

# Accrual of adolescents and young adults with cancer to clinical trials

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Cancer is the most common disease-related cause of death in 15- to 29-year-olds in Canada, with more than 2000 new cancer cases and more than 300 deaths per year<sup>1</sup>. Between 1996 and 2005, the cancer incidence in that population rose by approximately 1%<sup>1</sup>. Although mortality rates have declined<sup>1</sup>, rates of improvement have been less than those observed in younger and in older patients<sup>2</sup>. Statistics alone are an inadequate reflection of the personal and societal impact of cancer in the young adult age group. Statistics Canada estimated that, in 2004, 16,000 potential life-years were lost to cancer in individuals 15–29 years of age<sup>1</sup>.

Accrual to clinical trials has been a major contributor to the steadily increasing 5-year survival rates in cancer. Compared with children and older adults, adolescents and young adults (AYAs) have been enrolled on clinical trials at a much lower rate in Canada<sup>3,4</sup> and internationally<sup>5,6</sup>, leading to the plausible postulate that lower trial participation accounts at least in part for lesser survival gains in that age group<sup>7,8</sup>. Improving access to clinical trials for AYAs is a priority<sup>6,9</sup>.

## Development of Dedicated AYA Cancer Networks

The impact of a cancer diagnosis for AYAs during this period of immense change in relationships, family, education, and employment requires a unique approach and unique support. In recent years, the gap in clinical care and research for AYAs with cancer has been recognized internationally, triggering the development, by philanthropic organizations, of programs specific to AYA needs. CanTeen (<http://www.canteen.org.au>) was formed in Australia in 1985 and has received funding support from the national government. The Teenage Cancer Trust (<http://www.teenagecancertrust.org>) was established in the United Kingdom in 1989 and has built 25 centres in England, Scotland, and Wales for AYAs with cancer. The Lance Armstrong Foundation, now LIVESTRONG (<http://www.livestrong.org>), was founded in 1997 and, in 2006, enabled the development of the Young Adult Cancer Alliance (a coalition of 150 support and advocacy groups) that has become a self-standing organization, Critical Mass (<http://www.criticalmass.org>).

The Children's Oncology Group, the largest cooperative clinical trials group in the world for children and AYAs with cancer, formed an AYA discipline committee in 2000 (<http://www.childrensoncologygroup.org>). In 2005, encouraged by LIVESTRONG and the Children's Oncology

Group, the U.S. National Cancer Institute convened a Progress Review Group focused uniquely on a population (AYAs) rather than on a disease and partnered for the first time with a nongovernmental organization (LIVESTRONG)<sup>9</sup>. International Society of Paediatric Oncology symposia on AYA oncology have focused on the challenges of accruing AYAs to cancer clinical trials, as reflected in national initiatives in Australia<sup>10</sup>, Italy<sup>11</sup>, the United Kingdom<sup>12</sup>, and the United States<sup>13</sup>. Recognizing that cancer is the leading cause of death from disease for AYAs, the American Society of Clinical Oncology launched their Focus Under Forty initiative (<http://university.asco.org/focus-under-forty>) and, in collaboration with philanthropic and professional organizations, designed education programs to increase awareness of the unique biology and care issues associated with cancer in this age group, including clinical trials.

In Canada, early interest in AYA oncology was driven by the Pediatric Oncology Group of Ontario<sup>14</sup> and the C17 Council (<http://www.c17.ca>), a consortium of all pediatric cancer centres in Canada. The Canadian Task Force on Adolescents and Young Adults with Cancer was established in 2008, funded by the Canadian Partnership Against Cancer. From its first international workshop in 2010<sup>15</sup> came 6 recommendations and, from the second workshop in 2012, a Framework for Action<sup>16</sup>; both included an impetus to enhance clinical trial accrual<sup>17</sup>.

## Importance of Cancer Clinical Trials

Medical practice has been transformed and tremendous advances for patients realized through randomized clinical trials<sup>18,19</sup>. In childhood cancers, survival rates have quadrupled since the mid-1970s and now exceed 80%<sup>19</sup>. As stated in the Canadian Cancer Research Alliance report on the state of cancer clinical trials in Canada, "without clinical trials, the outcomes of cancer patients will not continue to improve"<sup>20</sup>.

Generalizability is key to ensuring that clinical trial results can be reliably extrapolated and used to guide health policy and health care for the general population. In the United States, more than 60% of children with cancer are enrolled on clinical trials<sup>19</sup>; accrual drops to 2%–4% of those 20–29 years of age<sup>21</sup>, raising real concerns about the generalizability of clinical trial results within the wider population of young adults with cancer. Differences in cancer subtype, disease biology, and patient physiology limit

the applicability to young adults of research conducted in children. For instance, relative to younger patients, AYAS experience increased treatment-related toxicity<sup>22</sup>.

Defining the AYA age range is important. The lower bound is uncontested, given that the international registration of children with cancer encompasses the group 0–14 years of age. Furthermore, there is growing acceptance that, for this purpose, “adolescence” comprises the teenage (15–19) years. Much less agreement exists on the upper bound for AYAS. It has been argued that the boundary will vary according to circumstance—for example, 24 years for active care, 29 for epidemiology, and 39 for “long-term” follow-up<sup>23</sup>. However, the U.S. National Cancer Institute’s Surveillance, Epidemiology, and End Results Program has adopted 29 years for the upper age limit<sup>24</sup>, as has the Canadian Cancer Society.

The debate is not artefactual. The classification system proposed for cancer in AYAS<sup>25</sup> and adopted by the Surveillance, Epidemiology, and End Results Program is pertinent to the 15–29 age range. It is also clear that the distribution and biology of malignant diseases in AYAS varies appreciably not only from the nosologically same diseases in children and older adults<sup>26</sup>, but also across the AYA age range. Focused translational and clinical research is required to understand the malignancies prevalent across the age groups that constitute this young population.

### The Landscape in Canada

The Canadian Task Force on Adolescents and Young Adults with Cancer established a Clinical Trial Accrual Working Group in 2013. As a prerequisite to addressing barriers to enrolment and improving recruitment, that group, comprising oncologists in pediatric and adult practice, with representation from the Canadian Cancer Society and academic clinical trial cooperative groups, was charged with determining national accrual rates for AYAS to clinical trials. Obtaining data about clinical trial accrual for AYAS in Canada has proved to be a greater challenge than anticipated. There is no single, national, comprehensive, and accurate source of such information, because the databases that include age as a variable reside with the numerous sponsors of clinical trials or represent fragments of the population.

Health Canada, the federal department responsible for the review of clinical trial applications, recently created an online database of Canadian clinical trials involving human pharmaceutical and biologic drugs (<http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdonclin/index-eng.php>). Health Canada does not collect information about accrual.

The Canadian Cancer Trials Group (previously the NCIC Clinical Trials Group) is an adult cooperative group that conducts academic clinical trials for individuals with cancer across Canada. A retrospective review of enrolment to Canadian Cancer Trials Group trials between 2000 and 2013, which accounted for disease incidence by age, revealed that individuals 18–29 years of age were, overall, underrepresented by a factor of almost 2 when compared with individuals 30 years of age and older<sup>3</sup>. However, AYA accrual in certain disease types, including non-Hodgkin lymphoma and breast and cervical cancers, was greater than expected.

The U.S. National Cancer Institute’s Cancer Therapy Evaluation Program records age at time of accrual for the small proportion of Canadian patients enrolling on National Clinical Trials Network (NCTN) studies in the United States. Pharmaceutical sponsors of clinical trials hold detailed data about patients enrolled on their studies, but collating such information from those sources is impractical; numerous individual data-sharing agreements would be required.

Recently launched, with the aim of supporting researchers conducting academic-sponsored multicentre clinical trials that will benefit patients, the Canadian Cancer Clinical Trials Network (<http://www.3ctn.ca>) will collect data about accrual to academic clinical trials across Canada. Currently, collection of individual patient characteristics (such as age) and of data about accrual to studies sponsored by the pharmaceutical industry and to single-institution trials is not planned (Dancey J. Personal communication).

The Pediatric Oncology Group of Ontario maintains a comprehensive database of children diagnosed with cancer in the province of Ontario. The data captured include information about clinical trial participation, but represent only individuals less than 18 years of age treated at pediatric institutions in Ontario. Between 2010 and 2013, 12.2% of the 15- to 17-year-olds captured in that database were enrolled on a clinical trial (DiMonte B. Personal communication).

The Ontario Institute for Cancer Research began collecting aggregate data about clinical trial enrolment of 15- to 29-year-olds at adult institutions in 2012. Data provided by clinical trial units were incomplete in the first year, major centres did not participate, and only 3 AYA accruals were identified. The information collected prospectively in 2013 is more robust, with 40 accruals reported, 32 of them registered from a single centre. In 2014, reported accrual dropped to 32 patients overall. The data collection process is currently unfunded and not validated. A limited review suggested minor underreporting from at least 1 institution.

Cancer Care Ontario used accrual to clinical trials as a quality indicator until 2011, but no longer does.

The Childhood, Adolescent, and Young Adult Cancer Survivors research program records accrual of patients 15–24 years of age to clinical trials in British Columbia<sup>27</sup>. As detailed in Table 1, clinical trial enrolment declines with increasing age. Good accrual in the early 1990s has not been maintained over subsequent years.

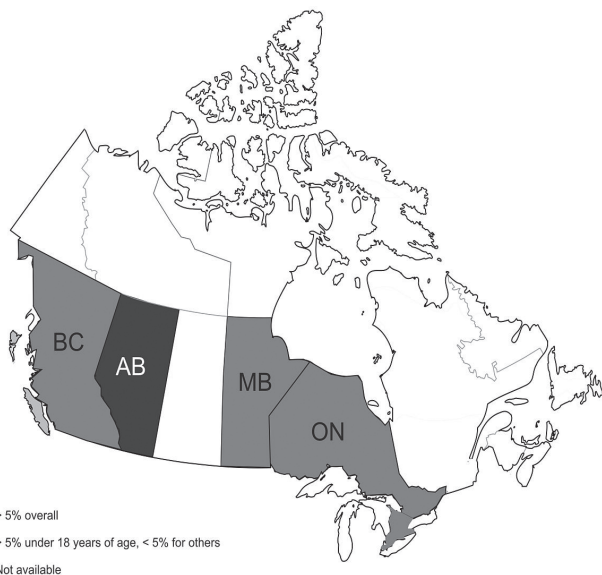
Table 1 and Figure 1 summarize provincial data, including those from CancerCare Manitoba and Cancer-Control Alberta. Notably, the age range and disease types included vary from one database to the next.

At an institutional level, major systemic barriers hinder clinical trial accrual across the AYA spectrum. Dichotomous pediatric and adult approaches to patient care and clinical research have evolved over decades and become established. Even in institutions in which care is provided within the same hospital, the infrastructure, funding model, and clinical trial research office are completely separate for children and young adults. In institutions that are geographically separated, additional challenges are present.

**TABLE 1** Reported accrual of adolescents and young adults with cancer to interventional clinical trials in Canada, presented as proportion of incident cases by province

Province	Age range (years)	Year	Accrual (%)	Source
Alberta	15–29 <sup>a</sup>	2000–2009	11.7	Alberta Cancer Registry <sup>b</sup>
British Columbia	15–19	1990–1994	29.3	Children, Adolescent, Young Adult Cancer Survivorship research program
		1995–1999	12.1	
		2000–2004	7.4	
		2005–2010	8.2	
	20–24	1990–1994	22.2	BC Cancer Agency
		1995–1999	3.1	
		2000–2004	2.3	
		2005–2010	6.9	
	25–29	1990–1999	2.3	BC Cancer Agency
		2000–2010	2.6	
Manitoba	15–17	2003–2013	7.0	CancerCare Manitoba
	18–30	2003–2013	0.4	
Ontario <sup>c</sup> (pediatric centres)	15–17	2010–2013	12.2	Pediatric Oncology Group of Ontario
Ontario <sup>c</sup> (adult centres)	15–29	2013	4.7	Ontario Institute for Cancer Research
		2014	3.5	

<sup>a</sup> Sarcoma and lymphoma only.  
<sup>b</sup> Combined with retrospective chart review.  
<sup>c</sup> Estimated cancer incidence.



**FIGURE 1** Reported accrual of adolescents and young adults with cancer to interventional clinical trials by province, presented as percentage of incident cases between 1990 and 2014. Note variation in reporting as detailed in Table 1.

### Opportunities for Progress

Collaboration is key to increasing the opportunities for AYAs with cancer to participate in clinical trials and the uptake to available trials. An AYA working group has been established that bridges the U.S. National Cancer Institute’s NCTN cooperative groups: the Children’s Oncology Group, the Alliance for Clinical Trials in Oncology, swog

(formerly the Southwest Oncology Group), NRG Oncology, and the ECOG-ACRIN Cancer Research Group in the United States, and the Canadian Cancer Trials Group in Canada. Goals include identification of gaps in which clinical trials are needed, systematic change in age eligibility requirements for AYA-relevant trials, monitoring of AYA accrual patterns over time on NCTN trials, and development of NCTN-wide strategies to promote and facilitate AYA accrual<sup>6</sup>.

Within Canada, the C<sup>17</sup> Council (pediatric) and the Canadian Cancer Trials Group (adult) have partnered to span the arbitrary age divide by developing a unified platform that enables children and adults to use a single clinical trials application from Health Canada to enrol on clinical trials. A harmonized approach for all aspects of clinical trial conduct, including monitoring and safety reporting, is being piloted in a clinical trial for patients 2 years of age and older with sarcoma (NCT02180867). The approach will continue to evolve as more trials are made available through that mechanism.

The Ontario Cancer Research Ethics Board, which has conducted ethics reviews of multicentre adult cancer trials since 2004, began reviewing pediatric submissions in 2015. Streamlining the ethics review system will make it easier to initiate cancer clinical trials at multiple centres for multiple patient age groups. Individual institutions in which treatment and research for AYAs is divided between pediatric and adult services are beginning to explore opportunities for closer working relationships between the associated clinical trial research offices and for minimization of duplicated workload. Effective operationalization of a unified platform for AYA clinical trial accrual will require major systemic change and drivers to champion institutional buy-in.

The Clinical Trials Working Group of the Canadian Taskforce on Adolescents and Young Adults with Cancer, having established indicators of poor national clinical trial accrual, continues to seek opportunities to develop a more robust and encompassing record, with the goal of developing a national source for clinical trial accrual data and using it as a benchmark for improvement. Acknowledging the time pressures affecting physicians and the financial constraints under which hospital clinical trial units operate, progress must be efficient and affordable. Discussion with the Canadian Association of Provincial Cancer Agencies will continue to explore whether provincial cancer agencies can work with their regional cancer centres to obtain the requisite data at the level of individual clinical trial units, where the raw information resides. Engagement of AYAs who have cancer is crucial to ensure that new clinical trials are acceptable, available, and accessible to them<sup>28</sup>.

In the United Kingdom, a national focus<sup>29</sup> on AYAs with cancer has resulted in improved participation in clinical trials for that group. Factors contributing to the U.K. success include the establishment of a Teenage and Young Adult Clinical Studies Group, an increase in the profile of AYAs among researchers conducting clinical trials, expansion of the age eligibility criteria for clinical trials, and increased collaboration between the pediatric and adult communities<sup>12</sup>. Through the ongoing collaboration of relevant stakeholders in Canada, the effort to better understand the hindrances to clinical trial participation and to actively develop strategies and systems to overcome those hindrances continues, in pursuit of the ultimate goal of improved survival and quality of life for AYAs with cancer.

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#### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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