VICTORIAN
COMPREHENSIVE
CANCER CENTRE

Overcoming cancer together

ESTABLISHING A CANCER CLINICAL TRIAL WITH AGE ELIGIBILITY ENCOMPASSING ADOLESCENTS AND YOUNG ADULTS (AYA)

AYA Cancer Clinical Trials

Research Ethics and Governance Guidelines

The Victorian Comprehensive Cancer Centre (VCCC) has developed this guideline to provide assistance generally and to help decision making and implementation. The guideline is not specific advice or a set of recommendations in respect of any particular set of circumstances or for any particular group or organisation. The VCCC encourages all organisations to have regard to its own objectives and circumstances when adopting and implementing its own frameworks and procedures. Accordingly, the VCCC is not responsible for any particular outcome or result arising from the information provided.

These guidelines are based on standard operating procedures observed by research ethics and governance offices of the Royal Children's Hospital and Melbourne Health in Victoria, Australia. As such, some processes may not be broadly applicable in all settings.

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I. LIST OF ABBREVIATIONS

APREG	Australian Paediatric Research Ethics & Governance Network
AYA	Adolescent and Young Adult
EU	European Union
FDA	Food and Drug Administration (USA)
HREA	Human Research Ethics Application
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MH	Melbourne Health
National Statement	NHMRC National Statement on Ethical Conduct in Human Research
NHMRC	National Health & Medical Research Council
NMA	National Mutual Acceptance
ICF	Information and Consent Form
IIT	Investigator Initiated Trial
RCH	Royal Children's Hospital Melbourne
REG	Research Ethics and Governance
TGA	Therapeutic Goods Administration (Australia)
VCCC	Victorian Comprehensive Cancer Centre

II. PREAMBLE

The NHMRC National Statement on Ethical Conduct in Human Research (National Statement) [1] outlines four key values and principles of ethical conduct of human research: respect, research merit and integrity, justice, and beneficence.

Adolescents and young adults (AYAs, defined here as people aged 15-25 yrs) participate in cancer clinical trials at a rate that is lower than younger children, or older adults [2]. In 2017, there were 306 AYAs diagnosed with cancer in Victoria, but only 27 AYA enrolments in a therapeutic clinical trial (source: Cancer Council Victoria). As a consequence of this low enrolment rate, survival rates for AYAs with cancer are not improving at the same rate as for younger children and older adults [2]. A major barrier to AYA participation is a lack of availability of trials across the AYA age range, as determined by the inclusion/exclusion criteria defined by the trial protocol [3].

For clinical trials focussed on adult-type cancers (e.g. melanoma), the lower age limit for eligibility is almost always stated as 18yrs; conversely, for paediatric-type cancers (e.g. leukaemia), the upper age limit for eligibility is often set at 17-18yrs (source: Cancer Council Victoria - Victorian Cancer Trials Link, accessed November 2018).

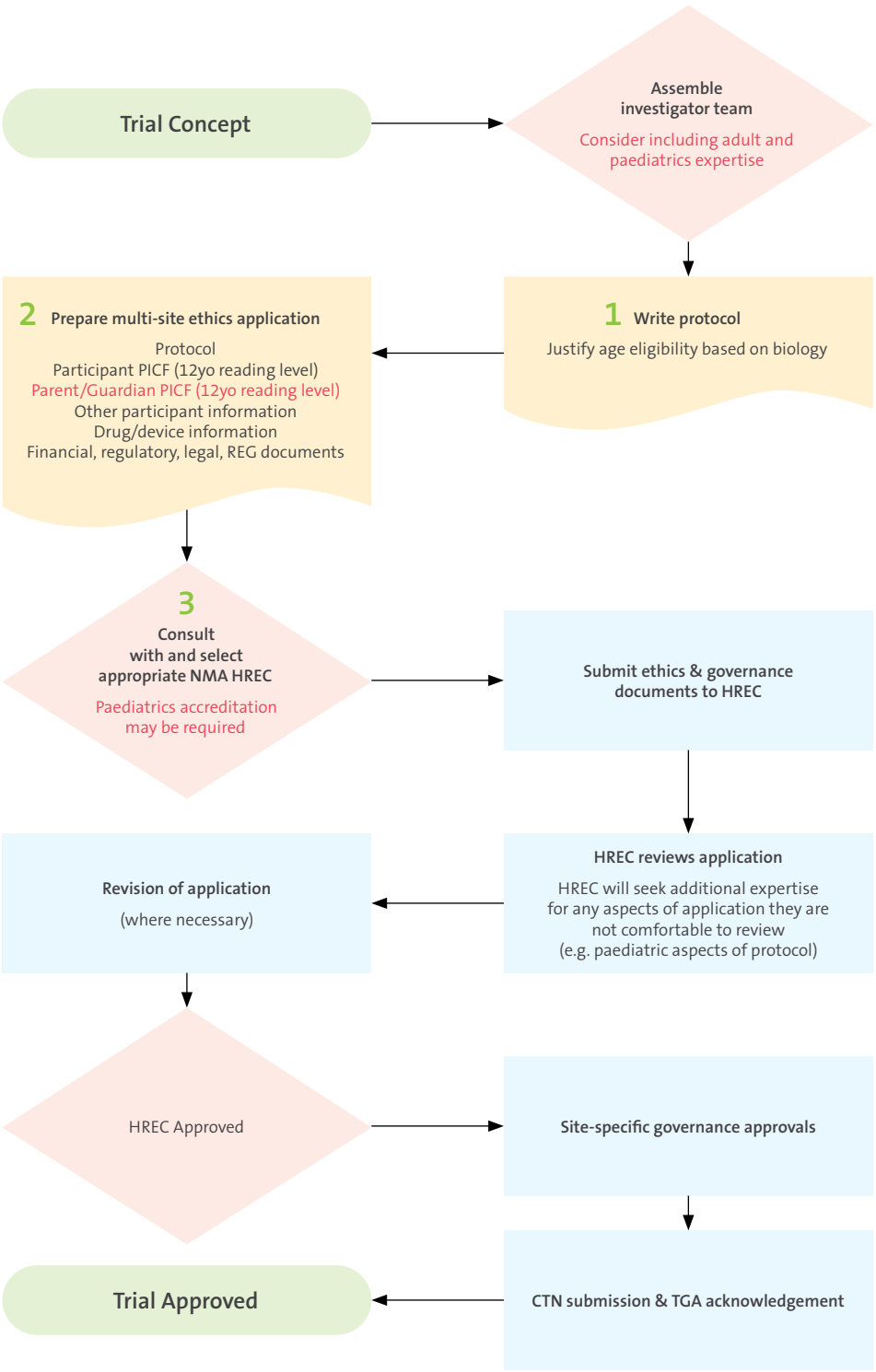
Yet, both melanoma and leukaemia are amongst the top 10 AYA cancers in Australia, both by incidence, and by mortality [4]. The consequence of exclusion of participation based on age is a lack of data pertaining to the outcome of trials in the excluded age range and a resultant inability to advance standard care practices.

When restrictions to eligibility based on demographics are not fully scientifically justified, the value of 'justice' in ethical conduct, as set out in the National Statement, is not being observed. In section 1.4, the National Statement notes that, "in research that is just, taking into account the scope and objectives of the proposed research, the selection, inclusion and exclusion of categories of research participants is fair... the process of recruiting participants is fair.... There is fair distribution of the benefits of participation in research... (and) there is fair access to the benefits of research" [1].

There are many potential contributors to decisions by trial investigators to restrict age eligibility despite the trial's relevance to a broader population. One such potential contributor is the perception that including both children and adults as potential trial participants makes the process of ethics approvals more complex. A recent survey of Cancer IIT Investigators and Research Ethics and Governance Officers conducted by the VCCC showed that IIT stakeholders commonly believe that there is an adult-paediatric HREC 'divide', and that separate ethics applications would be needed to gain ethical approval for a trial involving participants both under and over the age of 18 years. Investigators of traditionally adult trials also indicated a lack of understanding of the consent process for participants under the age of 18 years.

This document is intended as a guide to the ethical approval processes required to establish a multi-centre cancer IIT open to participants both over and under the age of 18 years. It specifically addresses and aims to alleviate stakeholder-identified barriers highlighted by the VCCC survey. The information provided is based on guidelines provided by the National Statement, processes required to submit an ethics application for a multi-centre trial through the NHMRC National Mutual Acceptance (NMA) scheme, and on standard operating procedures of the Research Ethics and Governance Offices of the Royal Children's Hospital and Melbourne Health in Victoria, Australia, that were in effect at the time of writing.

III. OVERVIEW OF PROCESS



Process summary: From trial concept to research ethics & governance approval for an investigator-initiated multicentre clinical trial

Items show in RED *may* be additionally required to establish a trial with an age eligibility both above and below the age of 18 years. All other processses and documents are the same.

Steps numbered in GREEN are futher detailed in this Guideline document.

Note that this flow chart is not intended as a complete overview of the clinical trial establishment process. Steps such as trial funding, sponsor engagement and trial registration have been omitted.

1. AGE ELIGIBILITY FOR A CANCER CLINICAL TRIAL

Age eligibility in cancer clinical trials commonly ceases (for paediatric trials), or begins (for adult trials), at 18 years. In Australia, this aligns with the age at which paediatric patients are usually required to transition to adult care. However, in terms of cancer biology, this age division is relatively arbitrary – adolescents under the age of 18 years can develop adult-type cancers, and young adults over the age of 18 years can develop paediatric-type cancers. Similarly, in terms of drug pharmacokinetics, current evidence suggests that drug pharmacokinetics are similar in adolescents and adults after accounting for body size [5]. Excluding clinical trial participants based on age alone can result in data that is not fully representative of the patient population [6]. Improvements to standard care resulting from the outcomes of the trial may be delayed for AYA until further trials are conducted, or prevented entirely due to the relative rarity of the cancer in the AYA age group making AYA-specific trials infeasible.

1.1 FDA guidelines for the inclusion of adolescents in adult cancer clinical trials

In 2019, The US Food and Drug Administration (FDA) released Guidelines around cancer clinical trial age eligibility, particularly as it pertains to adolescence [7] and paediatrics [8]. The guidelines provide non-binding recommendations, compiled by the FDA Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Oncology Center of Excellence, for the criteria for including patients under the age of 18 years in adult cancer clinical trials, dose selection, safety monitoring, and ethical considerations in the United States.

These FDA Guidelines were adopted by the Therapeutic Goods Administration (TGA) for use in Australia on 28 February 2020.

The recommendations contained in the FDA Guideline, as related to adolescents 12-17 years, are briefly summarised below.

1.1.1 Phase-related criteria for inclusion

For cancers in adolescents that are similar in histology and biologic behavior as those found in adults, or where the molecular target is the same as for adults, the FDA recommends:

- For first-in-human or drug escalation trials, adolescent patients with a cancer that is relapsed or refractory with no remaining curative options should be permitted to enrol once some initial adult toxicity information has been generated.
- For later-phase trials, adolescents should be permitted to enrol at the same time as adults.

1.1.2 Dose selection

The FDA considers that drug pharmacokinetics are similar in adolescents and adults.

- For drugs requiring body-size dosage adjustments in adults, the same should be applied to adolescents.
- For fixed-dose drugs, in general, adolescents who weigh at least 40kg (approximate average weight of a 12 year old) can receive the same dose as for adults (but this may vary depending on the characteristics of the drug).

Adolescents weighing less than 40kg should generally switch to a body-weight-adjusted dose based on an adult reference body size.

1.1.3 Safety monitoring

The FDA Guidelines recommend that safety data be evaluated by age to identify any age-associated differences. Adolescents enrolled in adult trials should have access to appropriate care (e.g. paediatric oncologists) capable of managing any unexpected toxicities.

1.1.4 Ethical considerations

The FDA believes that, given the life-threatening nature of cancer, inclusion of adolescent patients in appropriately-designed adult cancer clinical trials is justified.

1.2 EU guidelines adopted by Australian TGA

In addition to the FDA guidelines, there are some EU and ICH guidelines adopted by TGA with aspects that are of relevance to AYA clinical trials. These include:

ICH Topic E11 – Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population [10]

The document notes that the potential impact of hormonal changes on the study of medicinal products in adolescents (defined as 12 – 18 years of age) should be considered. It acknowledges that older adolescents may be included in adult studies and encourages collaborative research with experts in AYA clinical care. It recommends that review of protocols involving the paediatric population be performed in consultation with experts in paediatric ethical and clinical issues.

Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population [11]

This EU guideline aligns with the FDA with regard to similarity between adult and adolescent (12 – 17 yrs) pharmacokinetics. It states that limited confirmatory adolescent pharmacokinetic data are sufficient in most cases to determine dosage of a medicinal product where adult data is already available.

1.3 Recommendations for trial investigators

Based on the FDA recommendations and ethical considerations, it is pertinent to make decisions around cancer clinical trial age eligibility based on biology, rather than assuming a standard arbitrary cut-off at age 18 years. For example:

- For adult cancer clinical trials, where the cancer type occurs across the AYA age range (e.g. leukaemia, lymphoma, germ cell, sarcoma, brain cancers), the lower age limit should be routinely placed at 15 years.
- For paediatric clinical trials, where the cancer type occurs in those over the age of 18 years, the upper age limit should reflect the upper age incidence.

In writing the clinical trial protocol, it is important to be able to provide justification for the selected age range based on cancer biology, prevalence/incidence, drug safety, and patient need. When justified appropriately, separate paediatric/adult ethics applications are rarely needed in order to gain approval for broader age eligibilities such as in the above two examples.

These recommendations are relevant not only to IITs, but also pharmaceutical and co-operative group clinical trials.

Access to clinical trials can be difficult across the AYA age range. It may not be considered an efficient use of research resources to open clinical trials at sites that would expect to enrol low numbers (for example, opening an adult cancer clinical trial at a paediatric site to provide access to AYAs aged 15-17yrs where the cancer is relatively rare under the age of 18). Hospital access policies that are based on age can be a barrier to participant enrolment to clinical trials above and below the age of 18 years. However, in general, adult hospitals in Victoria are accessible by adolescents aged 16 years and over, and paediatric hospitals will generally consider accepting young adults to their paediatric trials on a case-by-case basis. Therefore, institutional access policies should not be used as a justification for a restricted age eligibility.

1.4 Recommendations for research ethics and governance offices

Equitable access to cancer clinical trials is an important issue, and should be a consideration in reviewing HREC applications for clinical trial approval. It is commonplace for investigators to utilise protocol templates in preparing their HREC application, and for details regarding age eligibility to be stated in the inclusion criteria section of the template. It is highly recommended that protocol templates request justification of both inclusion and exclusion criteria, and that HRECs request further information where a full biological justification for the age eligibility is not provided by investigators.

2. INFORMATION AND CONSENT FORMS FOR PARTICIPANTS AND PARENTS OR GUARDIANS

For clinical trial participants under the age of 18 years, consent from a parent or guardian is generally required. The Australian Paediatric Research Ethics & Governance Network (APREG) has produced a useful guide to consent for child participants in clinical trials [12]. The APREG Guidelines should be used in conjunction with the NHMRC National Statement [1], in particular, Chapter 4.2: Ethical Considerations Specific to Participants – Children and Young People. Key points are summarised below.

2.1 Informed consent requirements for research participants under the age of 18

In Australia, there are no laws governing the requirements for consent to medical research by a person under the age of 18 years. The NHMRC National Statement [1] provides guidance around when parent consent is required, when child consent should be obtained, and the rights of the child where child and parent consent differs. The APREG Guide to Child Consent [12] draws on the National Statement, and represents what is considered best practice by APREG member organisations (including The Royal Children's Hospital and Monash Health in Victoria).

In general, for a young person under the age of 18, written informed consent must be obtained from the parents or legal guardians in order for the young person to participate in research.

If the young person is judged to have sufficient capacity to understand the research in order to provide informed consent, consent should also be obtained from the young person. In these cases, the consent from the young person is more important than that taken from the parent, and any decision by the young person not to consent should be treated with respect and should not be overruled by the parent.

As a guide, sufficient capacity may be reached at around the age of 12 years, but must be judged on a case by case basis by the research team.

In some limited circumstances, the reviewing HREC may approve participation of mature young people in research without parental consent. Such circumstances are set out in the National Statement, section 4.2.8 & 4.2.9. These circumstances must be fully reasoned in the application for ethical approval.

2.2 Information and consent forms

In order to include adolescents in adult cancer clinical trials, both a participant and a parent/guardian information and consent form will usually be required, and must be submitted to the reviewing HREC for ethical approval before work can commence.

In order for ICFs to be broadly understandable by members of the general public, RCH, MH and APREG recommend that language used in any ICF should be aligned with a reading age of 12 years.

For clinical trial participants under the age of 18 years, the participant ICF should mirror the parent/guardian ICF in terms of information presented, and language used.

Therefore, for an AYA clinical trial open to enrolment for participants aged both above and below the age of 18 years, two ICFs will be required – a participant ICF (which can be used for both adolescent and adult participants when written at the required reading age of 12 years), and a parent/guardian ICF. Essentially, the parent/guardian ICF should be identical to the participant ICF, except that the word "you" is replaced with "your child" throughout.

ICF templates to be used for multi-centre research have been formulated by NHMRC. Links to these templates can be found on the NHMRC website [13].

Useful guides to plain language writing for ICFs can be found on the RCH Research Ethics and Governance Unit [14] and the MH Research Governance and Ethics Unit [15] websites.

2.3 When the parent/guardian and child view on research participation conflict

APREG notes that conflicting views between parents/guardians and child in relation to research participation is rare. APREG recommends that a child's view be respected especially in the case where the child is competent. The researcher should consider the competence of the child, benefit and best interests. If a decision cannot be reached, the reviewing HREC should be consulted for further advice [12].

2.4 Re-consenting when the adolescent turns 18 years of age

If the adolescent has been deemed sufficiently mature to provide written consent (in addition to the parent/guardian consent) at the start of their participation in the clinical trial, then legally this consent remains valid, and they do not need to provide a second written consent (i.e. re-consent) when they reach 18 years of age. However, if the requirements of the trial have changed, or a long time has passed since the original consent there may be ethical reasons to seek re-consent. Additionally some sites and sponsors may have additional requirements related to re-consent that need to be taken into consideration.

2.5 Recommendations for trial investigators

The following recommendations are based on advice contained in the National Statement [1], and the APREG Guide to Child Consent [12].

- Both Parent/Guardian and Participant consent is required to enroll an adolescent under the age of 18 years to a clinical trial in almost all circumstances.
- Both the Participant and Parent/Guardian ICFs should be essentially identical, except that the word 'you' is replaced with 'your child' throughout. All ICFs should be written to a reading age of 12 years. All ICFs must be submitted for HREC approval.
- It is rare for adolescent participant and parent/guardian views on participation to conflict, but if this occurs, the competent child's wishes should be respected.

In the case that the child is not competent the investigator should consider level of competence, reasons for not agreeing, benefit and best interests. The reviewing HREC can provide advice and assistance to resolve the conflict if needed.

2.6 Recommendations for research ethics and governance offices

- Support should be available for investigators of adult trials to guide the development of ICFs for parents/guardians and adolescent participants. If all ICFs are routinely written to a reading age of 12 years, then they can be easily adapted for all purposes.
- Addition of a 'Paediatrics' or 'Adolescent' information resource on adult REG Office websites may be an appropriate way of providing support to Investigators planning on including the AYA age group in a clinical trial.
- Examples of parent/guardian and adolescent participant ICFs should be made available to investigators to help facilitate the adaptation of a participant ICF to a parent/guardian ICF.
- A link to the APREG guidelines referred to above is also recommended.

3. SELECTING AN APPROPRIATE REVIEWING HREC

The National Mutual Acceptance (NMA) scheme is a national system for mutual acceptance of ethical review of multi-centre human research projects. Ethical approval granted by any NMA-certified HREC will be accepted by publicly-funded health services across the six participating Australian states (at time of writing: Victoria, NSW, Queensland, South Australia, ACT and Western Australia). This means that multi-centre clinical trial investigators need only submit their trial for ethical approval to one HREC, rather than multiple HRECs.

Investigators of multi-centre clinical trials submitted for ethical review via the NMA system can choose to submit their application to any NMA-certified HREC in a participating jurisdiction that is certified in the relevant area of research. They are not limited to submission to the HREC associated with the trial's Lead Institution.

Further information on the NMA scheme, and an up-to-date list of each NMA-certified HREC in each participating Australian State can be found on the NHMRC website [16].

3.1 Selection of a Victorian NMA-certified HREC based on trial protocol age eligibility

As discussed in Section 2, clinical trial considerations for adolescents (especially those aged 15 years or older) should generally be no different than for adults. Therefore, in general, all Victorian NMA-certified HRECs should be comfortable to review cancer clinical trial protocols with minimum age eligibility of 15 years. However, based on its membership, each HREC must feel sufficiently qualified to review any individual application in order to ensure a thorough review, and at its discretion, may request that an application is reviewed elsewhere.

For protocols with a minimum age eligibility below 15 years (for example a predominantly paediatric trial that is open to young adults), review by a HREC with specific paediatrics certification is required. A subset of Victorian NMA-certified HRECs have paediatrics certification. At the time of writing, these are Royal Children's Hospital [17], Monash Health [18], and Melbourne Health [19]. Further details about paediatrics certification, and an up-to-date list of paediatrics-certified NMA HRECs can be found on the NHMRC website [16]. However, bearing in mind the need for HREC membership expertise that covers all aspects of the protocol to be reviewed, in many cases, a predominantly paediatric trial is often best placed with a HREC affiliated with a paediatric hospital. Note that paediatric HRECs are also certified for review of trial protocols open to adults aged 18 years and over.

In summary, the selection of a reviewing HREC should be a two-step process.

First, a HREC should be selected that generally meets the age-based reviewing requirements for an AYA-inclusive multi-centre trial through the NMA scheme. The following scenarios can be used as a guide to age-based selection:

a) For a predominantly paediatric trial open to AYAs 15-25 years, review is best placed with a HREC affiliated with a paediatric hospital (in Victoria, RCH or Monash Health)
b) For a trial specifically targeted at AYAs (age range 15-25 years), any NMA-certified HREC should be positioned to review the application (check with the selected HREC to confirm)
c) For a predominantly adult trial open to adolescents 15 years and older, any NMA-certified HREC should be positioned to review the application (check with the selected HREC to confirm)
d) For a trial protocol with an age eligibility encompassing children, younger adolescents, older adolescents and adults, it is recommended to select a HREC with paediatrics certification. Additionally, a HREC affiliated with a paediatric hospital may be better-placed to review the protocol, based on expertise amongst the committee membership.

Second, investigators should consult early with the selected HREC with regard to the protocol content to ensure that the best fit between HREC expertise and trial protocol is identified. This will ensure that a thorough, informed ethical review of the trial can be achieved. Once again, for multi-site trials participating in the NMA scheme, the HREC reviewing the trial does not need to be affiliated with the trial's Lead Institution. The correct fit between HREC and trial is of far greater importance.

3.2 Recommendations for trial investigators

> Select a reviewing HREC based on HREC expertise. This does not need to be the HREC associated with the trial's Lead Institution
> Step 1: select an appropriate HREC based on the age eligibility for your trial – predominantly paediatric trials with extension into young adulthood are best placed with a HREC associated with a paediatric hospital, while predominantly adult trials with extension into adolescence can be reviewed by any HREC.
> Step 2: make contact with the selected HREC early to discuss the trial and ensure a good fit between the trial protocol and the HREC expertise. Where a HREC feels it is not a good fit, they will usually make a recommendation for an alternative HREC.
> While all HRECs have the capacity to seek external expertise in order to thoroughly review a trial protocol, sourcing such external reviews can be time-consuming and may significantly increase the time taken for ethical review.

3.3 Recommendations for research ethics and governance offices

> Early consultation to ensure a good fit between trial protocol and HREC expertise should be encouraged, and the process for such consultation should be outlined on an externally-accessible website.

4. PROTOCOL AMENDMENTS TO PROVIDE AYA ACCESS TO ALREADY ESTABLISHED TRIAL PROTOCOLS

If you wish to make ongoing alterations to the age eligibility in an already approved trial protocol, for example to lower the age eligibility below 18 years in an adult trial, or increase the age eligibility above 18 years in a paediatric trial, you can apply to the reviewing HREC for a protocol amendment. The application will require, with trial sponsor approval, the submission of a revised protocol that includes justification for the new age eligibility. Any additional documents required in order to collect written informed consent from participants/parents/guardians within the extended age range must also be submitted. Additional investigators (e.g. paediatrics expertise if required) can also be added through the amendment process. Following ethics approval of the amendment, site notifications will also be required for governance authorisation.

An additional option might be to add an AYA sub-study to the main protocol, specifically to include AYAs outside of the main protocol's age range. Such a sub-study would allow for additional dosing options and procedures for those enrolled to the sub-study only, without alteration to the main study practices going forward. A sub-study can be added to the main study through application to the lead HREC for an amendment as above.

Often, the need to expand the age eligibility of a trial is stimulated by the circumstances of a specific patient who is otherwise eligible for the trial but whose age is outside of the approved eligibility. Where approval for an individual patient is required more quickly than an amendment can be reviewed, it may be possible to request an individual protocol deviation, in order to accommodate the individual patient while the amendment request is in process. Contact the reviewing HREC to discuss this temporary option, if required.

In these cases, it is best practice for the HREC to consider whether following the approval of the deviation for a single patient, the protocol should be amended in one of the 2 ways described above to allow ongoing access by other AYA; some HRECs may even require this amendment as a condition of approving the deviation. As such researchers should consider and discuss with sponsors what is most ethical and appropriate for their individual studies.

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We acknowledge the Traditional Owners of the lands on which we work and pay our respects to their elders past and present.

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The VCCC Increasing AYA Clinical Trial Access Program is supported by the Victorian Government.

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