nervous system (41%) and soft tissue cancers (49%).<sup>1</sup> Despite recent treatment advances, survival gains have been smaller for AYAs than other age groups,<sup>2</sup> in part, due to AYAs being disproportionately diagnosed with rare cancers, which tend to have poorer prognoses<sup>1,3</sup> and are responsible for the majority of AYA cancer deaths.<sup>4</sup> Establishing treatment efficacy in this population is particularly important, as mounting evidence suggests that cancers diagnosed in the AYA age range may have distinct biology, prognosis and clinical behaviour (eg, likelihood of metastasising or recurrence in distant organs), and different responses to otherwise successful paediatric or adult treatments.<sup>5,6</sup>

Diagnostic and treatment advances have reduced common cancer mortality rates, but rare cancer treatments have not similarly advanced and can be prohibitively expensive and less accessible.<sup>4</sup> Moreover, research into these cancers is complicated by their rarity, making it challenging to conduct traditional large, late phase randomised controlled trials. These often require access to hundreds (if not thousands) of patients and typically seek to recruit from a small number of academic treatment centres with high concentrations of suitable patients.<sup>4</sup>

Embedding clinical research within paediatric care has driven dramatic improvements in childhood cancer survival.<sup>7</sup> While factors including delayed diagnosis may influence AYA cancer outcomes, limited survival gains are also driven by poorer clinical trial access and participation.<sup>2,3</sup> Due to the low availability of relevant trials in AYA treatment settings, and because of inclusion criteria that may prevent AYA enrolment, fewer Australian AYAs participated in trials (4–8%) compared with children (40%).<sup>3,8</sup>



Strategies enacted in the United Kingdom — including research awareness campaigns, mandated broader trial age limits and streamlined approval processes — saw participation rates rise from 24% to 37% in 15–19-year-olds and from 13% to 18% in 20–24-year-olds between 2005 and 2010.<sup>9</sup> Corresponding initiatives may similarly increase Australian participation rates. However, improved outcomes for this population are not likely to be realised by action directed at AYAs alone, but rather through coordinated efforts targeting rare and low survival cancers more broadly.

## Rare cancers, rarer funding opportunities

In line with broader developments in cancer therapeutics, rare and low survival cancer treatments increasingly use innovative targeted approaches and experimental delivery methods, which are more expensive to develop and evaluate than traditional therapies.<sup>4</sup> Incorporating precision medicine strategies in rare cancer-focused trials that facilitate participant enrolment to enhance prior probability of benefit may offset evaluation costs somewhat by increasing trial efficiency and the likelihood of identifying a drug effect.<sup>10</sup> However, without foundational government support during early development and simplified processes for registering treatments for extended indications, these therapies are still likely to remain less attractive targets for industry investment due to their narrower applications.

Australian research and infrastructure-funding approaches have historically favoured areas with a substantial evidence base and researchers with established, field-specific track records. This funding approach has disadvantaged rare and low survival cancer research, in which the evidence base and opportunity to establish a competitive track record are lacking. Moreover, historic

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preferences for funding shorter duration research projects using existing infrastructure have also disadvantaged rare cancer research. Rare and low survival cancer research may benefit from program-based approaches, giving researchers freedom to explore novel treatment pathways from pre-clinical discovery, through clinical trials, to implementation over a longer period of time, facilitated by investment in new infrastructure to reach these patients in a diversity of treatment contexts.

Recent changes to the grant schemes of the National Health and Medical Research Council, with increased funding opportunities for novel and innovative ideas judged primarily on scientific merit rather than investigator track record ([www.nhmrc.gov.au/restructure/changes/ideas-grant](http://www.nhmrc.gov.au/restructure/changes/ideas-grant)), and prioritised funding for rare cancer and rare diseases from the Medical Research Future Fund<sup>11</sup> may help address these disparities. The prioritisation of novel trial designs (eg, historically controlled trials, tele-trial models or basket designs), which are more economically, practically and ethically appropriate for rare and low survival cancers with their low incidence and high geographic dispersion,<sup>12,13</sup> may be of substantial benefit in future funding allocations, alongside efforts to improve access to large international trials targeting these cancers. Establishing critical enabling infrastructure, such as biobanks and national minimum datasets for these cancers, can also create research efficiencies and generate historical controls.<sup>13</sup>

### Clinical trial complexities discourage drug development

The poor access of Australians with rare and low survival cancers to world-class trials partly results from a complex local clinical research environment, which varies considerably across jurisdictions and between paediatric and adult settings. The latter variation particularly disadvantages AYAs, for whom inconsistent age restrictions and accreditation requirements can prevent them from accessing both paediatric and adult trials.

Trials are inconsistently embedded into standard care, and administrative resources and research capacity are often insufficient. Increasingly complex national and international infrastructure and regulatory requirements exacerbate these challenges, as do poorly defined partnerships between industry and government in this area. These regulatory complexities are particularly discouraging for the small and often widely dispersed AYA patient population.<sup>3</sup> The gap created by poor access to trials for patients with rare cancers is unfortunately filled by off-label use of existing therapies, increasing the evidence gap.<sup>14</sup> Even when this approach is subsidised, substantial out-of-pocket expenses are common.

Rare and low survival cancer diagnoses can be accompanied by rapid disease progression, particularly when diagnosis is delayed, making recruitment, treatment and data collection windows short and traditional late phase trials unfeasible. Despite the positive impact that Australian clinical trials networks have had on cross-institutional collaboration, multicentre research and translation,<sup>15</sup> there is no coherent network focused on rare and low survival cancer, thus limiting the capacity to conduct multicentre trials for these cancers. Establishing such a network will be critical in achieving a

unified approach to developing evidence and standards of care. By operating across geographical and organisational divides and concentrating patient care in centres of excellence, with clinical research embedded within standard care, such a network could improve access to international multicentre trials, increasing their reach and efficiency, and could drive translational efforts.<sup>15</sup> Enabling infrastructure such as a rare and low survival cancer registry and a linkage-capable minimum clinical dataset will likewise provide critical data-driven insights.<sup>16</sup> The funding, critical to the success of such a network, could likely leverage industry co-investment, and minimising cost and regulatory barriers to opening trials and incentivising trial enrolment will likewise improve patient access.

Meeting the challenges of conducting trials in small populations will become increasingly critical, as targeted therapeutic research advances and personalised medicine becomes commonplace for all cancers, including rare diagnoses. With these developments, eligible patient populations will become smaller and more selective, and traditional trials models will become decreasingly relevant, thus exacerbating existing problems with potentially unethical and unattractive use of placebos or less effective control therapies in rare and low survival cancer trials. Alternative trial models for these cancers will be increasingly needed, including externally controlled approaches using linked registries, minimum datasets and biobanks, and Bayesian designs.<sup>16</sup> This is not without its challenges, as the frequent lack of a clear standard of care as an appropriate comparator in many low incidence cancers contributes to challenges in establishing trial control arms and can contaminate external control data. As the clinical trials landscape shifts, expanding the range of study designs accepted as sufficient evidence for approval and listing of new therapies on the Pharmaceutical Benefits Scheme may also become necessary.<sup>12</sup> Given the low incidence of many of these cancers, well developed approaches to post-marketing evaluation will need to match the evolution of accepted endpoints for therapeutic registration and reimbursement in order to reassess therapeutic benefit in real world conditions and ensure the ongoing appropriateness of approved therapies.

### Coordinating advocacy, strategy and investment

The need for a coherent strategy for rare and low survival cancers is increasingly being recognised and addressed internationally. The US example, the *Recalcitrant Cancer Research Act*,<sup>17</sup> requires the National Cancer Institute to develop and action scientific frameworks coordinating prevention, early detection and treatment-focused research in cancers with survival rates below 50%. The Australian Government currently lacks such a strategy to guide research investment and related policy development. While the recent Senate inquiry is a critical step towards a nationally consistent approach to rare and low survival cancers, an overarching Australian strategy to address these cancers is urgently needed. Local efforts to deal with survival deficits in rare and low survival cancers (and populations disproportionately affected by

these cancers) through greater policy, advocacy, investment and research coordination could be facilitated by a government-supported rare and low survival cancer taskforce uniting consumer, government, academic, industry, not-for-profit and service delivery stakeholders.

In addition to supporting and informing the development of a comprehensive Australian rare and low survival cancer strategy, enabling sustainable and well resourced research and implementation efforts, this group should work to raise the public profile and priority of these cancers, drive the establishment of an appropriate trial network with supporting infrastructure, and advocate for change in Australia's complex clinical trials environment. Building on the momentum of the recent Senate inquiry into the impact of funding models on rare and low

survival cancer research presents a real opportunity to improve outcomes for AYA patients with cancer and the broader Australian population affected by rare and low survival cancers by taking a coordinated, affirmative action approach leveraging cross-sectoral coordination and investment.

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