Curr Pediatr Rep
DOI 10.1007/s40124-015-0075-y

HEMATOLOGY/ONCOLOGY (C COLE, SECTION EDITOR)

The Clinical Trials Gap for Adolescents and Young Adults with Cancer: Recent Progress and Conceptual Framework for Continued Research

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Abstract Over the past 30 years, adolescents and young adults (AYA, 15–39 years of age) with cancer have shown significantly less improvement in survival than younger and older patients. Because evidence suggests this may be related to their low participation in cancer clinical trials, increasing accrual to these trials has become a priority for closing this "AYA gap." This paper reviews data documenting low AYA enrollment, presents a conceptual framework for research and intervention (Clinical Trials Pathway to Enrollment) and summarizes recent developments in the United States National Cancer Institute-sponsored clinical trials enterprise that are expected to improve AYA enrollment, including the National Clinical Trials Network (NCTN) and expanded scientific collaboration between the Children's Oncology Group and adult NCTN groups. While time will be required for the effects of these changes to be fully realized, they offer a mechanism for facilitating the breadth of clinical/translational research needed for advancing AYA oncology and measuring its impact.

This article is part of the Topical Collection on *Hematology/Oncology*.

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Keywords Adolescent and young adult (AYA) · AYA gap · Clinical trials · Clinical trials accrual · Clinical trials enrollment · National Clinical Trials Network (NCTN)

Introduction

Over the past three decades, the number of cancer survivors in the United States (US) has increased from about 3 million to over 12 million [1]. While improvement in survival has been dramatic for children under 15 years of age and substantial for older adults, the same has not been true for adolescents and young adults (AYA, age 15–39 years). The term "adolescent gap" was introduced to the oncology lexicon in 1997 by Bleyer and colleagues in reference to their seminal observations linking age, clinical trial participation, and survival improvement [2]. Subsequently, several population-based analyses documented a striking and sustained failure to improve 5-year survival for AYAs at rates comparable to either younger or older patients [3–7]. A variety of factors are proposed to contribute to this survival disparity, including age-related differences in cancer biology [8, 9], increased treatment-related toxicity and mortality [10•], differences in developmental pharmacology [11], lower adherence to prescribed therapy [12•], and delayed access to appropriate treatment [13, 14]. However, the historically low participation of AYAs in US National Cancer Institute (NCI)-funded clinical trials may be particularly important [5]. Additional detriments resulting from non-participation of AYAs in NCI-funded clinical trials include forfeiting access to potentially beneficial investigational therapies, missing biospecimens that are essential for basic and translational research, and not informing studies of supportive care, quality of life, cancer

Published online: 18 February 2015

epidemiology, and other non-survival endpoints relative to this age group. Thus, while deficits in areas such as health insurance and psychosocial support also constitute important gaps for AYAs [15, 16], enrollment onto NCI-funded clinical trials remains pivotal for improving survival and related outcomes. For that reason, the AYA gap in clinical trial enrollment is the focus of this paper.

Defining the Enrollment Problem

It is well established that a significantly lower proportion of AYA patients than younger are enrolled onto cancer clinical trials. The first study to describe this was published by Krailo and colleagues in 1993, where cancer registry data maintained by the Los Angeles County Cancer Surveillance Program (CSP) were linked with patient registration data from the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) for patients from birth to 19 years; lower clinical trial enrollment was noted among patients 15 years and older [17]. Based on clinical trials enrollment data from the US NCI and population-level cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program, Bleyer and colleagues found that the proportion of new cancer patients registered with CCG and POG from 1989 to 1991 was lower than expected for patients 15–19 years of age compared with younger children (21 vs. 94 %); they also reported a substantially smaller reduction in the national mortality rate for the older patients over a similar period [2]. The extent to which clinical trials were actually available for cancers most prevalent among AYAs was not described. Using similar methods, other analyses in the US [3–7, 18] and elsewhere [19] also have described lower AYA enrollment, generally in the range of 10–20 % compared with 40–60 % for younger patients. While large sample size is a strength shared by all of those studies, a relative weakness is that enrollment proportions are estimates representing aggregate numbers of NCI-registered trial entries divided by SEER-identified incident cases of cancer over similar time frames. Using registry data to identify incident cases of cancer in patients from birth to 22 years, Shaw and colleagues found that in the setting of a children's hospital, 27 % of patients 15 years and older were enrolled on a clinical trial compared with 38 % of younger patients [20]. In that study, lack of a clinical trial was cited as the reason for non-enrollment in 57 % of older versus 41 % of younger patients. At the same academic institution, a significant difference in enrollment proportion for AYAs 15–22-year old was noted for the children's hospital (24/91, 26 %; derived from cancer registry data) and adult cancer center (5/121, 4 %; derived from billing and coding data); data regarding clinical trial availability were not reported [21]. In the NCI Patterns of Care Study, physician recall was used to determine clinical trial enrollment proportion for a cohort of 1358 AYAs identified through the SEER registry, which was 34 % for 15–19 years, 9 % for 20–24 years, and 3–5 % for 25–39 years [22]. Similar proportions were recently calculated in a study of patients 15–39 years of age performed at University of Southern California hospitals, where incident cases of cancer registered with the Los Angeles CSP from 2008 to 2012 were linked to patient-specific clinical trial enrollment data; 29/191(15 %) of AYAs at the children's hospital were enrolled compared with only 10/320 AYAs (3 %) in the adult cancer hospital [23]. Collectively, these studies indicate that even in academic cancer centers, AYA enrollment on clinical trials not only is lower than younger children but also approximates the historically very low participation levels of adults age 25 years and older on NCI trials, generally less than 5 % [7]. They also indicate a need for national-level mechanisms to link incident cancer cases with clinical trial enrollments so that accurate enrollment proportions can be tracked in this vulnerable population, in order to measure the impact of new strategies aimed at increasing study participation. Also apparent is the need for capturing reasons for non-enrollment, including whether a clinical trial is concurrently available.

Poor representation on clinical trials is probably associated with lower survival gains for AYAs. Though it is difficult to prove causality in this regard, a strong correlation has been established between proportional enrollment onto NCI-funded clinical trials and average annual improvement in 5-year survival for both soft tissue and bone sarcomas ($p = 0.003$ and 0.04, respectively) [4]. This relationship is thought to apply to other diagnoses. Although average annual survival improvement for AYAs did not increase when the intervals 1975–1988 and 1989–2003 were compared [24], more recent increments in US clinical trial enrollments documented between 2002 and 2005 for patients age 15–25 years are encouraging [25]. Hopefully, these will be followed by greater survival improvements in the years ahead.

Specific explanations for low AYA enrollment are unclear, but some data suggest a relative lack of clinical trials may be available for this age group, as least for certain diagnoses and age thresholds [21, 23, 26]. It is recognized that access to clinical trials is confounded with treatment site, as more AYAs than younger patients tend to be treated in community settings by oncologists who may not have access to NCI-sponsored clinical trials [3, 27, 28, 29•]. Population-based data reveal that although treatment at NCI-designated Comprehensive Cancer Centers benefits survival for AYAs with CNS tumors, these same patients are less likely than children to receive care at those sites, where insurance, socioeconomic status, and distance constitute significant barriers [29•]. In the NCI Patterns of Care

Study, AYAs who were uninsured, older, and treated by non-pediatric oncologists were less likely to be enrolled [22]. A variety of patient-level psychosocial factors are also thought to influence AYA clinical trial enrollment, including the psychological response to a cancer diagnosis; attitudes, perceptions, and beliefs about clinical research; information, knowledge, and awareness about clinical trials; issues concerning informed consent; and relationships with providers, peers, and family [30•]. Recently, Fern and colleagues reported increased enrollment of AYAs age 15–24 years onto cancer trials in the United Kingdom (UK) following broad application of a strategy focused on eliminating age as a barrier through more appropriate trial design and implementation [31••].

Conceptualizing the Enrollment Problem: The Clinical Trials Pathway to Enrollment

In ultimately identifying opportunities for increasing AYA participation in clinical trials, it is important to appreciate that enrollment is not a single step but rather the culmination of several steps along what may be conceived as a "Clinical Trials Pathway to Enrollment" (Fig. 1). Following diagnosis of de novo or relapsed cancer, a series of questions must each be answered "yes" in order to result in patient enrollment. The first question, "Does a clinical trial exist?" refers to whether a study for that disease and patient population has been developed and activated by an NCI-funded cooperative study group. "Is the clinical trial accessible?" refers to whether that study is available at the site where the AYA patient has sought cancer treatment. "Has the clinical trial been presented?" refers to whether the treating physician has offered study participation as a treatment option to an eligible patient. "Has the clinical trial been accepted?" refers to whether the patient has provided written informed consent to be enrolled onto that study. Only after all these steps are attained, each being necessary but none sufficient, can patient enrollment occur. Akin to a cellular signaling pathway, each step of the Clinical Trials Pathway to Enrollment is multifaceted and offers opportunities for research and development of targeted interventions. This conceptual understanding supports a systematic approach to solving the complex challenge of increasing AYA clinical trial enrollment.

Understanding the Enrollment Problem: Issues Related to the Clinical Trials Pathway to Enrollment

As summarized in Table 1, each step in the Clinical Trials Pathway to Enrollment involves key determinants, major loci of influence, relevant processes and mechanisms, and potential barriers and facilitators. In order to consider these further, an overview of recent changes in the US cancer clinical trials network will be given.

The NCI National Clinical Trials Network

On March 1, 2014, after several years of extensive consultation and coordination with many stakeholders, NCI transformed its longstanding Cooperative Group Program into the new National Clinical Trials Network (NCTN) [32]. Guided by recommendations in a 2010 Institute of Medicine report [33], the design and implementation of the NCTN incorporated feedback from Cooperative Group investigators, NCI Comprehensive Cancer Center directors, several NCI working groups, leading cancer researchers, industry representatives, and patient advocates. The NCI NCTN now consists of four US cooperative groups (SWOG, Alliance Oncology, ECOG-ACRIN, and NRG Oncology) plus one Canadian cooperative group (NCIC-CTG) focused on adult cancers, and one cooperative group focused on pediatric and adolescent cancers (Children's Oncology Group, COG). In developing and carrying out clinical trials, the NCTN works with Lead Academic Participating Sites that are typically university-based NCI-designated Comprehensive Cancer Centers, as well as NCI Community Oncology Research Program (NCORP) institutions, funded through a different mechanism to increase

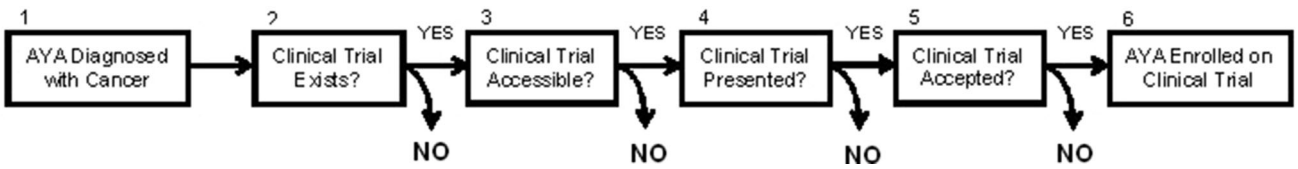

Fig. 1 The Clinical Trials Pathway to Enrollment. Successful enrollment of an AYA patient onto a cancer clinical trial is not a single event but the culmination of several steps requiring availability, accessibility, presentation, and acceptance of the clinical trial. All steps involve a question that must be answered "yes" in order to result in successful enrollment of the patient; an answer of "no" to any question is enough to prevent enrollment. This pathway serves as a conceptual framework for developing targeted interventions to reduce barriers and increase enrollment of AYAs to cancer clinical trials

Table 1 Factors influencing enrollment of adolescents and young adults on cancer clinical trials

	Existence of clinical trial	Accessibility of clinical trial	Presentation of clinical trial	Acceptance of clinical trial
Description	Whether an active NCTN clinical trial exists for AYAs with this diagnosis	Whether the NCTN trial is available at site where the AYA has sought treatment	Whether the NCTN trial is offered to the AYA as a treatment option	Whether the AYA agrees to participate in the NCTN trial
Key determinant(s)	•Age 15–39 years •Relevant diagnosis	•Site affiliation with NCTN group •Decision to open trial at site	•Protocol-specific eligibility criteria •Appropriateness of AYA for study •Oncologist-dependent factors	•AYA/family perception of trial and its value (burden/risk vs. benefit)
Major loci of influence	•NCTN groups •NCI/CTEP •NCI/CIRB	•Treatment site •Oncologist	•Oncologist •Multidisciplinary team	•AYA •Family/other support
Relevant processes and mechanisms	•Study development, review, and funding processes	•NCTN •NCORP	•AYA screening and recruitment processes	•Informed consent
Potential barriers	•Limited federal funding •Competing scientific priorities within NCTN groups •Lack of pediatric and adult intergroup collaboration	•Trial not opened due to limited local resources •Excessive distance to site with NCTN group affiliation	•Ineffective screening •Unfavorable patient-related social factors •Low priority for oncologist	•Insufficient understanding of trial •Ineffective presentation of trial
Potential facilitators	•Enhanced mechanisms to support intergroup collaboration •Supplemental funding supporting specialized trial consortia •Expansion of age-eligibility for early phase trials	•Referral of AYA to site with NCTN group-affiliation •Increased local resources for opening trials •Partnerships between NCTN sites and rural practices	•AYA-focused recruitment strategies •AYA programs •Practical resources for AYA (e.g., child care, transportation) •Oncologist education, research support and incentives	•AYA-focused approaches to enhance informed consent process

access to NCTN trials among smaller communities and populations defined by health disparities [34]. Under this system, new clinical trials may be proposed by any NCTN group and are peer reviewed by Steering Committees that include experts in the disease area, as well as NCI representatives. Concept review encompasses not only the scientific rationale but also resources required, projected accrual, other competing studies, and how the proposed study contributes to strategic goals for the disease area. Approved concepts are then developed into protocols that are reviewed by NCI and, if approved, by the appropriate Central Institutional Review Board (CIRB) [35]. There are currently four NCI-sponsored CIRBs (Pediatric, Adult Late-phase, Adult Early-phase, and Cancer Prevention CIRBs). Protocols involving AYA patients are reviewed by either the Pediatric or Adult CIRB depending on the sponsoring NCTN group, and additional reviewers with AYA expertise are included as needed. Approval by either the Pediatric or Adult CIRB is mutually accepted by the other CIRB. Approved studies are posted on the NCI/Cancer Trials Support Unit (CTSU), allowing NCTN member institutions to activate the protocol for entry of patients by investigators affiliated with any of the NCTN groups [36].

While formation of the NCTN largely represents a response to declining funding, inefficient processes, complex regulatory oversight, and inadequate resources [33], it has created important opportunities that may benefit AYA oncology research. One of these is increasing enrollment of AYAs onto NCTN clinical trials. As discussed further below, it is hoped this will be facilitated by the NCTN platform, which supports cross-group enrollment of new patients onto appropriate clinical trials sponsored by any of the NCTN groups. In principle, an AYA patient from any NCTN group could be enrolled onto a study sponsored by another NCTN group, including COG, as long as the patient meets eligibility criteria. In this way, the NCTN provides access to a greater breadth of studies for AYA patients, which hopefully will translate into increased AYA clinical trial participation.

Issues Related to the Clinical Trials Pathway

Factors influencing enrollment of AYAs are summarized in Table 1. Whether a clinical trial is available largely depends on whether an NCTN group, separately or in collaboration with others, has established study of that disease in AYAs as a scientific priority meriting financial, biostatistical, operational, and administrative support. In the current era of diminished resources, it could be debated whether continued study of cancers for which standard therapy produces excellent outcomes is justified, although there may be rationale for studying non-survival endpoints, such as reducing late effects or cost. In some cancers, increased access for AYA patients can be achieved simply through expanding age-eligibility criteria of existing clinical trials. In other diseases, it may be necessary and more compelling to develop jointly new studies that combine expertise from the pediatric and adult groups. While the NCTN offers potential for increased AYA enrollment, actual protocol development still requires strong commitment to scientific integration and the challenge of melding of treatment approaches across participating groups. When development of a new AYA-focused trial is needed, potential barriers could include limited funding, competing priorities to address diseases with higher prevalence or worse outcomes, and a lack of existing scientific collaboration between NCTN groups in certain disease areas. Facilitators could include identifying sources of supplemental funding for AYA-focused trials through cooperative group foundations and other philanthropy, increasing regular NCTN group interaction in relevant disease areas, and leveraging disease-focused trial consortia such as the Sarcoma Alliance for Research (SARC) [37]. A recent study compared the proportional enrollment of AYA patients among all newly diagnosed patients with selected cancers, using NCI data, to the proportional incidence of AYA patients among all patients with the same cancer, using SEER data, for the period 2000–2010. Interestingly, AYA enrollment proportions were actually higher than expected for certain diseases [38]. For example, adolescent enrollment proportions for Hodgkin lymphoma, bone tumors, acute leukemias, and brain tumors exceeded corresponding SEER incidence proportions. Young adult enrollment exceeded SEER incidence proportions for acute myeloid leukemia, breast cancer, and colon cancer. Only ten percent of adolescent and 17 % of young adult clinical trial participants were enrolled from community sites, suggesting that setting may offer opportunities for further development.

Accessibility of a clinical trial moves the discussion to the local level (Table 1). Here the key determinants are whether the treatment site and oncologist participate in NCTN group studies and whether a particular study has been opened at that site. This is particularly relevant for AYAs, as a higher proportion of AYAs than younger patients appear to be treated in community settings by oncologists who do not participate in NCTN trials [3, 22, 29•]. More than one mechanism exists for cancer treatment sites to gain access to NCTN trials. As an alternative to being an NCTN group member and receiving per-case reimbursement for enrolling patients, qualified institutions may apply for funding as an NCORP member and be able to enroll patients onto any NCTN trial [34]. A facilitator for AYA accrual might be referral of more patients by community-based oncologists to higher-volume NCTN or NCORP sites [39], but distance and other resource limitations may still make travel impractical. Linkages between NCTN sites and community-based oncologists may represent another alternative, though this may not be feasible without addressing current federal regulations limiting where treatment on NCI-supported trials can be administered [40].

Whether an available clinical trial is presented to a new patient also arises at the local level (Table 1). First, effective screening procedures must be in place to identify potentially eligible patients. For AYAs who meet eligibility criteria, the treating oncologist must decide whether to offer the trial as a treatment option. This may depend on whether the trial-based treatment is considered appropriate, and whether the patient is suitable for participation in light of medical, psychosocial, and other considerations. The decision also reflects other physician-level factors that appear to influence clinical trial recruitment such as practice type, knowledge of the trials, and time and economic constraints [41, 42]. Barriers include missing potential research subjects through ineffective screening mechanisms, study recruitment being a low priority for the physician, and patient-level psychosocial/financial issues perceived as potentially compromising protocol adherence. Facilitators could include development of site-specific AYA-focused screening and recruitment strategies, practical support for motivated patients who wish to participate, and additional awareness-training, research infrastructure, and other strategies to incentivize oncologist participation. Development of a dedicated institutional program for AYAs involving a high degree of collaboration between pediatric and medical oncology has been shown to result in increased clinical trial enrollment [43••] and is recommended, where feasible [39, 44].

Finally, the patient must accept the clinical trial as the final step to enrollment (Table 1). Whether to participate is a decision that turns largely on the AYA patient's perception of study-related burden and potential benefit. In this regard, the influence of other persons is relevant, including family and peers, as well as the oncologist and other members of the treatment team [30•]. While it is known that younger AYAs express a high degree of

altruism in deciding whether to participate in clinical research, it is also true that the informed consent process is often perceived as overwhelming following a new diagnosis [45]. This may limit whether the AYA's understanding is sufficient for making an informed judgment. Facilitators for this process could include AYA-friendlier approaches to enhance the informed consent process, including novel methods of information presentation and oncologist training [30•].

As noted previously, increased clinical trial enrollment of patients age 15–24 years was noted for several cancer types in the UK between 2005 and 2010, an improvement attributed to changes related to the "five As" of availability, accessibility, awareness, appropriateness, and acceptability [31••]. These have relevance to many of the above considerations and are recommended by those authors as a basis for strategically improving recruitment of AYAs to clinical trials.

Addressing the Enrollment Problem

A truly comprehensive and coordinated approach to close the AYA gap in clinical trials accrual awaits development, in part because further research is needed to characterize the above issues and determine their relative importance. Nonetheless, several initiatives are already underway at the national level.

AYA-Focused Clinical Trials in the NCTN: Current and Planned

As summarized in Table 2, clinical trials are currently available on the CTSU for patients with newly diagnosed Ewing sarcoma (AEWS 1031 and 1221) or non-rhabdomyosarcoma soft tissue sarcoma (ARST 1321), and recurrent osteosarcoma AOST 1322). Another trial is approved and soon to be opened for relapsed or refractory malignant germ cell tumor (A031102), and others are in development for rhabdomyosarcoma (ARST 1431) and recurrent osteosarcoma (AOST 1321). All encompass the AYA age range. NCTN members have access to the protocols and can download them at any time.

The NCI Molecular Analysis for Therapy Choice (MATCH) Program will include young adults whose tumors are no longer responding to standard therapy. Biopsies from tumors from as many as 3000 patients will undergo next-generation DNA sequencing to identify individuals whose tumors have genetic abnormalities that may respond to select targeted drugs. These genetic mutations have been chosen based on the availability of targeted drugs, including those that have been approved by the US Food and Drug Administration (FDA) for another indication, or that are still investigational but have shown some efficacy against tumors with one of the genetic alterations. As many as 1000 patients will then be assigned to one of the phase II trials, each involving approximately 30 patients, based not on their type of cancer but on the genetic abnormality that is thought to be driving their cancer. In each phase II trial, patients will be treated with one of approximately 25 drugs initially available for the molecular target of that study. Up to 25 % of the tumor types for each phase II trial will consist of rare tumors. ECOG-ACRIN will lead this study along with the NCI, and it will be open to all members of the NCTN. A similar study is in under development in the COG for pediatric and adolescent patients. Both trials are discovery trials, where hopefully new leads will be found that can be explored in larger phase II trials [46].

NCTN AYA Working Group

In 2002, under the leadership of Dr. Archie Bleyer, the COG became the first cooperative oncology group in North America to establish a committee for AYA oncology. Since 2009, the COG AYA Oncology Discipline Committee has defined its objective as improving survival and quality of life for AYAs through understanding differences in cancer and host biology and in their adjustment to the cancer experience. Through close partnerships with other COG committees defined by disease-specific expertise, the COG AYA Committee has published research from COG datasets clearly demonstrating age-related differences in survival and toxicity that have better characterized AYAs with cancer, generated testable hypotheses, and are informing development of prospective trials focused on this age group [47]. Prior to development of the NCTN, the COG was already seeking to increase accrual of AYAs to selected trials through raising upper age limits to 30 or even 50 years in diseases such as acute lymphoblastic leukemia, bone sarcomas, and rhabdomyosarcoma. However, numerous regulatory and administrative barriers remained. While some of these have been resolved with operationalizing the NCTN, the facts remain that many AYAs are well above the pediatric age range, have cancers outside the scope of expertise of pediatric oncologists, and receive care from medical oncologists in adult-focused hospitals. For these reasons, the only research paradigm capable of addressing the full spectrum of the AYA age range and cancer types is one of collaboration between the COG and the adult NCTN groups. To this end, SWOG, under the leadership of SWOG Group Chair Dr. Charles Blanke, approved formation of its own AYA Committee in 2013, and the other NCTN groups are currently developing similar AYA initiatives.

Table 2 US NCTN clinical trials for adolescents and young adults

Study no. (current status)	Title	Year opened	Lead group(s)	Age range (years)	Clinicaltrials.gov identifier
AEWS 1031 (Available)	A Phase III Randomized Trial of Adding Vincristine-Topotecan-Cyclophosphamide to Standard Chemotherapy in Initial Treatment of Non-Metastatic Ewing Sarcoma	2010	COG NRG	1–50	NCT01231906
AEWS 1221 (Available)	Randomized Phase II Trial Evaluating the Addition of the IGF-1R Monoclonal Antibody Ganitumab (AMG 479) to Multiagent Chemotherapy for Patients with Newly Diagnosed Metastatic Ewing Sarcoma	2014	COG	≤50	NCT02306161
ARST 1321 (Available)	Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib	2014	COG NRG	≥2	NCT02180867
AOST1322 (Available)	Phase II Study of Eribulin in Recurrent or Refractory Osteosarcoma	2014	COG	16–50	NCT02097238
A031102 (Approved)	A Randomized Phase III Trial Comparing Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotherapy Using Mobilizing Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors		Alliance	≥14	
AOST 1321 (In development)	Phase II Study of Denosumab, A RANK Ligand Antibody, for Recurrent Osteosarcoma		COG	11–49	
ARST 1431 (In development)	A Randomized Phase III Study of Vincristine, Dactinomycin, Cyclophosphamide (VAC) Alternating with Vincristine and Irinotecan (VI) versus VAC/VI plus Temsirolimus (TEM) in Patients with Intermediate Risk Rhabdomyosarcoma		COG	≤40	

Recognizing the potential benefit of the new NCTN structure for AYAs, the COG and SWOG AYA Committees have joined in developing the NCTN AYA Working Group. The overall goal of this Working Group is to facilitate advancement of AYA research in the NCTN through regular, ongoing, AYA-focused interactions of all NCTN groups and stakeholders. A high priority for this Working Group is increasing enrollment of AYAs onto NCTN trials. Working Group members include AYA representatives from each NCTN group, NCI/CTEP, and both pediatric and adult components of NCORP institutions. The NCTN AYA Working Group held its inaugural meeting in November, 2013 and now meets regularly in person or by conference call every three months. Specific objectives emerging from Working Group discussions include identifying gaps where new AYA trials are needed, facilitating disease-focused intergroup collaborations for trial development, monitoring AYA accrual to current and future NCTN trials, increasing awareness of AYA-focused trials in the NCTN groups, developing general and protocol-specific interventions to improve AYA accrual across NCTN, harmonizing adult and pediatric guidelines for study observations and supportive care in joint protocols, and collaborating with NCI/CTEP to support effective review of AYA-focused concept proposals.

Conclusions

A clear deficit exists in proportional enrollment of AYAs onto cancer clinical trials. While there is preliminary evidence this situation may be starting to improve as a result of greater awareness, a pressing need remains to gain a greater understanding of the barriers and facilitators influencing recruitment of AYAs to cancer clinical trials and to develop rational interventions for modifying them. The Clinical Trials Pathway to Enrollment delineates the required process eventuating in enrollment of an AYA patient, beginning with having clinical trials focused on cancers relevant to this age group that are available, accessible, effectively presented, and ultimately acceptable to an eligible patient. Addressing all of these will require continued research in areas as diverse as cancer biology and therapeutic decision-making, involving institutions ranging from NCI to community-based hospitals. Recent developments in the US cancer clinical trials enterprise, especially the NTCN and related initiatives, offer encouraging opportunities at the national level to increase AYA accrual and advance AYA oncology research. However, improved mechanisms for accurately measuring proportional enrollment are needed in order to monitor the impact of these changes longitudinally.

Acknowledgements This project was supported by NCI grant U10 CA98543 (DRF) and by funds from the COG Foundation and Aflac (DRF). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCI, COG Foundation or Aflac.

Disclosure The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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