Neuro-Oncology Advances
6(1), 1–16, 2024 | https://doi.org/10.1093/noajnl/vdad159 | Advance Access date 10 December 2023

Challenges and limitations of clinical trials in the adolescent and young adult CNS cancer population: A systematic review

Emma M. Byrne,[†] Maeve Pascoe,[†] Diane Cooper, Terri S. Armstrong, and Mark R. Gilbert

Neuro-Oncology Branch, National Cancer Institute, National Institute of Health, Bethesda, Maryland, USA (E.M.B, M.P, T.S.A., M.R.G.); National Institute of Health Library, National Institute of Health, Bethesda, Maryland, USA (D.C.)
[†]These authors are co-first authors.

Corresponding Author: Mark R. Gilbert, MD, Neuro-Oncology Branch, National Cancer Institute, National Institute of Health, 9030 Old Georgetown Road, Building 82, Room 235A, Bethesda, MD 20892, USA (mark.gilbert@nih.gov).

Abstract

Background. The adolescent and young adult (AYA) cancer population, aged 15–39, carries significant morbidity and mortality. Despite growing recognition of unique challenges with this age group, there has been little documentation of unmet needs in their care, trial participation, and quality of life, particularly in those with primary brain tumors.

Methods. A systematic literature review of 4 databases was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards. Studies included editorials, reviews, and practice guidelines on the challenges and limitations faced by the AYA population. Papers had to address CNS tumors.

Results. Sixty-eight studies met the inclusion criteria. The challenges and limitations in clinical trials in the AYA population were synthesized into 11 categories: molecular heterogeneity, tumor biology, diagnostic delay, access to care, physician factors, patient factors, primary brain tumor (PBT) factors, accrual, limited trials, long term follow up, and trial design. The published papers' recommendations were categorized based on the target of the recommendation: providers, coordination of care, organizations, accrual, and trial design. The AYA cancer population was found to suffer from unique challenges and barriers to care and the construction of trials.

Conclusions. The AYA CNS cancer population suffers from unique challenges and barriers to care and construction of trials that make it critical to acknowledge AYAs as a distinct patient population. In addition, AYAs with primary brain tumors are underrecognized and underreported in current literature. More studies in the AYA primary brain tumor patient population are needed to improve their care and participation in trials.

Key Points

- The challenges and limitations in construction of clinical trials in the AYA cancer population are varied and interconnected.
- There is unmet need in understanding the challenges faced by AYAs with primary brain tumors.

The adolescent and young adult (AYA) cancer population is comprised of persons with cancer ages 15–39 years old.[1] It was estimated to make up 89 500 new cancer cases and 9270 cancer deaths in 2020.[2] Excluding depression-related suicide, cancer accounts for more deaths in 20- to 30- year-olds than any other disease.[3] Although the incidence of cancer is almost 3 times greater in ages 15–30 compared to ages 0–15, survival rates for AYA patients are worse than survival rates in the pediatric population.[4–8] Despite the significant morbidity and mortality of cancer in this population, there has been insufficient

Importance of Study

This is one of the first systematic reviews to summarize the past 3 decades of literature on the challenges and limitations of the AYA cancer population, which has had slower progress and under enrollment in trials compared to adult and pediatric populations. This review highlights the significant unmet need of the primary brain tumor AYA population, which has been underrepresented in previous literature.

progress in the discovery and development of new therapies or investigations on the multi-faceted challenges of molecular differences, clinical trial enrollment, and social determinants of health.[9,10]

Most literature discusses the challenges AYAs face in broad terms, focusing on the most common AYA cancers, such as leukemias, lymphomas, and bone cancers.[11,12] CNS neoplasms are of particular interest as they make up 6% of cancers,[4,13] and are the most common cause of cancer-related death in AYA men, and are the second leading cause of cancer-related death for all in ages 15–39.[2,14] Moreover, the rate of CNS neoplasms in the AYA population has been steadily increasing, with an annual percentage change of 0.3% from 1975 to 2019.[13] Like other AYA cancers, the brain tumor population has a low rate of clinical trial enrollment, correlating with a lack of survival rate improvement.[15] This systematic review aims to survey and summarize the challenges and limitations of clinical trials in the AYA population, especially those with CNS neoplasms.

Methods

Papers that addressed challenges in conducting clinical trials in the AYA CNS population were included. The inclusion and exclusion criteria were created a priori and are outlined in Table 1. Only English language studies were included.

PubMed, Web of Science, Scopus, and Google Scholar were queried in December 2022, resulting in 1614, 75, 553, and 84 publications, respectively. The specific search strategy, including keywords, is outlined in Supplementary Material 1. The reference list of a recently published AYA article,[16] was screened by title by E.B and M.R.G; titles that included the AYA population and challenges of research were included, which led to an additional 14 papers. Once 259 duplicates were removed, 2081 papers were screened. E.B. and D.C. performed the initial search and E.B. and M.P. screened the 2081 references by title and abstract. Figure 1 outlines the entire process.[17] Data was extracted by reviewers separately and then tabulated together.

Risk of bias (ROB) was not conducted on reviews and editorials ($n = 40$) due to their inherent subjective nature. However, screening was performed on all other studies using the Effective Public Health Practice Project (EPHPP)[18,19] and the Assessing the Methodological Quality of Systematic Reviews (AMSTAR),[20] described in Supplementary Material 2.

Results

Included Studies and Study Characteristics

Sixty-eight studies met inclusion criteria (Supplementary Material 3). Included studies were published between 1993 and 2022 and were most commonly conducted in the United States ($n = 30$ US alone & $n = 11$ multi-national including the United States). Supplementary Material 4 summarizes the countries and journals of publication for these studies. Study types included retrospective cohort studies ($n = 18$), reviews ($n = 41$ total, $n = 5$ systematic), editorials ($n = 4$), qualitative cross-sectional analyses ($n = 3$), and prospective observational studies ($n = 2$).

The included studies had heterogeneous age criteria. Twenty-three studies used the US National Cancer Institute age criteria for AYA of 15–39 years. Three studies included both children and adolescents,[21–23] and so their age criteria included individuals under 15; the youngest AYA age minimum was 13 years.[24] The maximum ages for AYA were more varied than the minimums, with a median of 39 years and a range of 18–55 years.

Of the 23 nonreview studies, only 9 studies reported demographic characteristics.[16,25–32] These 9 studies had a

Table 1. Inclusion and Exclusion Criteria Used for the Systematic Review.

Inclusion Criteria	Exclusion Criteria
1. Papers on the adolescent and young adult population (age 15-39) a. median age of > 12 or a median age < 39 2. CNS malignancies, brain tumors, spinal tumors 3. Mention of challenges to trials 4. Review articles 5. Conferences 6. Recommendations 7. Position papers 8. Primary research on molecular heterogeneity	1. Pediatric population, median age < 12 2. Adult population, median age > 39 3. ClinicalTrials 4. NonEnglish Articles 5. Veterinary oncology

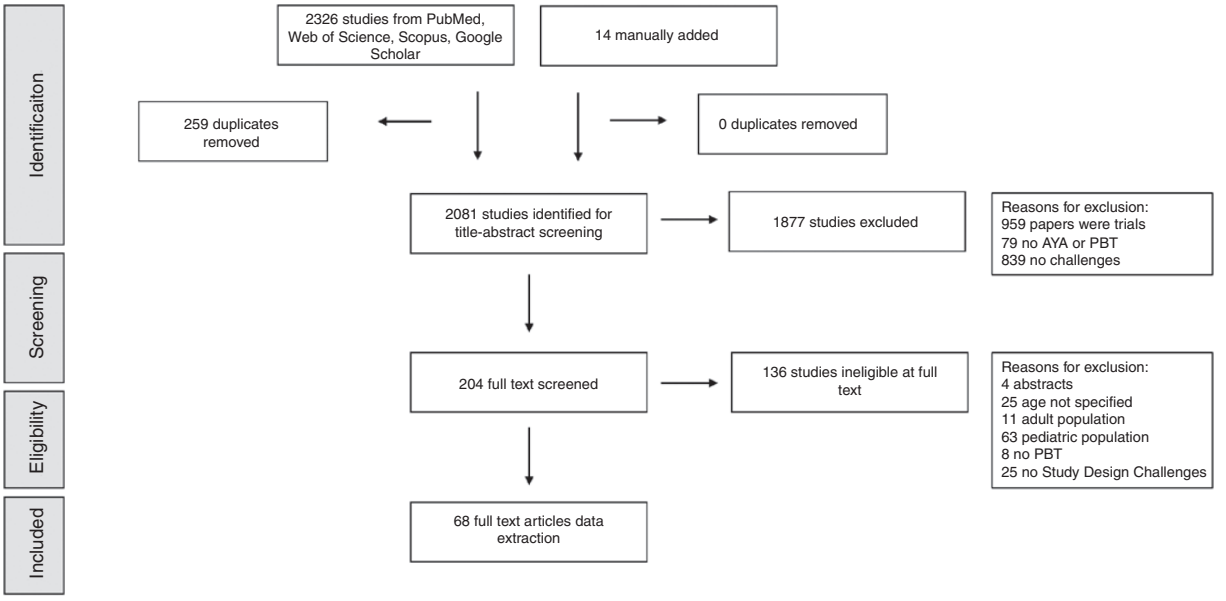

Figure 1. PRISMA diagram for systematic review on the challenges and limitations of AYA CNS clinical trials.

median sample size of 20 patients (range 16–208). Median age of participants was 17.6 years (range 10–55), with a mean of 46% women and 56% with primary brain tumors.

Though all 68 studies included some mention of PBT patients, specific PBT discussion covered a wide range of tumors: ependymoma ($n = 6$)[16,22,26,30,33,34]; medulloblastoma ($n = 6$)[16,34–38]; glioma ($n = 4$)[16,25,34,39]; primitive neuroectodermal tumor (PNET) ($n = 3$)[26,38,40]; atypical teratoid rhabdoid tumors ($n = 2$)[36,38]; diffuse intrinsic pontine glioma (DIPG) ($n = 1$)[40]; germ cell tumors ($n = 1$)[40]; astrocytoma ($n = 1$)[26]; and meningioma ($n = 1$).[41]

Challenges

The challenges addressed in the papers were organized into categories, defined in Table 2. Frequency of challenges is shown in Table 3; most common challenges were accrual ($n = 51$), patient factors ($n = 50$), and access to care ($n = 49$).

Molecular Heterogeneity—Fourteen papers discussed the molecular heterogeneity of primary brain tumors (PBTs).[10,22,24,25,33,34,37,39–45] The molecular characteristics of medulloblastoma, which is divided into 4 subgroups, influence prognosis, location of tumor, and age at presentation.[24,34,37,40,42] IDH-mutation and H3K27M mutation are important factors in distinguishing pediatric gliomas and AYA/adult gliomas.[24,25,34,39,42,43] The different mutations impact the pattern of malignant transformation in AYA glioma patients compared to children with gliomas, further complicating disease trajectory and susceptibility to therapy.[43]

Five papers addressed challenges of the molecular profile of ependymomas.[22,33,34,42,43] As the second most common malignant brain tumor of childhood, ependymomas can arise in the supratentorial region, infratentorial region, or in the spinal cord. The complex molecular characteristics and differences in treatment susceptibility pose challenges to enrollment and construction of treatment trials.

Only one paper addressed the molecular heterogeneity of meningiomas, stating meningiomas of children and young adults are molecularly distinct from adult meningiomas.[41]

Tumor Biology—Twenty-three papers[10,30,38,41,42,44–55] discussed the challenge of tumor biology, of which 17 address tumor biology generically. Five studies[3,33,40,42,56] identified the lack of a tissue bank as a contributing factor to challenges of tumor biology, articulating that because trials are not collecting tissue, it is not possible to study and understand these differences. The lack of a centralized database ($n = 1$)[5] and insufficient preclinical models ($n = 1$)[39] were other factors contributing to challenges in AYA tumor biology.

Diagnostic Delay—Twenty-three studies addressed diagnostic delay as a challenge.[2,3,5,21,27,30,41,43,44,46,47,49,51,55,57–63] Because the AYA population is more susceptible to a unique group of cancers, their symptoms often differ from the typical symptoms seen in adults, which can prolong the time to diagnosis (TTD). Lethaby et al. 2013 proposed that TTD is the summation of patient interval (PI: time between symptom onset and first clinical presentation) and diagnostic interval (DI: time from engagement with a health care provider to diagnosis). Nine papers discussed patient factors, such as socioeconomic (SEC) status, symptom denial or a sense of invincibility, or lack of patient awareness and education, as contributing to the patient interval of diagnostic delay.[24,30,43,46,47,57,59,63,64] Six papers discussed physician factors, such as physician unawareness of AYA cancer risk, presentation, or trial availability as factors contributing to the diagnostic interval

Table 2. Definitions of Challenges Discussed Throughout Papers.

CHALLENGES
Molecular heterogeneity: paper addresses known differences in mutations, histology, or epidemiology (ages, tumor type) that lead to challenges in enrolling, constructing, executing trials
Tumor biology: paper discusses the challenges of unknown differences in the disease spectrum, presentation, etiology, and pathology, which can alter a patient's entrance/eligibility into a trial ◦ Lack of tissue bank: trials (or lack thereof) are not collecting tissue samples so fewer tests and studies can be performed to better understand tumor biology ◦ Lack of centralized data: data on tumor biology and biologic markers are not logged or documented in a centralized database for future studies ◦ Lack of preclinical models: unknown differences in tumor biology are attributed to the lack of preclinical models
Diagnostic delay: paper describes factors that lead to a diagnostic delay, defined as a delay in time from symptom presentation to official diagnosis or enrollment on trial, which could include: ◦ Tumor biology: unknown aspects and differences in tumor biology contribute to diagnostic delay ◦ Location of care: place of evaluation and/or treatment leading to delay in diagnosis (i.e. adult vs pediatric centers; community vs. city hospital) ◦ Symptom interval: slowly progressive symptoms or nondescript symptoms may be underrecognized ◦ Patient factors: SEC status (lower income leading to delayed presentation to doctor), symptom denial (a patient denying or ignoring symptoms, so they present later), lack of awareness/education (unaware of the risk of cancer leading to delayed presentation) ◦ Physician factors: physician may be unaware of AYA cancer risk and presentation or unaware that AYA trials exist, leading to a delay in diagnosis or delay in referral to trial ◦ Insurance: lack of insurance can impact how likely a patient is to seek care; level of insurance and rates of insurance approval can impact the start of treatment or referral to providers
Access to care and trials: paper discusses problems with access as a major challenge in AYA trials, which can include: ◦ Eligibility: problems with eligibility, such as age criteria to enroll on a trial, or insurance approval, as limitations to access/enrolling on trials ◦ Insurance: the type of insurance (private, government-funded, under-insured, un-insured, etc.) and the financial burden of paying for insurance impacts a patient's access to trials ◦ Location of care: the impact of being treated at a pediatric or adult hospital can alter access to trials ◦ Language accessibility: access to trials may be limited by the languages spoken at the trial center; whether a patient's primary language is spoken can impact a patient's education or awareness of trials ◦ LMIC (Low Middle-Income Countries): access may be limited by the lack of comprehensive healthcare system in certain countries ◦ Collaboration between centers: access may be hindered by collaboration, or lack thereof, between centers/institutions
Physician factors: paper discusses challenges of care and AYA trials as created by physicians, which can include: ◦ Transitions of care: the continuity of care, transitions between pediatric to adult care, and cooperation between these providers acts as a challenge to AYA care ◦ Expertise: the expertise of the physician the patient sees can influence the direction of care (i.e. pediatric oncologists are more likely to refer to trial) ◦ Physician education: lack of awareness that AYAs get cancer, not knowing what symptoms to look for, and lack of awareness that trials exist may impact the trajectory of care or referral ◦ Referrals: physicians may not refer to centers that have access to trials ◦ Professional bias: a physician's own bias influencing referral and enrollment in trials ▪ Perception of nonadherence: a physician's assumption that AYAs would not be good candidates or follow the guidelines of the trial ▪ Perception of trial impact/efficacy: a physician's assumption of how trial will impact him or herself (increased workload, efficacy of trial) ◦ Racial bias: implicit racial bias can alter how physicians educate and refer patients to trials
Patient factors: paper discusses challenges of care and trial conduct that relate to the patient, which can include:◦ Reluctance: patients may be reluctant to seek care/trials due to fear of not being taken seriously by physicians, perceived lack of time for self-care, mistrust of healthcare, personal beliefs, etc. ◦ Transitional time of life: AYAs are in a period of great change and development; changes in priorities and life goals can alter a patient's willingness to participate and adds to difficulty to maintain on trial; transition in relationship with parents and the level of parental advocacy/oversight ◦ Psychosocial factors: ▪ Sense of invincibility ▪ Body image ▪ Isolation from peers ▪ Sexual awakening ▪ Interruption to school/work/social growth ▪ Premature confrontation of mortality/ uncertainty about future ◦ Under-represented populations: race, gender, ethnicity can impact inclusion in trials, resulting in biased outcomes ▪ Language barriers: limited interpreters or other language accessibility issues leading to under-representation of certain populations ▪ Distrust of physicians: lack of trust in physicians leading to under representation/decreased presentation of certain populations ◦ Socioeconomic status (SES) differences: a patient's SES impacts trial knowledge, referral to trials, or willingness to participate ◦ Adherence: challenges of conforming to the trial protocol or following treatment regimen is due to patient nonadherence ◦ Education: AYA patients' awareness of disease, of cancer risk, or preventive medicine ◦ Lack of usual care: lack of PCP/regular follow-up, leading to fewer interactions with health care providers ◦ Fertility: onco-fertility and discussions of fertility preservation exist as challenges for inclusion, adherence, and follow up ◦ Response to therapy: differences in treatment tolerability based on age or different responses to therapy based on tumor can lead to challenges in the construction and compliance of protocols ◦ Financial constraints: the financial burden/toxicity and consequences of paying medical bills or the lack of consistent income due to treatment in this age group can limit willingness to enroll, maintenance on protocol, etc.

Table 2. Continued

CHALLENGES
PBT factors: paper addresses challenges to AYA trials as it relates specifically to primary brain tumor patients, which include: ◦ Molecular profile: the molecular profile of CNS tumors makes stratification for trial purposes difficult ◦ Reception of symptoms: how a patient's symptoms are received by providers impacts recognition, urgency of workup, and enrollment in trials ◦ Perception of symptoms: how a patient advocates or recognizes their own symptoms impacts recognition from providers, urgency of workup, and enrollment in trials ◦ Accrual: paper provides specific information/anecdotes on the accrual of AYAs with CNS tumors ◦ Referrals: referral patterns (i.e. to COG and POG sites) alter care/access to trials specific to PBTs ◦ Morbidity and survivors: morbidity and long-term survivorship (i.e. cost of cure) in PBT patients impacts trial design, enrollment on trials, and follow up ▪ Lower education attainment: AYAs with CNS tumors may achieve a lower educational level which alters their ability to re-enter society ◦ Response to therapy: differences in treatment tolerability based on age; differences in responses to therapy based on tumor ◦ Access: PBT patients lack access to certain therapies/treatment ◦ Epidemiology: the wide variety of tumor types based on age differences in the AYA population is a challenge to trial construction, follow-up, etc.
Accrual: paper addresses low enrollment in any way, or provides data on recruitment ◦ Recruitment: specific recruitment techniques or efforts by the trial or cooperative group are addressed
Limited trials: paper discusses lack of trials available ◦ Based on AYA age: limited trial availability due to age of the patient ◦ Based on tumor type: limited trial availability due to rarity of tumor ◦ Based on sponsorship: limited trial availability due to lack of financial support, funding, or infrastructure
Long term follow-up: paper discusses the burden of sequelae from treatment as a challenge to trials
Trial design: paper discusses issues with trial design as a challenge for AYA trials ◦ Inconsistent response criteria: trials use different response criteria which can alter how we evaluate the results and efficacy of a proposed therapy ◦ Molecular profiling: molecular stratification and tumor mutation in eligibility and analysis can alter how we evaluate the results and efficacy of a proposed therapy ◦ Endpoints: challenges with endpoint collection, lack of instruments for the AYA population, lack of HRQOL data collection ◦ Consent/assent: difficulties in obtaining consent or assent in the AYA population ◦ Acceptability: the trial design impacts how easily AYAs can participate and how likely they are to want to go on trial ◦ Feasibility: the feasibility of certain trial designs and the realistic nature of incorporation of certain study characteristics ▪ Cost: paper discusses the cost of running a trial ◦ Standardized protocols: whether there are standardized protocols (or care pathways) for certain interventions ◦ Preclinical models: limited preclinical models hinder understanding of tumor biology and testing new drugs

of diagnostic delay.[24,43,44,46,58,61] Location of care affects diagnostic delay with facility type, e.g. adult or pediatric, influencing care.[46,63] Globally, lack of resources and expert opinions and the high cost of care in lower-income countries contribute to diagnostic delay.[63] Finally, insurance, whether public or private, may affect patient willingness and ability to present to physicians, and insurance coverage, reimbursement, and denials may delay work up.[2,3,5,27,30,49,55,58,62,63]

Access to Care and Trials—Forty-nine papers discussed access to care as a major challenge for AYA trials.[3,5,9,10,16,21,26,27,30–32,36,38,40,42,43,45–48,50–59,61–79] Of the six sub-factors, eligibility was most frequently discussed ($n = 37$).[5,9,10,16,26,27,30,31,38,40,45–47,50–56,58,59,61,62,64–67,69–75,78,79] Because the AYA age range is considered a transitional age, crossing both the pediatric and adult spectrum, AYAs are often excluded from trials due to age eligibility in trial inclusion criteria. Although adult institutions are more likely to have trials with an age eligibility inclusive for AYA patients,[9] not all AYA patients have "adult" tumors. Although age restrictions for trials are typically based on the tissue or organ of origin rather than biologic incidence,[70] age criteria are not constructed using a defined method of scientific rationale.[50] However, even trials that encompass the entire AYA age range still had problems with recruitment, suggesting the multi-factorial and intricate nature of the challenges of AYA trials.[70]

Insurance—the type of insurance (private, government funded, under-insured, un-insured, etc.) and the financial burden of paying for insurance—is an important barrier to care and trials ($n = 19$).[3,16,27,31,32,45–48,51,55–57,62,64,65,70,71,73] The strength of insurance coverage is considered influential in access to care for patients; patients with private insurance are more likely to enroll on a trial and private insurance appears to confer a survival benefit.[31,48,73] While some argue that lack of insurance is a challenge for care, others report that un-insured patients have decreased in the United States since the implementation of the Affordable Care Act, meaning insurance is no longer a strong predictor of enrollment.[48,62,73] Additionally, even though the AYA population is under-insured, low accrual of AYAs persists in countries with universal healthcare.[70] A retrospective cohort study that compared insurance approval rates and time intervals to authorization between pediatric patients and AYA patients found that AYAs had more insurance denials, a longer time to approval of RT, and a lower successful appeal rate.[27]

Location of care or diagnostic evaluation is another major determinant of access ($n = 34$).[3,5,9,10,16,26,31,32,36,40,42,45,47,48,50,51,54,55,57,61–66,68–74,76,78,79] AYAs evaluated at pediatric

Table 3. Summary of Challenges by Paper

Reference	Molecular heterogeneity	Tumor biology	Diagnostic delay	Access to care/ trials	Physician factors	Patient factors	PBT specific	Accrual	Limited trials	Long-term follow up	Trial design	TOTAL
Ahrendsen 2021	■											1
Albritton 2008		■	■	■	■	■	■	■	■			8
Alken 2015	■	■		■	■	■	■	■	■	■		9
Barr 2016			■	■	■	■		■			■	6
Bautista 2017							■		■		■	3
Beltrami 2022		■	■	■	■	■		■				6
Bennett 2020	■	■		■		■	■	■				6
Bernig 2013				■		■		■				3
Bishop 2021			■	■		■		■	■			5
Bleyer 2016				■	■		■	■				4
Bleyer 2007			■	■	■	■	■	■	■			7
Bleyer 2006		■	■	■	■	■	■	■	■			8
Bleyer 2007		■	■	■	■	■	■		■		■	8
Bleyer 2009			■						■			2
Bleyer 2002			■	■	■	■	■	■	■	■		8
Bradford 2018				■		■	■	■	■			5
Calaminus 2008							■				■	2
Capra 2003				■	■	■	■	■	■		■	7
Cavalli 2018	■	■					■					3
Close 2019		■		■		■		■	■			5
Collins 2015				■		■		■	■			4
Dekking 2015				■	■	■		■				4
deRojas 2019	■	■		■				■	■			5
Downs-Canner 2009								■	■			3
Epelman 2013	■		■			■	■					4
Fern 2014				■		■		■	■		■	5
Fern 2010		■		■	■	■	■	■	■			7
Ferrari 2013			■	■	■	■		■				5
Ferrari 2007			■	■	■	■		■	■			6
Ferrari 2008		■	■		■	■		■				5
Ferrari 2016						■		■	■			3
Fontebasso 2013	■	■										2
Freyer 2015				■	■	■		■	■		■	6
Gajjar 2015	■						■					2
Gaspar 2016		■		■	■	■		■	■		■	7
Gupta 2014				■		■		■	■		■	5
Hinds 2005					■						■	2
Holland 2021		■	■	■	■		■					5
Jacob 2017			■	■	■	■		■	■			6
Keegan 2018				■	■	■		■	■		■	6
Kelly 2022				■	■	■		■	■		■	6
Krailo 1993				■		■		■	■			4
Lee 2022				■	■	■		■	■		■	6

Table 3. Continued

Reference	Molecular heterogeneity	Tumor biology	Diagnostic delay	Access to care/trials	Physician factors	Patient factors	PBT specific	Accrual	Limited trials	Long-term follow up	Trial design	TOTAL
Lethaby 2013			■	■	■	■	■					5
Lindsay 2022	■						■				■	3
Magrath 2013			■	■	■		■	■	■	■	■	8
Majd 2019	■							■	■			3
McCabe 2016		■						■	■			4
Miller 2020			■			■	■	■	■	■		6
Miller 2013					■						■	2
Moreno 2009		■	■	■	■	■		■	■			7
Nass 2015				■		■		■		■		4
Nooka 2016				■		■		■				3
Osborn 2019				■	■	■		■	■		■	6
Papageorgiou 2020	■		■	■	■	■		■	■	■	■	9
Patterson 2015		■		■	■	■	■	■		■	■	8
Pentheroudakis 2005		■		■	■	■		■	■	■	■	8
Pollock 2007		■		■		■		■				4
Roth 2016				■		■		■	■			4
Sanford 2017				■	■	■		■	■		■	6
Sarvode 2022				■		■		■	■			4
Sender 2015		■	■	■	■	■	■	■	■		■	9
Soliman 2008						■			■	■		3
Szychot 2020	■	■	■						■			4
Thomas 2018				■		■		■	■		■	5
Tran 2014						■					■	2
Yamasaki 2022	■	■	■		■	■	■	■				7
Yeo 2021	■	■		■		■		■	■		■	7
Total	14	23	23	49	34	50	24	51	43	9	25	

institutions are more likely to enroll on studies than those evaluated at adult institutions.[9,48,73] Even when controlling for age confounding, the site of care is a predictor of enrollment, with children's hospitals enrolling a greater proportion of AYAs. Additionally, AYAs are more frequently seen at community hospitals, which have less specialized services and fewer referral pathways than large academic centers, decreasing their likelihood of enrolling in trials and impacting outcomes.[45,50,64,68,70,71] Academic centers and pediatric institutions are more likely to participate in cooperative groups, which help bolster enrollment with large trial portfolios.[32,45,78,79] In addition, clinical trial availability is concentrated in wealthier countries, specifically in North America.[10,63] Finally, AYA programs,[26,61,62,66] which are specialized units that contain interdisciplinary teams to improve access to care, exist in both pediatric oncology departments[36] and adult oncology departments.[61,62]

Other factors impacting access to care include language accessibility ($n = 3$),[4,72,74] low middle-income countries ($n = 2$),[56,63] and collaboration between centers ($n = 1$).[71] Variable and inconsistent language services at certain institutions may further the language barrier and impact the communication of eligibility and availability of trials.

Physician Factors—Thirty-four papers discussed how AYA trials and care are limited by factors created by physicians.[3,5,21,28–31,36,40,43,44,46,47,49–53,55,57–59,61–65,67,68,70,71,73,75,78] The transfer of care is challenging because best management involves both adult and pediatric oncology care[40,49,52,55,57,64,70,71]; poor communication between pediatric and adult healthcare providers often occurs after treatment, and, without a concrete health network, patients may be lost to follow up while in remission.[57]

Physician expertise ($n = 10$),[3,30,36,44,46,58,63,71,73,78] physician education ($n = 18$),[3,5,21,30,43,46,50,51,57–59,61,64,70,71,73,75,78] and referral patterns ($n = 11$)[3,5,31,46,55,58,59,61,75,78] are intricately related physician factors. Because AYAs get less common

cancers, expertise of the provider is important in starting age-specific and age-appropriate management, such as dose/frequency-adjusted radiation, which can impact trial eligibility.[46] Magrath et al. argue that patients are best managed by experts who specialize in a disease rather than specialists based on age.[63] Referral patterns influence the provider a patient sees; adolescents are less likely to be referred to a pediatric oncologist than younger patients.[61] Furthermore, oncologists working in academic centers are more likely to refer patients to trials than oncologists at community centers.

Professional bias is another important physician factor ($n = 15$).[5,28–30,46,53,58,59,62,64,67,68,71,73,75] Perception of nonadherence was the most frequently cited professional bias.[30,53,59,64,67] Other assumptions include physician perception that having a patient on trial increases their own workload, not wanting to refer because of preference on trial treatment arm, concerns about the ethics of the trial, false belief that AYAs do not need a trial because they have a good prognosis, or not wanting to add to a patient's burden by encouraging a trial. Lastly, implicit racial bias ($n = 1$),[47] and the poor assumption that minorities want less information about treatment options may influence who is informed of clinical trials.

Patient Factors—Fifty papers discussed how patient factors are an important challenge to AYA trials.[2,3,5,9,16,21,23,24,26,27,30–32,36,40,42–50,52–54,56–59,61,62,64,66–68,70–79] Patient reluctance ($n = 16$)[3,5,9,30,46,50,55,56,58,59,62,67,68,71,73,75] and adherence ($n = 8$)[3,36,40,45,47,57,71,73] are based on AYA attitudes. Attitudes towards the healthcare system include perceived fear of physicians, fear of not being taken seriously, lack of trust in the healthcare system, and perception that trial and therapy are too time-consuming.[3,5,46,59,67,68,73] AYA patients were often dismissive of their symptoms, reporting being too busy to seek care or ignoring their symptoms outright.[46,55] Alternatively, AYA patients were described as noncompliant, including being forgetful, deviating from the trial in an attempt to retain normality, lacking parental oversight, or having barriers to compliance, such as transportation, finances, or conflicts with school and work.[3,40] Psychosocial factors and the need for specific psychosocial support ($n = 21$)[2,3,24,26,30,40,43–45,48,50,52,53,55,57,59,61,66,76,78,80] are major contributors to challenges in enrollment, maintenance on trial, and follow up.

Psychosocial factors are unique to AYAs because they are in a transitional time of life ($n = 18$)[3,5,21,30,40,42,44,46,50,52,53,58,61,67,71,73,76,80] when a patient's life goals, priorities, and relationships with peers, partners, and parents are unstable.

Fertility preservation/family planning ($n = 14$)[3,27,40,44,45,48,52,53,57,59,61,76,80] was another patient-specific challenge to AYA care and trials. Unfortunately, AYAs frequently report that onco-fertility was never discussed; in a cohort of female AYAs with glioma, only approximately 30% recalled having discussions on fertility, despite wanting children.[44,45,52,76] Provider reasons for not discussing onco-fertility include provider discomfort in discussing the topic and a sense of urgency to start treatment.[52]

The effect of treatment on fertility raises another important patient factor: response to therapy ($n = 9$).[23,36,37,43,44,54,55,62,72] Response to therapy is variable in AYAs due to the spectrum of ages and tumor types. Differences in tolerability, such as worsening toxicity, may deter patients and have been cited as reasons for nonparticipation in trials.[37,44,54,55,62]

Education is another important patient factor ($n = 13$).[3,21,50,53,58,59,61,64,68,71,73,75,78] Most AYAs are unaware of clinical trials and they are also under-informed/educated on the prevalence of cancer in their age group which is related to the general lack of usual care,[3,30,58] defined as the lack of regular follow up or primary care provider.

Socioeconomic status, financial constraints, and under-represented populations were also recognized as barriers to care. Some studies reiterate a problem seen throughout medicine: those of a higher socioeconomic status have better outcomes and lower risk of death.[32,45,47,48] Alternatively, others report that socioeconomic differences and place of residence are not factors in AYA presentation to trials.[66,74] Similarly, financial constraints are a major barrier to AYA care.[2,3,55,80]

Multiple papers report that the nadir in recruitment of AYAs was not different among whites and ethnic minorities, suggesting that ethnicity is not a significant predictor of enrollment for AYAs 20-29.[9,32,49,70] However, minorities are still under-recruited in trials,[75,77] and within minority groups, the level of trial involvement differs; one study demonstrated that Hispanics and Asian/Pacific islanders had a significantly higher enrollment than African Americans for nontherapeutic trials.[9]

Primary Brain Tumor Specific Issues—Twenty-four papers addressed challenges that were specific to the primary brain tumor (PBT) population.[2,3,5,21,22,24,33–35,40,42,44,46,51,52,55,58,59,63,65–67,70,81] The different mutation types and molecular characteristics of PBT patients ($n = 7$)[22,25,33–35,40,42] make it hard to stratify patients in clinical trials, which introduces large variability in patients' response to therapy and risk of treatment toxicities.[24,44,67] Although issues of accrual, referral patterns, and access have been previously mentioned, only some papers address how these problems affect PBT patients specifically.[5,59,63,65,70] The morbidity in long-term survivorship of PBT AYAs ($n = 6$)[40,44,51,52,55,81] from targeted therapy to the brain, including the neuro-cognitive sequelae or endocrinologic sequelae, is an important consideration when recruiting patients, constructing trial design, and considering long-term follow up of trial patients.

Accrual—Fifty-one papers mentioned accrual or low enrollment, as an important challenge of clinical trials in AYAs.[2,3,5,9,10,16,26,27,30–32,36–38,40,42–50,52–57,59,61–79] Overall, there is a widespread lack of AYA patients on trials, which is attributed to an "accrual cliff,"[65] or the large drop in accrual of patients aged 20–29. Accrual data came from the "Surveillance, Epidemiology, and End Results" (SEER) database, which is useful in providing national data and generating data from more rural areas or areas with less healthcare access. However, not all states and counties contribute data and SEER may omit important biologic information.[54] Accrual data was reported for individual institutions in some retrospective cohort studies ($n = 7$), including Southern California ($n = 3$),[9,32,74] Pittsburgh ($n = 2$),[62,69] Chicago ($n = 1$),[31] and

Boston ($n = 1$).[16] These reports echo the national data that, when compared to pediatric and adult accrual rates, AYA accrual is significantly lower.

Limited Trials—Limited trials is another major challenge to AYA patients ($n = 43$).[2,3,5,7,9,10,16,27,30–32,35–38,40,41,43,45,46,48,50,53,55,56,58–60,62–64,66,67,69–75,78–80,82] Trials must be suitable, meaning they are available based on age ($n = 29$),[3,5,9,10,27,29,30,32,37,40,43,45,46,48,52,53,58–60,64,66,67,70,72–74,78–80] which is hindered by trial age eligibility, and suitable based on tumor type ($n = 12$),[9,10,30,37,38,40,46,50,59,70,71,75] which is challenged by the rarity of AYA cancers, particularly CNS cancers. A paucity of studies on these rare cancers creates challenges in finding funding or sponsorship, making it harder to open trials.[32,50,56,63,71–73,78]

Long Term Follow Up—Nine studies[2,40,43,52,53,59,63,76,80] discuss the burden of treatment sequelae, or "cost of cure." The most common treatment complications were the risk of secondary malignancy and the development of endocrinologic or cardiovascular complications.[40,52,53,76] However, concerns about body image, cognitive changes, and PTSD[2,52,76] were also important sequelae of therapy. Survivorship programs for AYAs are severely lacking,[76] and the absence of research into the quality of life of survivors is another demonstration of the neglect in research of this group.[59]

Trial Design—Issues with trial design were discussed in 25 papers.[22,23,28,29,31,32,36,43,45,52,53,55,63,72,73,75,78] The screening process, length of treatment regimen, and time spent in hospitals or at appointments may interrupt AYA social, educational, and vocational commitments,[50,56,71] making AYAs less likely to participate on trials. Knowledge and usage of patient-reported outcomes to understand psychosocial disturbance and patients' symptom burden is lacking in AYA trials,[63,81] with some advocating for the integration of "nontraditional endpoints" to better address clinically meaningful changes.[75] In addition, inconsistent response criteria[35] and selecting the appropriate endpoint for survival[22,75] are unknown territory in AYA trials, which may make conclusions from trials less generalizable. Challenges of consent are unique to the AYA population because the population spans an important transitional age of independence. Studies investigating adolescents' reasons for enrolling in phases I and II trials discuss the precarious nature of informed consent,[28,29] emphasizing that many adolescents report being the final decision maker but many struggle with relationships with parents and may not fully understand the whole trial. Finally, inadequate preclinical models limit the construction of future trials and hinder the understanding of AYA tumor biology.[36,50,63]

Recommendations

The recommendations provided by these papers were organized into 5 categories, defined in Table 4. The frequency of recommendations is shown in Table 5; the most common recommendations were in accrual ($n = 48$) and trial design ($n = 48$).

Recommendations for Providers—Twenty-seven papers advised how providers could be leveraged to improve AYA trials and care. Recommendations targeted education ($n = 25$),[2,3,5,26,31,42,46,47,49,50,52,56–59,61,63,66,71,73,75–79] referral patterns ($n = 7$),[3,31,56,63,66,71,73] and inter-specialty collaboration ($n = 13$).[9,26,31,32,42,49,50,56,61,64,71,78,79] Referral decisions should be made based on individual patient needs and where patients will receive the best psychosocial support.[66]

Recommendations for Coordination of Care—Twenty-seven papers provided recommendations targeted to coordinating care, including psychosocial support ($n = 12$),[26,30,43,48–50,52,57,61,63,71,76] education ($n = 17$),[2,3,28,29,31,46,47,49,50,55,56,58,59,61,75,77,79] advocacy ($n = 8$),[28,31,46,47,58,59,74,75] and adherence ($n = 1$).[63] Improving psychosocial support should include improving coping skills,[57] increasing access to support groups and mental health counseling,[48] providing age-appropriate teams as part of the trial protocol,[61] and providing family and fertility planning services.[43,61] Patients should be educated on health literacy to increase knowledge of risks and symptoms, improve alertness for early symptoms, and encourage health maintenance, which may also promote adherence to therapy.[47,58] Multiple papers recommended providing "resources" but did not specify an action plan.[2,59] Advocacy programs, such as family navigation, are also important support systems.

Recommendations for Organizations—Forty-five papers provided recommendations at the organizational level, including AYA programming ($n = 21$),[26,30,32,40,42–50,53,55,58,61,62,67,71,78] an AYA specialty ($n = 7$),[5,42,44,57,64,76,80] collaboration between centers ($n = 23$),[9,36–38,40,47,48,50,54,56,61,63,65,69–73,76,78–80] insurance considerations ($n = 6$),[27,49,50,58,63,73] education ($n = 4$),[59,61,64,75] telehealth follow up structure ($n = 2$),[51,66] and referral pathways ($n = 3$).[50,56,66] Although most agreed on the importance of an AYA-specific program to promote accrual and access, the proposed components of the programs varied, including health navigators,[46,47,78] oversight committee with the creation of best practices for providers,[3,46] designated group of researchers,[40,49,61] multi-disciplinary tumor board,[26] and a multi-disciplinary team with specialized clinics and/or inpatient units.[30,43,49,54,67,78] The creation of an AYA program may bolster collaboration between centers,[69] however, continued efforts are needed to improve collaboration between medical and pediatric oncology centers and/or adult and pediatric institutions. Some supported the creation of an AYA specialty, which would have its own residency or fellowship training to create providers that could cater to AYA's specific needs.[5,42,44,57,64,76,80] Lastly, 2 papers championed the importance and utility of telehealth and the impact it may have on long-term survivorship follow-up, continuity of care while on trial, or as part of an AYA program.[51,66]

Recommendations for Accrual—Forty-eight papers proposed recommendations to improve accrual. Most studies provided generic statements on the need to understand barriers ($n = 22$),[3,5,9,10,16,21,31,32,43,46,51,54–56,59,62,66,70,71,73,77,79] create targeted interventions ($n = 17$),[2,3,5,9,10,16,31,32,55,59,61,65,71,74,75,78,79] and increase

Table 4. Summary and Definitions of Recommendations Discussed Throughout Papers

RECOMMENDATIONS
Recommendations for health care providers: paper proposes recommendations that are provider-specific ◦ Inter-specialty collaboration: improve the relationship and cooperation between pediatric oncologists and medical oncologists ◦ Referral patterns: ensure correct referral between specialties and centers; improve referral habits to ensure referrals are made based on individual patient needs ◦ Education: improve physician education to better recognize AYA cancer symptoms and improve physician awareness of AYA cancer incidence and trials
Recommendations for Coordination of Care: paper proposes recommendations regarding coordinating care ◦ Psychosocial support: create resources and improve current psychosocial support provided to patients (i.e. educational, vocational, mental health, coping) ◦ Expand use of genetic testing: improve patient access to genetic testing ◦ Education: increase health literacy, knowledge trials exist, recognition of symptoms ◦ Advocacy: promote opportunities for advocacy (i.e. family navigation) ◦ Adherence: improve patient adherence to trial and therapy
Recommendations for Organizational Support: paper proposes recommendations that are organization-specific ◦ AYA programming: recommendation to create an AYA program, which includes health coaches/navigators to facilitate full access to and utilization of oncology care; describes staffing, resources, and training required to deliver care; describes the inter-disciplinary team; describes the need for a multi-disciplinary tumor board ◦ AYA specialty: addresses the need for a specialty specific for the AYA oncology population ◦ Collaboration between centers: addresses the importance of improved collaboration and coordination of trials between multiple centers and hospitals ◦ Insurance companies: recommendations on how insurance company policies can change to better include AYAs; how insurance company policies can change to better provide access ◦ Education: advocates for education of insurers and legislators on the prevalence of AYA cancers and importance of research ◦Telehealth follow up structure: advocates the need for integration of telehealth into the survivorship plan ◦ Referral pathways: recommends the improvement of referral pathways from an institutional level based on patient needs
Recommendations for accrual: paper proposes recommendations to improve accrual ◦ Understand barriers: improve understanding of the factors/variables leading to low accrual ◦Targeted interventions: develop specific interventions to target accrual ◦ Increase access: a generic/broad statement on recommending increasing access to trials
Recommendations for trial design: paper proposes recommendations to trial design ◦Variables of interest: development and integration of certain variables into trial design/endpoints (i.e. the addition of HRQOL data, create endpoints that are AYA specific, or construction of trials that are AYA specific or tumor-specific) ◦ Centralized data: recommends the need for centralized data for collection ◦ Physician factors: recommends that trial design should consider factors important for physicians (i.e. the feasibility of enrollment, referral of patients to study, etc.) ◦ Patient engagement: recommends trials should involve AYAs in trial design to combat barriers to trial involvement ◦ Data collection: improve mechanisms or frequency of certain data collection (i.e. biopsies for tumor biology) ◦ Longitudinal follow-up: improve long-term follow-up; improve investigations into long-term impacts of AYA programming ◦ Molecular stratification/profiling: advocates for the use of molecular stratification for enrollment and eligibility or construction of specific trials based on mutations ◦ Feasibility: recommendations addressing feasibility/realistic aspects of trial design ◦ Cost effectiveness: improving cost-effectiveness of a trial could help relieve barriers ◦ Cooperative groups: improve the use of co-op groups for trial conduct and recruitment ◦ Expand age eligibility: to be more inconclusive, expand age restrictions so AYAs can be included in more pediatric and adult trials ◦ Acceptability: improve acceptability of trial design by considering compatibility with lifestyle/ease of integration into life ◦ Preclinical models: emphasizes the importance of developing and use of preclinical models to further inform clinical trials ◦ Consent: improve the consenting process to ensure appropriate education and understanding of trial benefits and process

access ($n = 31$).[2,3,26,29–31,36,37,40,42,43,45,47–49,53,56–58,61,63,65–67,69,71,72,74,76,77,82] Concrete interventions proposed included increasing interpreters,[75] diversifying the healthcare workforce,[75] and increasing access to genetic testing.[25]

Recommendations for Trial Design—Forty-eight papers provided recommendations focused on trial design. Developing preclinical models ($n = 2$)[39,45] and the integration of these models into translational studies are important to better understand tumor biology. Molecular stratification ($n = 20$)[22,24,26,32–34,37–40,42–45,50,55,64,67,71,83] and feasibility of studies ($n = 4$)[57,63,72,81] should be considered during study construction. Improving the enrollment process and ease of participation through expansion of age eligibility ($n = 17$),[9,26,37,38,45,48–50,54–56,67,71–73,75,79] patient engagement ($n = 5$),[32,48,50,56,75] physician factors ($n = 2$),[46,48] consent ($n = 1$),[29] and acceptability ($n = 5$)[49,56,71,75,76] can promote patient accrual. Other recommendations included improving variables of interest ($n = 22$),[2,3,5,30–32,41–46,51,52,54,58,64,67,76,78,80,81] improving data collection ($n = 3$),[38,40,50] creating a centralized database ($n = 4$),[32,46,72,81] better incorporation of cooperative groups ($n = 1$),[32] and longitudinal follow-up ($n = 6$).[40,63,76,79,80,82]

Limitations

The most common limitation was a nonsystematic design of reviews ($n = 34$). Of the 68 papers, only 24 papers

Table 5. Summary of Recommendations by Paper

Author	None	Providers	Coordination of care	Organizations	Accrual	Trial design	Total
Ahrendsen 2021					■		1
Albritton 2008		■	■	■	■	■	5
Alken 2015				■	■	■	3
Barr 2016		■	■	■	■	■	5
Bautista 2017						■	1
Beltrami 2022			■	■	■		3
Bennett 2020		■		■	■	■	4
Bernig 2013		■	■	■	■	■	5
Bishop 2021				■			1
Bleyer 2016				■			2
Bleyer 2007		■	■	■	■	■	5
Bleyer 2006		■		■	■	■	4
Bleyer 2007		■	■	■	■	■	5
Bleyer 2009	■						1
Bleyer 2002		■	■	■	■		4
Bradford 2018		■		■	■		3
Calaminus 2008						■	1
Capra 2003				■		■	2
Cavalli 2018						■	1
Close 2019			■	■	■	■	4
Collins 2015		■		■	■	■	4
Dekking 2015	■						1
deRojas 2019					■	■	2
Downs-Canner 2009				■	■		2
Epelman 2013						■	1
Fern 2014		■	■	■	■	■	5
Fern 2010				■	■		2
Ferrari 2013		■	■	■	■		4
Ferrari 2007		■		■		■	3
Ferrari 2008		■	■	■	■	■	5
Ferrari 2016					■	■	2
Fontebasso 2013						■	1
Freyer 2015		■	■	■	■	■	5
Gajjar 2015						■	1
Gaspar 2016		■	■	■		■	4
Gupta 2014				■	■	■	3
Hinds 2005			■				1
Holland 2021				■	■	■	3
Jacob 2017				■	■		2
Keegan 2018		■		■	■	■	4
Kelly 2022				■	■		2
Krailo 1993			■		■		2
Lee 2022		■	■	■	■	■	5
Lethaby 2013					■		1
Lindsay 2022						■	1
Magrath 2013		■	■	■	■	■	5
Majd 2019				■	■	■	3

Table 5. Continued

Author	None	Providers	Coordination of care	Organizations	Accrual	Trial design	Total
McCabe 2016				■		■	2
Miller 2020		■	■		■	■	4
Miller 2013			■		■	■	3
Moreno 2009			■	■	■	■	4
Nass 2015		■	■	■	■	■	5
Nooka 2016		■	■		■		3
Osborn 2019		■		■	■	■	4
Papageorgiou 2020			■	■	■	■	4
Patterson 2015		■	■			■	3
Pentheroudakis 2005				■	■		2
Pollock 2007				■	■	■	3
Roth 2016		■	■	■	■	■	5
Sanford 2017		■	■		■	■	4
Sarvode 2022					■		1
Sender 2015			■	■	■	■	4
Soliman 2008				■		■	2
Szychot 2020						■	1
Thomas 2018		■		■	■	■	4
Tran 2014	■						1
Yamasaki 2022				■		■	2
Yeo 2021				■	■	■	3
Total	3	27	27	45	48	48	

focused on one or more PBT populations. Twenty studies used undefined age/AYA criteria, while 8 studies used inconsistent age criteria, which included discrepant maximum ages,[35] discussion of ages greater than those included in the study,[58] and inconsistent application of age criteria based on tumor types.[61] Papers had lack of comprehensive recommendations ($n = 15$) if they provided recommendations for relatively few of the challenges identified. Limited external validity ($n = 14$) came from the use of homogenous populations,[16,26,28,29] studies done at single institutions or within a single city,[9,16,26,30–32,62,66,69,74,82] country-specific insurance structures,[27] historical changes limiting modern applicability,[74] and sampling bias.[29] Issues with study design ($n = 4$) included lack of adequate statistical power,[30] patient stratification (manner of patient grouping and/or analysis is limited),[16,23,77] and the lack of accounting for confounders in data collection or analysis.[16] Finally, 3 studies provided no recommendations.

Risk of Bias (RoB)

EPHPP was used to evaluate 23 studies (retrospective cohort studies ($n = 18$), qualitative cross-sectional analyses ($n = 3$), prospective observational studies ($n = 2$)), while AMSTAR was used to evaluate 5 systematic reviews (Supplementary Material 5). Overall, only 12 studies had low RoB, with the rest having either moderate or high RoB. While not all studies addressed all confounders, confounding was felt to be adequately covered if the study addressed demographic, clinical, oncologic, and treatment-related factors. Studies that used nonstandardized, nonvalidated questionnaires for patient interviews had weak data collection methods. Finally, 4 of the 5 systematic reviews were low quality due to not considering individual funding for each paper, lack of a RoB assessment, or poor description of the review methods.[10,23,35,56]

Discussion

This systematic review summarized and synthesized 11 categories of intricately connected challenges that hamper the construction and execution of clinical trials in the AYA cancer population. The psychosocial needs in this patient population are unique and the tumor types are distinct from similar tumors of different age groups,[84] underscoring the importance of having a defined AYA population.

Despite the importance of recognizing this distinct population, various papers in our sample did not use specific or accepted definitions to describe AYA patients[25,28,35,41,47]; some studies only addressed the lower age range (15–29)[3,5,10,24,29,53,54,56,59,62,69,80,82] and excluded ages >30 from their discussion. This lack of uniformity may reflect different biases and impact our ability to compare between trials.

Physicians' perception of patient nonadherence and patients' actual nonadherence to therapy/trials was a frequently mentioned challenge. A review on treatment nonadherence in AYAs with cancer aptly highlights that adherence should be understood as a continuum. To combat treatment nonadherence, establishing a reasonable threshold allows for the integration of a formal adherence assessment, helping practitioners identify, and rectify treatment nonadherence.[85] Adherence is also promoted by providing AYAs with flexibility and integration into their lifestyle, giving them autonomy, and agency with their treatment. In addition, the promotion of self-care habits (e.g. through the use of video games) has been shown to increase medication compliance in adolescents.[86]

Importantly, AYA oncology (AYAO) programs have been recognized and supported since 2006. A recent survey study, which collected responses from 50 AYAO programs throughout NCI Cancer Centers, showed the variable usage of AYA programs: a small proportion of institutions (15%) had >300 new patient visits per month, but the majority (55%) had fewer than 0–50 new patients per month.[87] The prevalence of AYAO-specific providers was low and most services were provided at the main campus outpatient clinic with rare availability for satellite spaces or inpatient services. The results of this survey reflect similar findings in this review; there is consistent use of social work, psychology, and nurse coordinators (58%, 54%, 51%, respectively) in AYAO programs, but more varied use of other resources like child life services, music therapy, dieticians, and physical therapy (28%, 28%, 23%, 17%, respectively).[87] Finally, the survey demonstrated that only about half (51%) of centers provided guidance on fertility preservation, as seen in our results. Standardized education and care plans have proven effective in childhood cancer survivors,[88] but sexual health counseling was provided through education materials or through referral to a sexual health provider with no report of having a sex therapist as part of the team.[87] Other areas to expand on include integration of patient-reported outcomes and new trial endpoints (such as markers of functionality), early discussion of end-of-life, and use of palliative care.[89]

Many of the papers included in this review were editorial. Those with investigational designs were assessed through the risk of bias assessments. Overall, only 12 studies had a low risk of bias, with the rest having either moderate or high risk of bias. While SEER data collection is validated and reliable, not all states and countries contribute data to this database project, and the database may omit important biological information.[54] Thus, the database itself has limitations, and conclusions drawn from information derived from SEER must be interpreted within the context of these limitations.

Only 24 papers contained substantive discussion of PBTs, underscoring the unmet need of AYA patients with PBTs that produce a significant amount of morbidity and mortality and frequently go unrecognized and untreated in the AYA population.[90]

Conclusions

This systematic review highlights that care for AYA patients with cancer, particularly those with PBTs, remains an unmet need. A variety of challenges were identified by the selected literature and the summarized findings can serve as a roadmap to address these challenges.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

adolescents and young adults | oncology | CNS neoplasms | barriers to care | access to care

Funding

Research support was provided by the NIH Medical Research Scholars Program, a public-private partnership supported jointly by the NIH, and contributions to the Foundation for the NIH from the American Association for Dental Research and the Colgate-Palmolive Company.

Conflict of interest statement

None declared.

Authorship Statement

The study question was created by T.S.A. and M.R.G. D.C. and E.B. constructed search terms and D.C. conducted a database search. E.B. and M.P. reviewed literature, collected data, and wrote the first draft of the manuscript. All authors reviewed and contributed to the final manuscript.

References

1. Group AaYAOPR. *Closing the Gap: Research and Care Imperatives for Adolescent and Young Adults with Cancer—Report of the Adolescent and Young Adult Oncology Progress Review Group*. Bethesda, MD: National Cancer Institute; 2006.
2. Miller KD, Fidler-Benaoudia M, Keegan TH, et al. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin*. 2020;70(6):443–459.
3. Bleyer A. Young adult oncology: the patients and their survival challenges. *CA Cancer J Clin*. 2007;57(4):242–255.
4. Bleyer A, Viny A, Barr R. Cancer in 15- to 29-year-olds by primary site. *Oncol*. 2006;11(6):590–601.

5. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. *Cancer.* 2006;107(S7):1645–1655.
6. Bleyer A. The adolescent and young adult gap in cancer care and outcome. *Curr Probl Pediatr Adolesc Health Care.* 2005;35(5):182–217.
7. Bleyer A, O'leary M, Barr R, Ries L. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975–2000. U.S. Department of Health and Human Services National Institutes of Health. 2006;6(5767):65–80.
8. Keegan TH, Ries LA, Barr RD, et al.; National Cancer Institute Next Steps for Adolescent and Young Adult Oncology Epidemiology Working Group. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer.* 2016;122(7):1009–1016.
9. Collins CL, Malvar J, Hamilton AS, Deapen DM, Freyer DR. Case-linked analysis of clinical trial enrollment among adolescents and young adults at a National Cancer Institute-designated comprehensive cancer center. *Cancer.* 2015;121(24):4398–4406.
10. de Rojas T, Neven A, Terada M, et al. Access to clinical trials for adolescents and young adults with cancer: a meta-research analysis. *JNCI Cancer Spectr.* 2019;3(4):pkz057.
11. Siembida EJ, Loomans-Kropp HA, Trivedi N, et al. Systematic review of barriers and facilitators to clinical trial enrollment among adolescents and young adults with cancer: identifying opportunities for intervention. *Cancer.* 2020;126(5):949–957.
12. Burke ME, Albritton K, Marina N. Challenges in the recruitment of adolescents and young adults to cancer clinical trials. *Cancer.* 2007;110(11):2385–2393.
13. SEER*Explorer: An interactive website for SEER cancer statistics. 2023; *SEER 8 registries: SEER Incidence Data, November 2022 Submission (1975–2020).* Available at: https://seer.cancer.gov/statistics-network/explorer/. Accessed May 16, 2023.
14. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2015-2019. *Neuro Oncol.* 2022;24(Suppl 5):v1–v95.
15. Bleyer A, Hag-Alshiekh M, Montello M, et al. Older adolescents and young adults with brain tumors in the United States: lack of clinical trial participation and of survival prolongation and mortality reduction. Paper presented at: Neuro-oncology; 2004.
16. Sarvode S, Vogelzang JR, Sarvode Mothi S, et al. Clinical trial enrollment among adolescent and young adults with primary central nervous system tumors treated at the Dana-Farber cancer institute. *J Adolesc Young Adult Oncol.* 2022;11(6):543–549.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
18. Project EPHP. *Quality Assessment Tool for Quantitative Studies.* Hamilton: National Collaborating Centre for Methods and Tools, McMaster University; 1998.
19. Thomas B, Ciliska D, Dobbins M, Micucci S. *Quality Assessment Tool for Quantitative Studies Dictionary: The Effective Public Health Practice Project (EPHPP).* Faculty of Health Sciences McMaster Evidence Review & Synthesis Team: McMaster University; 2008.
20. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008.
21. Lethaby CD, Picton S, Kinsey SE, et al. A systematic review of time to diagnosis in children and young adults with cancer. *Arch Dis Child.* 2013;98(5):349–355.
22. Lindsay HB, Massimino M, Avula S, et al. Response assessment in paediatric intracranial ependymoma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. *Lancet Oncol.* 2022;23(8):e393–e401.
23. Tran TH, Lee M, Alexander S, et al. Lack of treatment-related mortality definitions in clinical trials of children, adolescents and young adults with lymphomas, solid tumors and brain tumors: a systematic review. *BMC Cancer.* 2014;14(1):612.
24. Epelman S. The adolescent and young adult with cancer: state of the art–brain tumor. *Curr Oncol Rep.* 2013;15(4):308–316.
25. Ahrendsen JT, Torre M, Meredith DM, et al. IDH-mutant gliomas with additional class-defining molecular events. *Mod Pathol.* 2021;34(7):1236–1244.
26. Bernig T, Jahn F, Witkowsky S, et al. Treatment of adolescents and young adults (AYA) with cancer in a multidisciplinary setting: on the way to a highly specialized AYA unit. *Klin Padiatr.* 2013;225(6):335–338.
27. Bishop AJ, Livingston JA, Ning MS, et al. Young adult populations face yet another barrier to care with insurers: limited access to proton therapy. *Int J Radiat Oncol Biol Phys.* 2021;110(5):1496–1504.
28. Hinds PS, Drew D, Oakes LL, et al. End-of-life care preferences of pediatric patients with cancer. *J Clin Oncol.* 2005;23(36):9146–9154.
29. Miller VA, Baker JN, Leek AC, et al. Adolescent perspectives on phase I cancer research. *Pediatr Blood Cancer.* 2013;60(5):873–878.
30. Moreno L, Bautista FJ, Zacharoulis S. Outcome of teenagers and young adults with ependymoma: the Royal Marsden experience. *Childs Nerv Syst.* 2009;25(9):1047–1052.
31. Sanford SD, Beaumont JL, Snyder MA, Reichek J, Salsman JM. Clinical research participation among adolescent and young adults at an NCI-designated Comprehensive Cancer Center and affiliated pediatric hospital. *Support Care Cancer.* 2017;25(5):1579–1586.
32. Thomas SM, Malvar J, Tran HH, Shows JT, Freyer DR. A prospective comparison of cancer clinical trial availability and enrollment among adolescents/young adults treated at an adult cancer hospital or affiliated children's hospital. *Cancer.* 2018;124(20):4064–4071.
33. Cavalli FMG, Hübner JM, Sharma T, et al. Heterogeneity within the PF-EPN-B ependymoma subgroup. *Acta Neuropathol.* 2018;136(2):227–237.
34. Gajjar A, Bowers DC, Karajannis MA, et al. Pediatric brain tumors: innovative genomic information is transforming the diagnostic and clinical landscape. *J Clin Oncol.* 2015;33(27):2986–2998.
35. Bautista F, Fioravantti V, de Rojas T, et al. Medulloblastoma in children and adolescents: a systematic review of contemporary phase I and II clinical trials and biology update. *Cancer Med.* 2017;6(11):2606–2624.
36. Kelly SM, Effeney R, Gaze MN, et al; QUARTET Project and the SIOPE Radiation Oncology Working Group. QUARTET: a SIOP Europe project for quality and excellence in radiotherapy and imaging for children and adolescents with cancer. *Eur J Cancer.* 2022;172:209–220.
37. Majd N, Penas-Prado M. Updates on management of adult medulloblastoma. *Curr Treat Options Oncol.* 2019;20(8):64.
38. McCabe MG, Valteau-Couanet D. Pediatric cancers and brain tumors in adolescents and young adults. *Prog Tumor Res.* 2016;43:74–86.
39. Fontebasso AM, Liu XY, Sturm D, Jabado N. Chromatin remodeling defects in pediatric and young adult glioblastoma: a tale of a variant H istone 3 Tail. *Brain Pathol.* 2013;23(2):210–216.
40. Alken SP, D'Urso P, Saran FH. Managing teenage/young adult (TYA) brain tumors: a UK perspective. *CNS Oncol.* 2015;4(4):235–246.
41. Szychot E, Goodden J, Whitfield G, Curry S. Children's Cancer and Leukaemia Group (CCLG): review and guidelines for the management of meningioma in children, teenagers and young adults. *Br J Neurosurg.* 2020;34(2):142–153.
42. Bennett J, Bouffet E. Neuro-oncology in adolescents and young adults—an unmet need. *Neuro Oncol.* 2020;22(6):752–753.
43. Papageorgiou GI, Razis ED. CNS tumors in adolescents and young adults: the need for a holistic specialized approach. *JCO oncology practice.* 2020;16(4):155–162.

44. Yamasaki F. Adolescent and young adult brain tumors: current topics and review. *Int J Clin Oncol*. 2022;27(3):457–464.
45. Yeo KK, Burgers DE, Brodigan K, et al. Adolescent and young adult neuro-oncology: a comprehensive review. *Neuro-Oncol. Pract.* 2021;8(3):236–246.
46. Albritton KH, Eden T. Access to care. *Pediatr Blood Cancer.* 2008;50(S5):1094–1098.
47. Beltrami A, Hilliard A, Green AL. Demographic and socioeconomic disparities in pediatric cancer in the United States: current knowledge, deepening understanding, and expanding intervention. *Cancer Epidemiol*. 2022;76:102082.
48. Close AG, Dreyzin A, Miller KD, Seynnaeve BK, Rapkin LB. Adolescent and young adult oncology—past, present, and future. *CA Cancer J Clin.* 2019;69(6):485–496.
49. Ferrari A, Montello M, Budd T, Bleyer A. The challenges of clinical trials for adolescents and young adults with cancer. *Pediatr Blood Cancer*. 2008;50(S5):1101–1104.
50. Gaspar N, Fern L. Increasing access to clinical trials and innovative therapy for teenagers and young adults with cancer-a multiple stakeholders and multiple steps process. *Tumors Adolescents Young Adults*. 2016;43:38–49.
51. Holland LR, Bradford NK, Youl P, et al. Cancer incidence, mortality, and survival for children, adolescents, and young adults in Queensland between 1987 and 2016. *J Adolesc Young Adult Oncol.* 2021;10(6):629–644.
52. Patterson P, McDonald FE, Zebrack B, Medlow S. *Emerging issues among adolescent and young adult cancer survivors*. Paper presented at: Seminars in Oncology Nursing; 2015.
53. Pentheroudakis G, Pavlidis N. Juvenile cancer: improving care for adolescents and young adults within the frame of medical oncology. *Ann Oncol*. 2005;16(2):181–188.
54. Pollock BH. Where adolescents and young adults with cancer receive their care: does it matter? *J Clin Oncol*. 2007;25(29):4522–4523.
55. Sender L, Zabokrtsky KB. Adolescent and young adult patients with cancer: a milieu of unique features. *Nat Rev Clin Oncol*. 2015;12(8):465–480.
56. Fern LA, Lewandowski JA, Coxon KM, Whelan J; National Cancer Research Institute Teenage and Young Adult Clinical Studies Group, UK. Available, accessible, aware, appropriate, and acceptable: a strategy to improve participation of teenagers and young adults in cancer trials. *Lancet Oncol.* 2014;15(8):e341–e350.
57. Barr RD, Ferrari A, Ries L, Whelan J, Bleyer WA. Cancer in adolescents and young adults: a narrative review of the current status and a view of the future. *JAMA Pediatr*. 2016;170(5):495–501.
58. Bleyer A, Budd T, Montello M. Older adolescents and young adults with cancer, and clinical trials: lack of participation and progress in North America. *Cancer in Adolescents and Young Adults*. Berlin, Heidelberg: Springer; 2007:71–81.
59. Bleyer WA. Cancer in older adolescents and young adults: epidemiology, diagnosis, treatment, survival, and importance of clinical trials. *Med Pediat Onco: Off J SIOP* 2002;38(1):1–10.
60. Bleyer A, Choi M, Fuller CD, Thomas Jr CR, Wang SJ. *Relative lack of conditional survival improvement in young adults with cancer*. Paper presented at: Seminars in Oncology 2009.
61. Ferrari A. The challenge of access to care for adolescents with cancer in Italy: national and local pediatric oncology programs International perspectives on AYAO, part 2. *J Adolesc Young Adult Oncol.* 2013;2(3):112–117.
62. Jacob SA, Shaw PH. No improvement in clinical trial enrollment for adolescents and young adults with cancer at a children's hospital. *Pediatr Blood Cancer.* 2017;64(12):e26638.
63. Magrath I, Epelman S. Cancer in adolescents and young adults in countries with limited resources. *Curr Oncol Rep.* 2013;15:332–346.
64. Ferrari A, Bleyer A. Participation of adolescents with cancer in clinical trials. *Cancer Treat Rev.* 2007;33(7):603–608.
65. Bleyer A. Adolescents and young adult cancer trial participation: Will the national community oncology research program also fail? and what about the rest of us? *J Oncol Pract*. 2016;12(5):398–402.
66. Bradford NK, Henney R, Walker R, et al. Queensland youth cancer service: a partnership model to facilitate access to quality care for young people diagnosed with cancer. *J Adolesc Young Adult Oncol.* 2018;7(3):339–348.
67. Capra M, Hargrave D, Bartels U, et al. Central nervous system tumours in adolescents. *Eur J Cancer.* 2003;39(18):2643–2650.
68. Dekking SAS, van der Graaf R, Kars MC, et al. Balancing research interests and patient interests: a qualitative study into the intertwinement of care and research in paediatric oncology. *Pediatr Blood Cancer.* 2015;62(5):816–822.
69. Downs-Canner S, Shaw PH. A comparison of clinical trial enrollment between adolescent and young adult (AYA) oncology patients treated at affiliated adult and pediatric oncology centers. *J Pediatr Hematol Oncol.* 2009;31(12):927–929.
70. Fern LA, Whelan JS. *Recruitment of adolescents and young adults to cancer clinical trials—international comparisons, barriers, and implications*. Paper presented at: Seminars in Oncology; 2010.
71. Freyer DR, Seibel NL. The clinical trials gap for adolescents and young adults with cancer: recent progress and conceptual framework for continued research. *Curr Pediatr Rep.* 2015;3:137–145.
72. Gupta AA, Indelicato DJ. Increasing the number of clinical trials available to adolescents diagnosed with cancer. *Pediatrics.* 2014;133(Supplement_3):S114–S118.
73. Keegan THM, Parsons HM. Adolescent angst: enrollment on clinical trials. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):154–160.
74. Krailo MD, Bernstein L, Sullivan-Halley J, Hammond GD. Patterns of enrollment on cooperative group studies: an analysis of trends from the Los Angeles county cancer surveillance program. *Cancer.* 1993;71(10 S):3325–3330.
75. Lee EQ, Camidge DR, Mehta G. Extending our reach: expanding enrollment in brain metastases and primary brain tumor clinical trials. *Am Soc Clin Oncol educ book.* 2022;42:166–174.
76. Nass SJ, Beaupin LK, Demark-Wahnefried W, et al. Identifying and addressing the needs of adolescents and young adults with cancer: summary of an Institute of Medicine workshop. *Oncologist.* 2015;20(2):186–195.
77. Nooka AK, Behera M, Lonial S, et al. Access to children's oncology group and pediatric brain tumor consortium phase 1 clinical trials: racial/ethnic dissimilarities in participation. *Cancer.* 2016;122(20):3207–3214.
78. Osborn M, Johnson R, Thompson K, et al. Models of care for adolescent and young adult cancer programs. *Pediatr Blood Cancer.* 2019;66(12):e27991.
79. Roth ME, O'Mara AM, Seibel NL, et al. Low enrollment of adolescents and young adults onto cancer trials: insights from the community clinical oncology program. *J Oncol Pract.* 2016;12(4):e388–e395.
80. Soliman H, Agresta SV. Current issues in adolescent and young adult cancer survivorship. *Cancer Control*. 2008;15(1):55–62.
81. Calaminus G, Barr R. Economic evaluation and health-related quality of life. *Pediatr Blood Cancer*. 2008;50(S5):1112–1115.
82. Ferrari A, Silva M, Veneroni L, et al. Measuring the efficacy of a project for adolescents and young adults with cancer: a study from the Milan Youth Project. *Pediatr Blood Cancer*. 2016;63(12):2197–2204.
83. Bautista F, Di Giannatale A, Dias-Gastellier N, et al. Patients in pediatric phase I and early phase II clinical oncology trials at Gustave Roussy: a 13-year center experience. *J Pediatr Hematol Oncol*. 2015;37(2):e102–e110.
84. Tricoli JV, Bleyer A. Adolescent and young adult cancer biology. *Cancer J*. 2018;24(6):267–274.

85. Kondryn HJ, Edmondson CL, Hill J, Eden TOB. Treatment non-adherence in teenage and young adult patients with cancer. *Lancet Oncol.* 2011;12(1):100–108.
86. Kato PM, Cole SW, Bradlyn AS, Pollock BH. A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. *Pediatrics.* 2008;122(2):e305–e317.
87. Daunov K, Daunov M, Noskoff K, et al. Are NCI cancer centers providing adolescents and young adults with cancer focused clinical services? A national survey. *J Natl Compr Canc Netw.* 2023;21(5):487–495.e15.
88. van der Perk MEM, van der Kooi ALF, van de Wetering MD, et al. Oncofertility care for newly diagnosed girls with cancer in a national pediatric oncology setting, the first full year experience from the Princess Máxima Center, the PEARL study. *PLoS One.* 2021;16(3):e0246344.
89. Jacobs S, Perez J, Cheng YI, et al. Adolescent end of life preferences and congruence with their parents' preferences: Results of a survey of adolescents with cancer. *Pediatr Blood Cancer.* 2015;62(4):710–714.
90. Boodman S. She thought anxiety and drinking made her ill. The truth was scarier; 2023. https://www.washingtonpost.com/health/2023/02/18/medical-mystery-anxiety-alcoholism-symptoms/. Date accessed May 16, 2023.