**Next Step for Global Adolescent and Young Adult Oncology: A Core Patient-Centered Outcome Set**

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**Abstract**

The relatively small number of cancers in the adolescent and young adult (AYA) age group, those aged 15-39 years, does not appropriately reflect the personal and societal costs of cancer in this population, as reflected in the potential years of life lost or saved; the decreased productivity and health-related quality of life due to the impact of the disease during formative years and long-term complications or disabilities. Improvements in care and outcomes for AYAs with cancer require collaboration among different stakeholders at different levels (patients, caregivers, healthcare professionals, researchers, industry, and policymakers). Development of a Core Outcome Set (COS), an agreed minimum set of outcomes that should be measured globally in research, routine clinical practice, specifically for AYAs with cancer, with outcomes that are well defined based on the perspective of those who are affected and assessed with validated measures is highly required. A globally implemented COS for AYAs with cancer will facilitate better pooling of research data and the implementation of high-quality healthcare registries, which by benchmarking not only nationally, but also internationally, may ultimately improve the value of the care given to these underserved young cancer patients. We reflect on the need to develop a COS for AYA with cancer, the arenas of application and the challenges of implementing an age-specific COS in research and clinical practice.

“….cancer changes your life but there is a life after cancer that is hard to adjust back into after treatment without adequate support for age-specific issues” (Cancer survivor, 19 years old)

In any healthcare system it is essential that patients have access to care most likely to deliver tangible and sustainable improvements in outcomes encompassing survival, health-related quality of life (HRQoL), the ability to attend school or work, get and raise children and actively participate in society(1, 2). This also holds for adolescents and young adults (AYA) with cancer, defined as individuals age 15 to 39 years at the time of initial cancer diagnosis (3). Approximately 1.2 million new cases of invasive cancer are diagnosed worldwide annually among AYAs (4), which represents around 5% of all cancer diagnoses (5). Over the last decades, cancer incidence increased slightly in all AYA age groups (6, 7). The distribution of different cancers varies dramatically across the AYA age range. For example, pediatric malignancies - hematologic malignancies and brain tumors - are the most common cancers in adolescents (ages 15-19 years), while adult cancers - melanoma, breast, and colorectal cancers - are more common in older AYA (ages 30-39 years), and there are also some cancers with the highest incidence among the AYA age group (e.g., germ cell tumors) (5). Over 80% of AYAs with cancer will survive long-term (>5 years) (8, 9).

AYAs with cancer are distinct from the pediatric (<15 years) and the older adult (>40 years) cancer populations with respect to their spectrum of diseases due to the epidemiology and biology of their cancers, their developmental status, their particular psychosocial needs and the long-term complications of their cancer and treatments (3, 5, 10, 11). A cancer diagnosis during the AYA life stage exacerbates typical developmental challenges and interferes with the attainment of important age-specific milestones (10), including identity forming, establishing autonomy, responsibility and independence, education and starting a career, romantic relationships and starting a family (12). The way in which AYAs adjust to their cancer experience might have life-long implications for the quality of their life (13-16). Although the global burden of cancer is disproportionately observed in healthcare settings with limited resources (17), in many parts of the world, AYAs with cancer face disparities of care as they are poorly served by the traditional dichotomy of the pediatric and adult oncology services (11). Life-long consequences of treatment are often not part of the primary treatment discussions where the strong focus is on optimal survival outcomes. Examples of themes that AYA cancer patients would like to see raised during (post-treatment) survivorship are fertility, education and work, romantic relationships and sexuality, raising young children, and financial consequences of disease and treatment. These are topics that are not part of standard clinical consultations, due to lack of awareness and routine (as AYA cancer patients are rare), time constraints and lack of knowledge and supportive staff to discuss and act on these issues.

**Current state of AYA oncology**

The relatively small number of cancers in the AYA age group does not appropriately reflect the personal and societal costs of cancer in this population, as reflected in the potential years of life lost or saved; the decreased productivity and HRQoL due to the impact of the disease during formative years and long-term complications or disabilities (18-21). Sparked by the United States’ National Cancer Institute (NCI) landmark report “Closing the Gap: Research and Care Imperatives for Adolescents and Young Adults with Cancer” (3), research on cancer diagnosed at AYA age has flourished and the discipline of AYA oncology has made considerable strides with the development of AYA care programs globally (10, 22). In 2016, the NCI updated the AYA cancer progress review group report and examined scientific gaps and opportunities for future AYA oncology (23). It was concluded that, in the era of precision medicine, one of the most important contributions to AYA research would be to pool data (e.g. patient-reported outcomes, clinical and treatment data) across institutions and countries and create large cohorts for researchers to address the burden of cancer in AYA (23, 24). In line with these NCI recommendations, the AYA Working Group of the European Society for Medical Oncology (ESMO) and the European Society for Paediatric Oncology (SIOP Europe) concluded in 2021 that finding rapid solutions to ‘speak the same language’ among healthcare professionals is essential to further improve outcomes for AYAs (11). They reported that commonly examined clinical trial endpoints, such as five-year overall survival, progression-free survival, and cancer-specific survival, often do not address the specific needs of the AYA population; and found a widespread geographic variation in AYA care programs nationally and internationally, and an absence of outcome measures for monitoring and evaluating AYA cancer care programs and control.

**Patient-centered outcomes and core outcome sets: What matters to AYAs with cancer?**

To be meaningful and relevant, outcomes should ideally focus on what matters to the population for whom an intervention or treatment is applied. Such outcomes are called patient-centered outcomes (25). Patient-centered outcomes could be survival, disease control, or aspects of HRQoL including physical, psychological, and social functioning and symptom burden. Priority setting exercises, such as the recent one for AYAs with cancer by the James Lind Alliance (26), show that one of the fundamental problems across many types of healthcare decisions is that outcomes and goals for treatment may not be aligned between patients and their treating healthcare team (27). In some cases “what matters to you” as a recipient of healthcare is more important than “what is the matter with you” (28).

Several initiatives were set up to identify standardized core outcome sets (COSs) of patient-centered outcomes and their relevant measures. The Core Outcome Measures in Effectiveness Trials (COMET) Initiative (https://www.comet-initiative.org/) brings together people interested in the development and application of COSs for clinical trials in specific areas of health or health care including therapeutic (curative and palliative) as well as psychosocial studies. The International Consortium for Health Outcomes Measurement (ICHOM) organizes global teams of healthcare professionals, researchers, policymakers, and patients (and/or their representatives) to define COS per medical condition for use in clinical practice rather than clinical trials (https://www.ichom.org/). For both, COMET and ICHOM, COSs represent the consensus between the different key stakeholders – e.g., patients, caregivers, healthcare professionals, researchers, industry, and policymakers - of the minimum that should be measured and reported in all research or healthcare initiatives (29). Both organizations provide clear guidance on how to develop and implement a COS, in short: convene stakeholders, leverage literature, build consensus, disseminate and implement findings, and evaluate and refine implementation.

Clinical trial groups are now increasingly developing COSs within their specific clinical areas, for example within cardiology, gynecology, neurology and oncology. In these disease-specific COSs, age is often considered as a case-mix factor (defined as a patient characteristic, outside the influence of actions by healthcare providers, which may impact outcomes) to allow for risk stratification or adjustment. While focusing on a single condition and ignoring chronological age of the patient may have advantages in medical interventions, it does not take into account that psychosocial priorities may vary based on sociodemographic differences such as age. Disease-specific COSs consist of outcomes like survival and disease control, disutility of care, degree of health and quality of death, whereas specific age-groups like AYA have unique biomedical and psychosocial needs that are not captured by these disease-specific COSs. Outcomes of importance for AYA with cancer should be assessed with age-specific measures and include: fertility, body image, sexual health, financial security, life plans (educational and employment goals), and independence (30, 31). A recently developed COS for AYAs with a spinal deformity consists of, among others, outcomes like recreation and leisure and self-image (32), while a COS for elderly captures loneliness and isolation, frailty, time spent in hospital, caregiver burden and polypharmacy outcomes (28). Age-specific COSs allow for integration of case-mix factors that are more relevant for that specific group, e.g. developmental life phase in the case of AYAs with cancer (33).

Thus, there is a pressing need to consider the development and implementation of a COS for AYAs with cancer, to supplement tumor-specific COSs, which can be used throughout the healthcare research ecosystem in order to facilitate efficient and relevant standard (routine) data collection, thereby increasing the usefulness of these data to inform healthcare, policy and research (Figure 1).

**How will the AYA oncology community benefit from a core outcome set for AYAs with cancer?**

**Healthcare delivery and surveillance**

To achieve value-based healthcare, the focus should be on increasing value for patients, in other words, improving health outcomes that matter to patients per dollar spent (2). By assessing outcomes of relevance for AYA with cancer, such as educational goals and fertility, healthcare professionals are able to respond to specific needs. At a health service level, most AYA cancer programs have been designed to enhance existing disease-specific medical services rather than duplicating these standard elements of cancer care delivery (34). The ultimate goal of AYA care programs is to deliver additional, high value, developmentally appropriate services such as fertility preservation, vocational counselling, mental health support and peer activities. Although many components of care will likely be similar between AYA cancer care programs, hospitals in different healthcare systems or even within one healthcare system will design their services in varied ways in order to best meet local needs. However, irrespective of the healthcare system, establishing an AYA program requires substantial investment of finances, effort, and infrastructure both upfront and over time which is not easy, despite the worldwide recognition of the age-specific care needs of AYAs with cancer. There is a huge discrepancy in the large amount of available (public) resources for centralized, multidisciplinary, often inpatient pediatric care services and the limited amount of resources for the dispersed, often outpatient adult oncology services serving many more patients; AYA services still fall in between these two worlds, while the societal burden of years-of-life lost for AYAs might be similar to pediatric cancer patients. Consequently, baseline and ongoing data collection and analysis of AYA care programs is warranted to justify the value of public or philanthropic investment, providing evidence for more and sustained funding (11).

A COS for AYAs with cancer will inform the set-up of quality standards (QSs), which are needed to determine the “real” value of existing AYA care programs. QSs set out the most important areas for quality improvement and are in turn used to determine healthcare quality indicators (QIs) (29, 35). QIs are standardized measures that are used to monitor the quality of healthcare provision, in order to gauge performance in terms of healthcare structure, processes and outcomes (29, 36). Some work has been done in Australia, United Kingdom and Canada to develop indicators for AYA cancer care (34, 37). For example, in Canada, 14 indicators are used, representing five themes (active care, survivorship, psychosocial issues, palliative care, and research) covering issues such as proportion of patients referred for fertility preservation, proportion of patients with a documented psychosocial care plan, proportion of patients enrolled on a clinical trial. It is crucial to build on this work with a rigorous international approach to ensure that QIs address key priorities for AYA cancer care and control and to facilitate the uptake and use of such indicators worldwide (37). Benchmarking between AYA care programs has the potential to reveal opportunities for (local) improvement such as gaps in referrals or inequitable access to care (34). In this way, an AYA-specific COS will support learning between different healthcare systems, driving further quality improvement and internal care pathways and could ultimately accelerate the adoption of best AYA practices (28). Furthermore, the establishment of an AYA COS will help to align existing and newly developing initiatives and unlock far greater global collaboration to deliver better care to AYAs with cancer.

**Policy**

Clinical trials, health technology assessments, systematic reviews and routine practice evaluations are all used as sources for policy makers to develop regulatory and clinical guidelines (29). For example, the FDA has recently recognized the value of COSs and launched a program to identify them (38). Most countries have not yet established national policy on AYA cancer care. In Australia there is a national model of care with well-defined key QIs (34). In the UK, Teenager and Young Adult (TYA) programs have been subject to annual peer review against a series of QSs derived from the National Institute of Health and Care Excellence guidance (34). In the United States, no QIs exist, however the National Comprehensive Cancer Network (NCCN) Adolescent and Young Adult Oncology Clinical Guidelines extensively detail the many unique medical and psychosocial issues in the AYA oncology population (39, 40). Although empirical data on the clinical impact of AYA programs are beginning to emerge (41, 42), the challenge for the AYA oncology community is to further enroll and continue assessments on how care is delivered, using rigorous standardized methodologies including the implementation of an AYA-specific COS. Ongoing data collection and comparison of models of care delivery will promote national and international standards for quality care and the improvements and development of guidelines. In addition, as “digital natives”, AYAs are primed to benefit from supportive care delivered through e-Health alongside usual care (43), and therefore an AYA-specific COS can also be of relevance for technology appraisals (29).

**Research**

COSs have already proven scientific utility in all parts of the research chain (knowledge generation, synthesis and translation). The ultimate goal of COSs is to standardize outcome reporting across studies, so we can better compare and contrast the effectiveness and safety of interventions or treatments across different contexts and circumstances. To answer the many pressing research questions that remain unanswered (for example studies to determine how nonmodifiable factors (e.g., potential biologic and genomic differences) can be overcome or circumvented (e.g., host-based therapies, exploitation of actionable mutations, preventive interventions) and how modifiable factors (e.g., access to trials, optimal (multidisciplinary) therapy and age-adjusted support) in the vulnerable AYA oncology population, (existing) data should be pooled and (inter)national cohorts should be created including the full range of AYA ages, diagnoses and cultures (23, 24). Data pooling is needed to increase the power to conduct sub-group analyses to identify AYA with cancer at risk for poor outcomes. A pre-requisite to pool data is that the same outcomes are collected in a standardized way by using valid and reliable measures guided by an AYA cancer-specific COS.

Furthermore, COS uptake contributes to reducing research waste by focusing only on the important outcomes and ensuring that results can be compared and combined in systematic literature reviews or meta-analyses (44, 45). For AYAs with cancer, it is particularly important to reduce research waste as patient numbers are low and it is hard to recruit sufficient samples for research (46). Focusing on endpoints that are meaningful for AYAs with cancer may help to improve study uptake, response rates and lower attrition rates. COSs will also facilitate the implementation of innovative study designs, to further diminish research waste, such as the Trials within Cohorts (47). Historically, AYAs’ access to trials was limited by the lack of existence of trials for this age group, institutional barriers, and restrictive ages of eligibility (48, 49). The use of cohorts and routinely collected standardized data might make RCTs easier and more feasible to perform by reducing costs, time, and other resources, and could facilitate the conduct of trials that more closely replicate real world clinical practice by supporting recruitment of large and representative samples (50).

**What are the challenges of developing and implementing an AYA patient-centered COS?**

Despite our advocacy for the development and implementation of an international COS for AYAs with cancer, there are also some challenges that need to be considered.

**Heterogeneity of AYA cancer population**

The heterogeneity of AYAs with cancer regarding developmental and life stages (adolescence, emerging and young adulthood), the high number of histological subtypes and hence, the broad treatment landscape, and the different places of care (e.g. pediatric vs. adult vs. AYA units; public vs. private institutions; urban vs. rural; academic vs. non-academic institutions; and availability of clinical trials at institutions) make it challenging to develop a single AYA-specific COS that meets the needs of research, clinical practice, policymakers and industry (51). We therefore propose a flexible strategy with a universally applicable AYA cancer measure that captures AYA specific health and HRQoL domains that crosscut a majority of cancers connected with disease-specific COSs (e.g., for colorectal cancer) that target domains that are unique to the cancer and its treatment. Important factors, such as developmental life stage and place of care can be accounted for as case-mix factors in the AYA-specific COS.

**Availability of PRO measures**

Related to the heterogeneity of the AYA population is the many available patient-reported outcome measures for cancer. Most of these measures are limited by content that is not specific to AYAs (developed for children (e.g., PedsQoL or adults only (e.g., EORTC QLQ-C30)) consisting of questions that are not perceived to be relevant to AYAs or covering only the needs of a part of this group (e.g., adolescents) (30). The need for developmentally appropriate, psychometrically-sound measures embracing the entire age spectrum of AYA with cancer and appropriate for varying levels of literacy and cultural backgrounds is needed. There are two measurement initiatives that may fill this space: the Patient-Reported Outcomes Measurement Information System® (PROMIS®) (US centered) and the European Organization for Research and Treatment of Cancer (EORTC) (European centered) (3, 23). Both measurement systems capture a broad range of HRQoL domains, many of them are important to AYAs. Importantly, both the PROMIS and EORTC measures involved multi-disciplinary teams of survey developers and clinicians and involved direct patient feedback. The EORTC system is specific to cancer; whereas the PROMIS is a universal system to be applied to a range of chronic diseases including cancer. Both systems use state-of-the-art methods for measurement science and have great flexibility to provide high quality measures that capture only those outcomes that are important for AYAs. Given the extensive efforts of both organizations it would be ideal if future initiatives could create calibration techniques to make the systems comparable.

**Alignment of healthcare, policy, and research initiatives**

Most published COSs have been developed separately for research or clinical care (29). A recent study showed that the COS for research (COMET) and the COS for care (ICHOM) for type 2 diabetes mellitus are almost identical and largely concur with the outcomes featured in drug regulators’ guidelines (EMA and FDA), which are in turn reflected in UK clinical guidelines and their associated QSs and QIs, as well as trial outcomes and data fields recorded within UK Electronic Health Records (EHRs) (29). Nowadays, an increasing number of COSs (47%) are being developed to be used in both research and routine care. Nevertheless, the heterogeneity of AYA cancers will make it challenging to develop one COS that meets the needs of all key stakeholders. Furthermore, it is important that although the content of the COS should ideally be aligned between research, healthcare and policy, the metrics and time points of assessment could be adapted based on purpose. For example, in healthcare settings, assessment can take place in conjunction with patients’ follow-up visits, and so the data can also be used as part of a clinical consultation (52). While in research, additional outcomes can be included depending on the research question to be answered.

**Uptake and implementation challenges**

Broad implementation of a COS is critical, otherwise COS research itself is in danger of being wasteful. COS uptake and implementation in research and clinical care is considered the ‘‘biggest challenge’’ by several COS developers (53). There are several actions that can be undertaken including multicomponent interventions targeting awareness, adherence, and acceptance (54) There are myriad ways to build awareness, from including COS utility in medical curricula to conference programming and editorial decision making. In addition, The COMET initiative promotes COS awareness and engagement through partnering with other agencies such as Cochrane, the National Institute for Health and Care Excellence (NICE) and the National Institute for Health Research (NIHR). Adherence is facilitated by more stringent funding, regulation and reporting requirements, such as mandating the inclusion (or explanation of exclusion) of a COS in ethics submissions, funding applications, and protocols for clinical trial and systematic review registries. Endorsement from regulatory agencies such as the FDA and European Medicines Agency is essential, and is considered partly responsible for the high rates of adherence in rheumatoid arthritis trials (82%) (55). In addition, COSs are also required, where available, for NIHR funding and approval by NICE. The success of these measures in improving uptake depends entirely on building deeper acceptance within the healthcare and research communities, which in turn requires wide and genuinely representative stakeholder involvement (generalizability), total transparency and clear demonstration of methodological rigor (credibility).

To enhance the generalizability of COSs, there is a need to involve a large number of relevant international stakeholders (e.g., patients, caregivers, healthcare professionals, researchers, industry, and policymakers) in their development. To enhance the credibility of COSs, there is a need to use methods that ensure the fair capture and preservation of the perspectives of all stakeholders. Nevertheless, the involvement of a large number of stakeholders from different countries (especially low and middle income countries (LMICs)) and cultures in COS development has been limited (56), specifically crucial stakeholders such as patients are still rarely involved. There are several international AYA cancer patient advocacy groups that could be involved in the development of an AYA-specific COS. Attention needs to be paid to the inclusivity of the developmental, sex and gender (Lesbian, Gay, Bisexual, Transgender, Queer, and/or Intersex (LGBTQI)), racial/ethnic and economic diversity (socioeconomic status, literacy and educational levels) of the AYA population that should be fully covered (57) and dominant voices of other stakeholders (e.g. regulators) should be averted.

Several barriers and facilitators of COS implementation are described in the literature, primarily of technical and behavioral nature. (58) While consensus building takes place at a global level, some inherent flexibility can be built in that respects the national/country-level differences. The implementation of a COS in clinical care requires a considerable upfront investment in information technology and/or data collection resources (59). Organizations will certainly vary in their readiness to adopt a COS. Therefore, adoption can be done in a piecemeal or stepwise fashion, beginning with pilot institutions from the COS development group members and only with a few feasible outcomes first (37, 60). For example, incorporating PROs into clinical practice is typically simpler, although still challenging in terms of when, where and by whom data is collected and how to make them available for decision-making (58), than collecting structured clinical data from EHR that requires specially trained medical record abstractors or redesign of clinical workflows. However, clinical data are necessary for quality improvement or value-based payment applications (60). Nowadays, more major EHR vendors focus on supporting patient-reported outcome data collection and integration into the EHR and creating structured, standardized, clinical data fields within specialty specific templates (61). Those systems will reduce the time and complexity of COS implementation. EHRs could also have a signaling function, when an AYA comes in for a new consult/diagnosis of cancer, a so-called “best practice alert” could be triggered so that the healthcare professional becomes aware of the young age of a patient and could inform the patient of potential age-specific issues (e.g. gonadotoxic effects of treatment), ask if the patient wants to be referred to specialist care (e.g. reproductive specialist) and, provide referral if the patient is interested. It should be recognized that this may be challenging in low to middle income health care settings, where EHR systems are less prevalent, although recently some positive implementation research efforts were reported in LMICs (62), and on the long-term COS implementation in care should be strived for. Alongside improvements in technical infrastructure, successful implementation of a COS will also require a fundamental change in clinical attitudes and workflow (63), starting with the desire to incorporate the individual patient’s perspective more systematically into the care process. Nevertheless, several studies found a promising impact of standard COS collection on patients (adherence, symptom distress, quality of life, acceptability, and satisfaction), healthcare providers (willingness to comply, clinical decision-making, symptom management) and care process or system outcomes (referrals, patient-provider communication, hospital visits) (58). Dissemination and implementation science has exploded in the past few years and can be especially helpful in navigating EHR integration, streamlining workflow, making PROs actionable, and more. In addition, protection and privacy concerns of (inter)national data aggregation are also important to consider. These issues are often successfully addressed in international clinical trials (59), while new innovative distributed learning techniques also offer privacy-preserving solutions to easily combine dispersed data (64).

**Conclusion**

Improvements in care and outcomes for AYAs with cancer require collaboration among different stakeholders at different levels. Development of a COS specifically for AYAs with cancer, with outcomes that are well defined based on the perspective of those who are affected and assessed with validated measures is highly required. We are set to embark on the development process, taking into account all challenges described above (Figure 1). A globally implemented COS for AYAs with cancer will hopefully facilitate better pooling of research data and the implementation of high-quality healthcare registries, which by benchmarking not only nationally, but also internationally, may ultimately improve the value of the care given to these underserved young cancer patients.

**Funding**

No funding was used for this commentary.

**Notes**

**Role of the funder:** Not applicable.

**Disclosures:** The authors declare no conflicts of interest.

**Author contributions:** OH: writing (original draft), writing (reviewing and editing). BBR: writing (reviewing and editing). ASD: writing (reviewing and editing). CKC: writing (reviewing and editing). SS: writing (reviewing and editing). WTAvG: writing (reviewing and editing). JMS: writing (reviewing and editing).

**Data Availability**

There are no new data associated with this article.

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**Figure Legend**

Figure 1. Development process and implementation arenas of a core outcome set for adolescent and young adults (AYAs) with cancer. HTA = Health Technology Assessment; COMET = Core Outcome Measures in Effectiveness Trials ICHOM = International Consortium for Health Outcomes Measurement