Purpose: International data demonstrate association between clinical trial participation and reduced cancer mortality. Adolescents and young adults (AYA) have low clinical trial enrollment rates. We established a program to understand local barriers and develop targeted solutions that lead to greater AYA clinical trial participation.

Methods: A steering committee (SC) with expertise in adult and pediatric oncology, research ethics, and consumer representation was formed. The SC mapped barriers related to AYA trial access and established working groups (WGs) around three themes.

Results: The Regulatory Awareness WG identified a lack of understanding of processes that support protocol approval for clinical trials across the AYA age range. A guideline to raise awareness was developed. The Access WG identified challenges for young adults (18–25 years) to access a pediatric hospital to enroll in a pediatric trial. A procedure was developed to streamline applications for access. The first six applications using this procedure have been successful. The Availability WG identified lack of pediatric–adult oncology reciprocal relationships as a barrier to awareness of open trials, and future collaboration. An AYA Craft Group Framework was established to grow relationships within tumor streams across institutions; two craft groups are now operating locally. An additional achievement was a successful request to the Therapeutic Goods Administration.
for Australian adoption of the Food and Drug Administration Guidance on Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials.

**Conclusion:** This multipronged approach to improving AYA clinical trial access has relevance for other health environments. Our knowledge products are available as an online toolkit.

**Keywords:** clinical trials, barriers, system, access

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**Introduction**

**Adolescents and young adults** (AYA, defined in Australia as individuals aged 15–25 years) with cancer sit at the interface between pediatric and adult oncology services. Although there is worldwide variation in the upper age limit of pediatric care, many Australian pediatric tertiary hospitals set an upper age limit of 18 years. Australian adult tertiary hospitals have varying age eligibilities, but usually set a lower limit of 16 years. However, cancer biology for AYA is not constrained by these settings; this subgroup may be managed across both settings depending on a range of system factors, expertise, and existing referral pathways.

International data demonstrate strong correlation between clinical trial participation and improved cancer survival. AYA have historically had lower enrollment onto cancer clinical trials compared with other age groups, with enrollment rates in the range of 5%–25% described internationally, compared with 40%–90% for children <15 years. As underrepresentation of AYA in cancer trials has been hypothesized to account for less improvement in survival than seen in other age groups, considerable international effort has been focused on improving AYA clinical trial access.

Barriers to clinical trial access in the AYA population and potential solutions have been extensively reported. For example, Fern et al. proposed a conceptual model to alleviate barriers to clinical trial participation, which focused on five “A”s: available, accessible, aware, appropriate, and acceptable. Similarly, Freyer and Seibel proposed an intervention framework based on the pathway to enrollment through trial availability, accessibility, presentation, and acceptance. In addition, Ferrari et al. published a European position paper recommending similar actions to improve AYA clinical trial availability and access. These conceptual frameworks and consensus statements focus on both systems- and patient-level barriers to trial participation rather than the practical implementation of related strategies.

Australian AYA face similar clinical trial barriers to those reported internationally, with similarly low participation rates. With primary interest in developing practical solutions, a program of work was initiated in Victoria, Australia that aimed to increase access to cancer clinical trials for AYA. A program steering committee (SC) with cross-sectoral expertise was assembled. Here, the scope, work products, practical solutions and outcomes of the program are presented.

**Methods**

**Increasing AYA access to cancer clinical trials program**

The Victorian Comprehensive Cancer Centre (VCCC) is a multisite multidisciplinary joint venture alliance with a shared goal of improving outcomes for Victorian cancer patients. The VCCC established the Increasing AYA Access to Clinical Trials Program (AYA Program) as part of 19 cancer programs forming its strategic research plan (SRP) (2017–2020). The VCCC SRP was supported by a $30 M investment by the Victorian Government, with ~$300,000 allocated to the AYA Program. A 10-member SC was formed in mid-2018, through an expression of interest process facilitated by the collaborative nature of the VCCC alliance. In recognition of the multifaceted problem to be addressed, multidisciplinary expertise in pediatric, AYA, and adult oncology, research ethics and governance, clinical trials, and consumer experience was assembled. A 0.8 equivalent full-time research program manager was funded to coordinate the work. Significant in-kind support was provided through member contributions to the SC and associated working groups (WGs). Research ethics board approval was not required given this work did not contain studies with humans or animal subjects.

**Mapping of local barriers and assembly of WGs**

The SC undertook a comprehensive review of local barriers to AYA trial participation, based on international literature and expert stakeholder (including consumer) experience. Identified barriers were grouped into key themes, with WGs assembled around these themes. Each WG consisted of both a subset of members of the SC, and additional members as required to address potential expertise gaps. An additional six experts were engaged in the program in this way, bringing further expertise in adolescent health, and conduct of international collaborative group-sponsored pediatric trials. WGs considered improvements to processes that might alleviate access barriers, taking into consideration the complexities of the local clinical trial environment and the broader impacts of process changes. Coordination of approaches among the WGs was facilitated through discussion at regular SC meetings.

**Broader stakeholder engagement and consultation**

Collaboration with a broad range of stakeholders was recognized as a necessary step in effecting systems change. First, wide-ranging consultation with key stakeholders was conducted. Second, a survey of research ethics managers and investigator-initiated trialists was conducted to understand regulatory processes, and barriers to establishing AYA-inclusive trial protocols. Third, a session was conducted at a national therapeutic goods conference to raise awareness of the AYA clinical trial gap including a panel discussion. Finally, individual discussions were conducted with senior representatives from the Therapeutic Goods Administration (TGA, Australia’s regulatory authority for therapeutic goods), a pharmaceutical company with a large Australian oncology portfolio, Victorian Hospital Executives and
In Australia, scientific and ethical review of most clinical trial protocols is conducted by Human Research Ethics Committees (HREC), followed by notification to the TGA through the Clinical Trial Notification scheme.

A survey of Australian research ethics managers and Victorian clinical trialists was conducted to identify barriers related to AYA-inclusive trial protocol development and HREC approval (questions available on request), attracting 34 responses. Responses indicated a lack of awareness of the AYA clinical trial gap and of the local regulatory processes to facilitate AYA-inclusive clinical trials. Generally, clinical trialists incorrectly believed that to gain HREC approval for a clinical trial open to both pediatric and adult participants, review by multiple HRECs (pediatric and adult) was required, significantly delaying approval and trial commencement. However, the National Mutual Acceptance (NMA) system, with which most Australian States and Territories participate, provides a mechanism for multisite approval provided by a single NMA-certified HREC. Lack of understanding of pediatric consent processes was indicated by adult researchers, as well as lack of questioning by HRECs around the age eligibility in trial protocols.

Table 1. Local Barriers to Adolescents and Young Adults Clinical Trial Participation, by Theme (Regulatory Awareness, Availability, and Access)

| Regulatory awareness | Availability | Access |
|----------------------|--------------|--------|
| • Lack of mechanisms to streamline research ethics and governance processes between adult and pediatric centers | • Age eligibility criteria | • Cooperative Trial Group membership requirements |
| • Lack of resources to set up trials across multiple centers | • Regulatory authorization process to give a new adult cancer drug to adolescents | • Trial governance requirements at regional centers |
| • Human Research Ethics Committees are specific to pediatric or adult settings and cannot review research that is AYA-inclusive | • Legal or regulatory barriers for inclusion of adolescents in adult trials or young adults in pediatric trials | • Access to adult trials in pediatric settings, and to pediatric trials in adult settings |
| • Uncertainty about pediatric consenting requirements among researchers in the adult sector | • Traditional separation of pediatric and adult drug development approaches | • Barriers to treating AYAs >17 years at pediatric hospital or AYAs <18 years at adult hospitals, including hospital age regulations, age-appropriate spaces, delivery of age-appropriate medical care, etc. |
| • Trial investigators are usually adult or pediatric oncologists, not both | • No trials for a particular cancer type | |
| | • No accurate baseline data for current AYA trial participation | |
| | • Lack of communication and collaboration between adult and pediatric oncology sectors | |

AYA, adolescents and young adults.

Cancer Centres. At each stage of the creation of new procedures, frameworks, and guidelines, feedback was sought from relevant groups to ensure “coal-face” utility.

Results

Identified barriers

The barrier mapping exercise, which drew from the collective knowledge of local experts, as well as national and international literature, identified 24 key barriers (Supplementary Table S1). A decision was made to focus on systems-level barriers that could reasonably be addressed within the 2-year program period. Eight identified barriers were, therefore, set aside. The remaining barriers were grouped into three themes—Regulatory Awareness, Availability, and Access (Table 1), with each was assigned a WG.

WG1: Regulatory awareness

In Australia, scientific and ethical review of most clinical trial protocols is conducted by Human Research Ethics Committees (HREC), followed by notification to the TGA through the Clinical Trial Notification scheme.

A survey of Australian research ethics managers and Victorian clinical trialists was conducted to identify barriers related to AYA-inclusive trial protocol development and HREC approval (questions available on request), attracting 34 responses. Responses indicated a lack of awareness of the AYA clinical trial gap and of the local regulatory processes to facilitate AYA-inclusive clinical trials. Generally, clinical trialists incorrectly believed that to gain HREC approval for a clinical trial open to both pediatric and adult participants, review by multiple HRECs (pediatric and adult) was required, significantly delaying approval and trial commencement. However, the National Mutual Acceptance (NMA) system, with which most Australian States and Territories participate, provides a mechanism for multisite approval provided by a single NMA-certified HREC. Lack of understanding of pediatric consent processes was indicated by adult researchers, as well as lack of questioning by HRECs around the age eligibility in trial protocols.

Given that the majority of identified regulatory barriers were about perceptions of issues, a guideline promoting stakeholder education and awareness was developed that focused on four key areas:

1. Justification of age eligibility based on disease biology rather than arbitrary age divisions
2. Consent processes for younger research participants
3. Selecting an appropriate HREC
4. Protocol amendment processes to broaden the age eligibility in existing trials.

The Guideline, entitled “Establishing a cancer clinical trial with age eligibility encompassing adolescents and young adults (AYA): Research Ethics and Governance Guidelines” underwent a wide consultation process and is publicly available as part of the VCCC AYA Clinical Trials Toolkit.

To further understand barriers for industry, parallel discussions were held with an international pharmaceutical company with a significant Australian oncology portfolio. Discussions indicated that a potential barrier to including adolescents younger than 18 years in adult clinical trials was an inability to include adolescent data in Australian adult drug registration applications. Subsequently, we approached the TGA to propose they adopt a similar stance to the United States Food and Drug Administration (FDA), which had released a guideline supporting the inclusion of adolescents from 12 years old in adult cancer clinical trials. The FDA guideline was subsequently adopted by the TGA for Australian use in February 2020, ameliorating this barrier, and
providing a foundation for HRECs to question the lower age eligibility in adult cancer trial protocols when this does not align with disease biology.

WG2: Availability

The lack of formalized communication between pediatric and adult oncology care was appreciated to impede clinical trial collaboration and consequently, to reduce awareness of trials outside the corresponding sector.

To address this, a framework for regular and deliberate pediatric–adult oncology collaboration was developed. This framework provides a structure for the creation of craft groups within tumor streams of relevance to AYA oncology with the following systems-level objectives:

1. Improved awareness of AYA treatment standards
2. Improved awareness of AYA clinical trials open across pediatric/adult oncology centers
3. Improved access to clinical trials for AYA through collaborative decision making around oncology care pathways
4. Improved availability of AYA clinical trials through collaborative trial development
5. Reduced duplication of research efforts
6. Improvements to AYA treatment standards over time.

The framework proposes that membership include pediatric and adult oncologists, clinical trial managers, and other multidisciplinary members. A logic model summarizing the inputs, activities, and proposed outcomes of the AYA craft groups is shown in Figure 1 and is publicly available as part of the VCCC AYA Clinical Trials Toolkit.

This process has so far led to the successful activation of AYA craft groups in sarcoma and brain cancer. These groups have mapped available trials, monitored incidence of AYA cancer cases with corresponding matching to trial opportunities, evaluated cross-site eligibilities and collaboratively discussed harmonizing trial pipelines.

WG3: Access

In Victoria, the magnitude of the problems of trial availability and access were found to be different for adolescents aged 15–18 years compared with those ≥18. We undertook a survey of age eligibility for treatment trials of relevance to the top 10 AYA cancers by incidence and mortality, as registered to the Cancer Council Victoria’s Victorian Cancer Trials Link database in November 2018.

We found that although 58% of pediatric treatment trials had an upper age eligibility ≥18, only 3% of adult treatment trials had a lower age eligibility <18 years (data available on request). Despite the availability of pediatric trials for young adults based on age eligibility, routine access is prevented by pediatric hospital access policies that are based on an age of ≥18 years. Conversely, although adult hospital access is usually open to young people from the age ≥16, very few adult trials are available to them based on age eligibility (Fig. 2).

FIG. 1. A logic model summarizing the inputs, activities, and proposed outcomes of the adolescents and young adults “craft groups”.
WG3, therefore, focused on alleviating access barriers for young adults to pediatric trials, devising two models of improved access (A: “patients to trials” model; B: “trials to patients” model). Consideration was given to various aspects of the local pediatric–adult oncology care environment, including current cooperative pediatric trial group requirements for adult oncology center membership; current local pediatric hospital access policies and procedures for gaining hospital executive approval for young adult trial access; current clinical trial governance arrangements in the local hospital precinct; suitability of pediatric ward environments for young adults; safety of pediatric patients in the presence of adults; and the preferences of AYA cancer consumers with regard to appropriate care environments. A decision was made that the best model of access for each young adult (trial to patient, or patient to trial) would depend on many factors, hence WG3 endeavored to progress both models.

Patients to trials. For this model, WG3 aimed to establish an efficient formal procedure for gaining pediatric hospital executive approval for young adult access to a pediatric trial. Approval had historically been possible in certain circumstances; however, a streamlined process did not exist. In consultation with hospital executive and senior members of the oncology center team, a standard operating procedure (SOP) was designed, setting out the circumstances within which young adult access may be justified, and the steps required to approval. The SOP includes an application form to provide information required by the hospital executive to make a swift decision, including age, diagnosis, prognosis, likely patient benefit, need for inpatient care, required resources, and ongoing care plans. The SOP is publicly available as part of the VCCC AYA Clinical Trials Toolkit. The SOP was activated in October 2019, and has successfully facilitated approval for pediatric cancer trial access for six young adults aged between 18 and 21 years, leading to trial enrollment in four. Interestingly, five of six approvals were for AYA with medulloblastoma potentially related to the (i) the lack of local adult-specific trials in this entity, (ii) existing open protocol at the children’s hospital, (iii) and existence of a functioning “AYA craft group” in brain cancer allowing awareness of this trial across the pediatric and adult sector.

Trials to patients. In Australia, the majority of pediatric cancer clinical trials are sponsored by cooperative groups or are investigator-initiated, which differs from adult oncology where pharmaceutical-sponsored trials dominate. In Victoria, a number of pediatric cancer trials are sponsored by the United States Children’s Oncology Group (COG). COG places strict restrictions on site and investigator membership requirements. In particular, COG’s site requirements currently prevent membership of adult oncology centers in most circumstances. This makes application of any “trials to patients” model difficult to achieve for COG trials. However, recently proposed pediatric–adult oncology COG dyad models may offer promise for AYA in the future, facilitated by cross appointments of pediatric oncologists to adult oncology services.

To enable access to other pediatric oncology trial types for young adults located in an adult center, two approaches were considered. First, a precinct-wide single trial governance arrangement, incorporating local pediatric and adult oncology care centers, would create an umbrella structure under which centers could be considered a single entity for trial management. Discussions are underway that explore the

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**Adolescents 15-17yrs**

| Adult Trial Available | Adult Trial Accessible | Trial Enrolment Possible |
|-----------------------|-----------------------|--------------------------|
| 3% Victorian trials with age eligibility <18yrs* | Access to adult hospital permitted | YES |

**Young Adults 18-25yrs**

| Paediatric Trial Available | Paediatric Trial Accessible | Trial Enrolment Possible |
|---------------------------|-----------------------------|--------------------------|
| 58% Victorian trials with age eligibility ≥18yrs* | Access to paediatric hospital restricted | NO |

*Therapeutic cancer trials relevant to AYA cancers, open for recruitment in Victoria in November 2018
Source: Cancer Council Victoria, Victorian Cancer Trials Link, manual search

**FIG. 2.** Difference in the magnitudes of trial availability and access for adolescents and young adults in Victoria. For adolescents the larger barrier is hospital access, whereas for young adults the larger barrier is trial availability based on age eligibility.
potential of this approach. Second, pediatric trials may be made available to young adults in adult centers using a teletrials model.42 Developed primarily to provide access for regional patients to clinical trials open in metropolitan centers, metro-to-metro teletrials may provide similar opportunity for access to pediatric trials in adult centers, and adult trials in pediatric centers, while the patient remains in an age-appropriate place of care. The teletrials approach also has potential for providing access to clinical trials for regional AYA. The VCCC Teletrials Program has developed SOPs to enable teletrials in Victoria.43 Work continues to identify the extent that teletrials may improve AYA clinical trial opportunities in Victoria.

Discussion

The AYA population are a vulnerable subgroup within the cancer population with lower survival gains achieved over the past two decades compared with children and older adults.14,15,44,45 Several studies have established that the proportion of AYA patients enrolled on cancer clinical trials is significantly lower than children4,46,47 and adults,48 which may partly account for this survival gap. Our clinical trial barrier mapping confirmed the local relevance of many published international barriers.13–15 In ameliorating these barriers, we focussed on changes to systems and processes with tangible outcomes. Stakeholder awareness was promoted about the AYA clinical trial gap and the current regulatory processes supporting the establishment of AYA-inclusive trials. A request to the TGA successfully led to the Australian adoption of the FDA guideline on inclusion of adolescents in adult cancer trials,37 which is anticipated will lower the age eligibility for relevant adult cancer trials over time. A framework for increased collaboration between pediatric and adult oncology was produced, an approach similar to that utilized in the United States by the National Clinical Trials Network AYA WG.15 An SOP was established that facilitates approval for young adult access to pediatric centers for specific cancer trials, resulting in approval for six young adults in the first 6 months. In addition, we continue to pursue alternative access pathways that might enable young adults to remain in adult care while participating in a pediatric trial.

Although conceptual frameworks for systems-level change to alleviate AYA clinical trial access barriers have been published,13–15,18,25,28 few programs have progressed to practical implementation of solutions. Systems change in health care settings is difficult,22 and the ability of this program to deliver systems-level solutions has heavily depended on two key aspects. The first was the nature of the VCCC as a multisite multidisciplinary partnership between 10 medical research, academic, and clinical institutions focussed on overcoming cancer. This alliance successfully facilitated strong cross-institution and cross-sector stakeholder collaboration, enabling the formation of an expert, committed SC and WGs. The second was sufficient resourcing to enable a dedicated, 2-year program coordinated by an experienced program manager. This allowed time for program development as barriers were more fully understood, current processes mapped, required expertise identified, and solutions carefully tailored to the local setting.

This AYA Program has focused on initiating systems-level change. A number of initiatives are ongoing (single site governance; exploration of teletrials model) and/or will take time to result in increased AYATrial participation (e.g., pediatric–adult oncology collaboration to establish new AYA trials). In addition, other major international obstacles remain in systems beyond our local reach, such as international collaborative trial group constitutional changes needed to allow pediatric trials to be open in adult centers. Similarly, critical patient-level issues also still need to be addressed, including an increased understanding of perceptions of clinical trials,27,40 as well as greater awareness of available clinical trials, among the AYA population. To some extent, this will be facilitated to an extent by increased awareness by health care providers, given that provider–patient communications are the most common way for AYA patients learn about clinical trials.17 However, additional mechanisms to increase AYA understanding will be required. Involvement of young people with a lived experience of cancer will be crucial in guiding the development of these mechanisms.16 Addressing acceptability of clinical trial participation, given the additional burden this may place on young people at a challenging time of life,14 will also be important.

A key limitation of the VCCC AYA Program has been an inability to accurately evaluate the impact of our efforts in terms of improvements to AYA clinical trial participation. In Australia, systematically collected data on the proportion of AYA enrolled in cancer clinical trials is currently unavailable.50 Owing to inherent differences in the Australian health care system, it is anticipated that participation rates may differ from more extensively reported areas such as the United States, where 10%–15% of AYA cancer patients are enrolled in clinical trials,6 with rates as low as 2%–5% in the 20–29 year age group.48 In a Victorian study of AYA with cancer diagnosed between 1992 and 1996, Mitchell et al. reported only 4% of patients aged 20–24 years treated on a clinical trial.19 Shirazee et al. reported that among patients with cancer aged 15–24 years attending an adult hospital in Western Australia between 2000 and 2004, only 1.8% were enrolled to a clinical trial.51 In 2018, White et al. published the first Australian population-based review of AYA cancer trial enrollment, demonstrating a 2007–2012 participation rate of 10.3%.52 Despite these reports, the lack of systematically collected data precludes a direct assessment of local program impact based on changes to participation rates over time.

In summary, the VCCC AYA Program identified AYA trial participation barriers in Victoria, Australia that are typical of those reported internationally. The Program worked closely with stakeholders to identify and initiate solutions at a systems level, with the goal of achieving lasting positive impact on participation rates. The short period since initiation of the Program’s work, and lack of accurate local AYA clinical trial participation data preclude an assessment of longer-term impact at this time. However, successful activation of guidelines, access procedures, and collaborative frameworks have already resulted in improved access for some patients. Given similarities in the barriers described internationally, we anticipate our work will have relevance for other health care settings. To facilitate knowledge sharing, all of the products produced by the program are freely available as part of the VCCC AYA toolkit at https://www.viccompcancerctr.org/aya-clinical-trials.
Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Table S1

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Address correspondence to:
Jeremy Lewin, MBBS, FRACP
Sir Peter MacCallum Department of Oncology
The University of Melbourne
305 Grattan St.
Melbourne, VIC 3000
Australia

Email: jeremy.lewin@petermac.org