Request for Proposals to Support the Development of ASH Clinical Practice Guidelines on Acute Lymphoblastic Leukemia in Adolescents and Young Adults

The American Society of Hematology (ASH) seeks to contract with a methodology team to support the development of new clinical practice guidelines on acute lymphoblastic leukemia in adolescents and young adults.

The team will conduct systematic evidence reviews to address 20 clinical questions to be defined by two ASH guideline panels and support the panels to develop recommendations to address each question using the GRADE approach. The team’s work will begin when ASH has appointed the guideline panels (expected by February 2022) and conclude upon publication of the guidelines. ASH invites proposals with a maximum budget of $400,000 to accomplish this work. The attached Project Plan describes the planned work in detail, including example clinical questions, methods, and schedule.

ASH will select a team on the basis of the team’s technical qualifications, past performance working with ASH if applicable, current relationship with ASH if applicable, and business terms including price of work.

Technical Requirements

The methodology team must have expertise conducting systematic reviews according to the methods described in the Project Plan and expertise with the use of GRADE for guideline development, also as described in the Plan. Expertise must be demonstrated through work history including publications of systematic reviews or guidelines. At a minimum, one member of the team must have a PhD in a relevant field such as clinical epidemiology or at least 10 years of relevant work experience conducting systematic reviews or supporting guideline development.

ASH has previously appointed a senior member of the methods team to serve in a named “co-chair” role on guideline panels. The Plan expects this approach to be used for this project. But this is not a requirement. Other models of support may be described within proposals.

The methodology team must be able to deliver the planned work according to the schedule in the Plan. Proposals should describe all proposed members of the methodology team, their technical expertise, planned role in the work, and planned time commitment.

The team must have the ability to work professionally with ASH members and ASH staff. Proposals should document the consultant’s work history supporting similar groups undertaking similar projects.
All members of the team must comply with ASH’s policy on conflicts of interest (included as an appendix to the Plan).

**Business Terms**
ASH will retain all intellectual property rights for the guideline, systematic reviews, and other work products of this project, including derivative works to be developed after guideline publication.

Individuals on the methodology team who contribute to publications will be listed as authors or acknowledged according to usual academic standards and ASH authorship criteria. Authorship will not affect ownership of work products.

ASH prefers a fixed price contract for this work. Pricing for project contingencies such as increased scope (e.g., additional questions), unusual methods (e.g., reviews of lower quality evidence, systematic collection of unpublished evidence), or work products (e.g., narrative reports of systematic reviews for separate publication) will be predetermined during contract negotiation and additional project planning with ASH staff and the guideline panels.

**Proposal Requirements**
Proposals for this work are requested by January 15, 2022.

The following information must be included with any proposal to be considered by ASH:

- Contact information: Name, address, telephone number, and email address of the team lead who is responsible for the proposal
- Description of scope of responsibility of the team, including services and deliverables to be provided by whom and when.
- Cost estimate, including contingency cost for addressing >20 but <31 questions
- Description of individuals who will participate in the work.

Proposals of approximately 10 or fewer pages are suggested, not including appendixes.

ASH welcomes proposals from all qualified teams.

In advance of the deadline, ASH will discuss this RFP with any party interested in submitted a proposal, e.g., to clarify ASH aims and expectations. Please contact Jenny Castano, Manager, Clinical Practice Guidelines, at jcastano@hematology.org.

**Instructions for Submission**
Please send proposals by January 15, via email attachment to Jenny Castano, Manager, Clinical Practice Guidelines, at jcastano@hematology.org.
Plan for ASH Clinical Practice Guidelines on Adolescents and Young Adults with Acute Lymphoblastic Leukemia

Background and Rationale
ASH experts advise that treatment of adolescents and young adults (AYAs) with acute lymphoblastic leukemia (ALL) is variable and not well addressed by available guidelines. This document describes the scope, organization, and process and methods for new ASH guidelines to be developed on this topic.

AYA ALL is a potentially curable disease with chemotherapy alone, but treatment variability is a potential problem. There is some evidence that suggests that treatment outcomes are substantially better in AYA patients with ALL who are treated with pediatric-inspired regimens than in AYAs treated with adult-inspired regimens. Pediatric-inspired regimens generally include the use of steroids, vincristine, asparaginase, early and frequent central nervous system (CNS) prophylaxis, and extended maintenance. With these regimens, retrospective studies suggest that AYAs have superior outcomes, with event-free survival over 70% (Curran and Stock, 2015). However, the use of such regimens appears to vary substantially according to setting of care: across all U.S. settings, two thirds of AYAs with ALL were treated with adult-inspired regimens, according to one study reviewed by Muffly et al., but in community settings, only one quarter. It is not known which patient characteristics inform the choice of regimen, and the impact of patient values and preferences, health equity, feasibility, and accessibility remain uncertain.

Available guidelines do not adequately address this topic. For example, recommendations from the National Cancer Center Network (NCCN) on pediatric ALL (Brown et al. 2020a) do not specify induction strategies or dosages for AYAs, and evidence for survivorship with different
treatment strategies is not considered. NCCN recommendations for adults with ALL (Brown et al. 2020) describe treatment options for AYAs but do not specifically compare or favor any of the options. Guidelines from the American Society of Transplant and Cellular Therapy (ASTCT) (DeFlipp et al. 2019) address transplant only. Other guidance on this topic is limited to opinion articles such as recent “How I Treat” articles in Blood, e.g., “How I Treat Acute Lymphoblastic Leukemia in Older Adolescents and Young Adults” (Curran, Stock, 2015) and “How Should We Treat the AYA Patient with Newly Diagnosed ALL?” (Boissel, 2017).

Scope
These guidelines will focus on treatment of ALL in AYAs. Areas of priority to be addressed include selection of induction therapy according to patient risk profile, supportive care including counseling for fertility preservation, and management of remission and relapse including measurable residual disease (MRD).

It is expected that the AYA population will be defined as being 15 to 39 years old, but this will be discussed and agreed upon by the guideline panels at project outset. Clinical studies on AYAs with ALL have included individuals with variable age ranges, including 15 to 39, 15 to 40, 18 to 39, and 15 to 50.

While important, the following are out of scope for this project: diagnosis, model of care delivery or setting of care, and specific psychosocial interventions.

These guidelines will provide recommendations for high-resource settings within North America, taking an individual patient perspective (i.e., rather than the perspective of a health system or of policymakers). It is expected that the recommendations may need to be adapted for other settings or perspectives.

Number and Charge of Guideline Panels
Two guideline panels will address the following topics within the scope as defined above:

Panel 1: Initial Therapy
Panel 2: Management of Remission and Relapse

Risk Stratification
A work group composed of experts from both panels will collaborate with a systematic review team to conduct a systematic review of the baseline risk of prioritized outcomes for the main populations to be addressed by the two guideline panels. The team will also conduct a systematic review of prognostic factors that may affect baseline risk and lead to different recommendations for subpopulations. Such factors may include clinical and molecular risk factors.

Initial Treatment
A guideline panel on initial treatment will address 10 clinical questions about the use of
pediatric- vs. adult-inspired regimens, choice of specific induction therapy, and management of treatment toxicities or complications. Therapies that may be addressed by specific questions and recommendations include cytotoxic therapies, immunotherapies, and allogeneic stem cell transplantation.

Based on the systematic review of baseline risk and prognostic factors, the guideline panel will consider offering different recommendations for subgroups with specific prognostic factors such as high-risk cytomolecular features. The guideline panel will not offer specific, graded recommendations about what specific risk factors should be assessed in AYAs. However, if recommendations for specific subpopulations are offered, assessment strategies may be offered within technical remarks associated with those recommendations.

**Example Questions**

**Should AYA with newly diagnosed ALL be treated with pediatric-inspired vs. adult-inspired protocols?** (Possible outcomes: r OS, PFS, EFS, DFS, MRD-negativity, response rate, CR, HRQOL, infertility, toxicity/adverse events, secondary cancers)

Subgroups: Ph-, Ph+, Ph-like, T-cell

**Should AYA with ALL in CR1 receive an allogeneic transplantation or continue with standard therapy?** (Possible outcomes: OS, PFS, EFS, DFS, MRD-negativity, response rate, CR, HRQOL, infertility, toxicity/adverse events, secondary cancers)

Subgroups: Ph-, Ph+, Ph-like, T-cell, additional high-risk subgroups defined by cytogenetics/MRD status

**Should AYA with ALL receive prophylactic CRT, other CNS prophylactic measures, or therapy without CNS prophylactic measures?** (Possible outcomes: OS, EFS, PFS, CNS relapse, toxicity/adverse events, cognitive outcomes)

Subgroups: Ph-, Ph+, Ph-like, T-cell

**Should AYA with ALL receive immunotherapy in CR1 or continue with standard chemotherapy?** (Possible outcomes: OS, EFS, PFS, DFS, MRD-negativity, response rate, CR, HRQOL, toxicity/adverse events)

Subgroups: Ph-, Ph+, Ph-like

**Should AYA with ALL and MRD+ disease be switched to alternative therapies (immunotherapy) versus continuation of standard therapy?** (Possible outcomes: OS, EFS, PFS, DFS, MRD-negativity, response rate, CR, HRQOL, toxicity/adverse events)

**Should administration of asparaginase be discontinued in AYA patients with ALL who are affected by toxicities (in particular, thrombosis and pancreatitis)? Should ASNase be dose-capped when treating AYA patients with ALL? Should AYA patients with ALL receive pre-medications along with ASNase?** (Possible outcomes: toxicity, OS, EFS, PFS, DFS)
Should psychosocial care interventions be incorporated into the care of AYA patients with ALL during upfront therapy?

Sample interventions for this question: psychosocial interventions, adherence interventions, exercise (Possible outcomes: adherence/compliance, QOL, OS, EFS, PFS, DFS)

Should supportive care interventions be incorporated into the care of AYA patients with ALL during upfront therapy?

Sample interventions for this question: glycemic control, anticoagulation, antimicrobial prophylaxis. (Possible outcomes: glycemic control, thrombosis/bleeding, infection, QOL, OS, EFS, PFS, DFS)

Should AYA with T-ALL receive nelarabine as part of upfront therapy?

Should AYA patients with Ph+ ALL receive indefinite TKI therapy or a shorter duration of therapy?

Management of Remission and Relapse
A second guideline panel will address 10 clinical questions about the management of remission and relapse, including management of patients with MRD.

It is expected that the guideline panel will offer different recommendations for patients with MRD positivity. The guideline panel may also offer recommendations about when to assess MRD positivity following induction of remission. Specific recommendations for subgroups with other clinical or molecular factors associated with poor prognosis may be offered depending on the results of the systematic review of these factors.

Example Questions
Should AYA with relapsed/refractory B-cell ALL receive immunotherapy, CAR-T, or chemotherapy?) (Possible outcomes: OS, PFS, EFS, DFS, MRD-negativity, response rate, CR, HRQOL, toxicity/adverse events)
Subgroups: Ph-, Ph+

Should AYA with ALL in first relapse receive allogeneic transplantation, or standard therapy? (Possible outcomes: OS, PFS, DFS, MRD-negativity, response rate, CR, HRQOL, toxicity/adverse events)
Subgroups: late isolated extramedullary/BM relapse

Should we treat AYA patients with relapsed/refractory ALL who have progressed following immunotherapy, have no immune-targeting therapies available, or are not candidates for immune-targeted approaches using chemotherapy protocols? (Possible outcomes: OS, PFS, DFS, MRD-negativity, response rate, CR, HRQOL, toxicity/adverse events)
Should AYA patients with relapsed/refractory ALL who receive CAR T cell therapy and achieve a CR receive allogeneic transplant?

Should AYA patients with relapsed/refractory ALL be assessed for MRD prior to allogeneic transplantation?
Note – may be encompassed within systematic review on MRD techniques/timing.

Should AYA patients with relapse after allogeneic transplantation be treated with chemotherapy protocols or other alternative treatment options?
Subgroups: management of concurrent vs. isolated CNS relapse in AYA patients with ALL

**Good Practice Statements**

Good practice statements are strong recommendations that are not based on a systematic review of evidence and are formed outside of the evidence-to-decision process used to develop graded recommendations for ASH guidelines. Under the GRADE approach, such statements endorse interventions for which the net benefit is overwhelmingly clear, such that it would be a poor use of resources to systematically review the evidence and apply a guideline process just to offer an obvious recommendation (Izcovich et al. 2020, Guyatt et al. 2016). As defined by GRADE, good practice statements should be valuable for clinicians and patients and should be clear and actionable.

Good practice statements may be developed by each guideline panel and incorporated into their final guideline reports. Alternatively, a working group composed of experts from both panels may develop statements to address questions recommended by either or both panels. Topics that may be addressed by good practice statements include, baseline prognostic characteristics, MRD methods and timing, supportive care during treatment of AYAs with ALL, fertility preservation in young patients with ALL, and the role of multidisciplinary and multispecialty care teams in AYA ALL treatment. All such statements must meet criteria for good practice statements as defined by GRADE.

The statements may be published within either or both guidelines.

**Panel Composition**

The guideline panels will include experts in the treatment of ALL, including experts in both adult and pediatric hematology. The panels will also include patient representatives, i.e., individuals with lived experience of the disease, such as a patient or a caregiver. Other professions, perspectives, and areas of expertise will include the following: geneticists, community oncologists, and early career hematologists.

If needed, the work group on good practice statements will consult with other experts such as psychosocial specialists or fertility preservation specialists. Individuals from these specialties will not be specifically included on the guideline panels.
One or more representatives from the ASH Guideline Oversight Subcommittee will serve on each panel as ex officio members. Their role will be to ensure that the guideline development process is conducted in accordance with this project plan and ASH policies and procedures, including ensuring that questions are within scope, reviewing participant disclosures and ensuring adherence to ASH COI policies, and critically reviewing the guideline report for publication.

A member of each guideline panel will be asked to serve in a “writer” role. Responsibilities of this role will include drafting background clinical content, recording panel decisions and discussion points, drafting the guideline report, integrating edits by authors into the guideline report, and addressing comments receiving during public review. At the beginning of the project, panel leadership will discuss and agree with writers how to appropriately recognize their contributions on publication.

Organizational Collaborators
ASH will not invite other organizations to collaborate in the funding, development, or approval of these guidelines. However, ASH may invite other organizations to recommend experts for the guideline panel, if experts are needed from outside the ASH membership, and to review and endorse the guidelines. ASH will also explore with other relevant organizations opportunities to promote and disseminate the guidelines. In addition to endorsement, this could include announcements, summaries, commentaries, or educational programs about the guidelines. Relevant other organizations for which such opportunities will be explored include the Leukemia Lymphoma Society, the National Comprehensive Cancer Network, the American Society of Clinical Oncology, the Association of Community Cancer Centers, and the National Pediatric Cancer Foundation.

Methodology Team
Under a paid agreement with ASH, a methodology team will support the guideline development process, including conducting systematic reviews of available evidence.

Methods
The ASH guideline development process includes the following steps:

1. ASH forms a guideline panel.
2. The panel prioritizes guideline questions.
3. The methodology team in collaboration with experts on the guideline panel systematically reviews available evidence.
4. The guideline panel reviews and finalizes evidence summaries and forms recommendations.
5. ASH makes the recommendations available for public comment.
6. The guideline panel and the methodology team write a report of the guidelines for publication and dissemination.
7. ASH committees and officers review and approve publication of the guidelines under the imprimatur of ASH.
8. Authors submit the guidelines report to *Blood Advances* for review and publication.

The GRADE approach will be used to assess certainty of evidence (Guyatt et al. 2008). The GRADE Evidence-to-Decision framework (Alonso-Coello et al. 2016) will be used to make judgments about the available evidence and form guideline recommendations using standardized language that has well-defined interpretations for clinicians, patients, and policymakers (Izcovich et al. 2020).

Systematic reviews will be conducted according to standards defined by the Cochrane Collaboration or equivalent. Specific methods used will depend upon the nature and quality of the best available evidence. For many questions, available evidence is expected to be from observational rather than randomized studies. For some questions, the best available evidence may be indirect or even unpublished. In this case, the methods team will support the panels to systematically find, synthesize, and interpret indirect evidence, evidence from registry data, or evidence from the clinical experiences of experts serving on the guideline panels. Complex evidence review may affect the project timeline or scope.

Some prioritized questions may include multiple comparisons that may result in multiple recommendations. This may affect the number of questions addressed by the panels.

For each guideline question, the best available evidence will be used to make estimates about the health effects of alternative interventions. These estimates, in combination with other judgments, will support recommendations by the guideline panels. If randomized controlled trials of directly compared interventions are available, this evidence will be systematically identified, appraised, and used. If not available, evidence from other study designs (e.g., nonrandomized studies or indirect comparisons from studies of alternative interventions against placebo) may be systematically collected, appraised, and used, or if the guideline panel agrees, evidence from studies in other populations (i.e., indirect evidence) may be used. Pragmatic methods may be used to identify indirect evidence. If no published studies can be found to make estimates, the guideline panel may choose not to answer the guideline question with a recommendation. Alternatively, the panel will base recommendations on the systematically collected clinical experiences of experts. These clinical experiences may be collected and synthesized from available registries or from surveys, including convenience surveys of the experts serving on the guideline panel (Legault et al. 2018).

Initial panel meetings will be held virtually via Zoom. In-person meetings could occur in 2022, if the COVID-19 pandemic allows, and if considered necessary. If not, the development process will be conducted virtually using online tools including the GRADEPro Guideline Development Tool, including to summarize evidence, obtain panel voting, and document panel judgments and decisions.
Management of Conflicts of Interest
Conflicts of interest of all participants will be managed in accordance with general ASH policies, as described on the ASH website (https://www.hematology.org/about/governance/conflict-of-interest), and with specific ASH policies and procedures determined by the ASH Guideline Oversight Subcommittee. The most recent version of these policies is attached as Appendix A.

Publication Strategy
Publication strategy for the guidelines and any other intellectual property will be determined by ASH, including the ASH Guideline Oversight Subcommittee. The current strategy is to submit and publish all work relating to this project including the guideline reports and systematic reviews within ASH’s online-only open access scientific journal, Blood Advances. If the editors of Blood Advances do not agree to receive any planned work as “invited,” if any invited work is not delivered on deadline, or if the work is rejected by the journal, it will be published on the ASH website. Exceptions to this strategy will be agreed upon in advance of preparation of the work. Such exceptions may include certain papers not relevant or invited by Blood Advances, including methods papers or opinion articles. At the beginning of the project, a presubmission inquiry to the editors of Blood Advances will describe all planned work. The inquiry and discussions with the editors will be led by the lead authors and by the GOS ex officio member(s) of the panels.

Two guideline reports are expected, i.e., (1) guidelines on initial treatment and (2) guidelines on management of remission and relapse.

Systematic reviews may be developed for submission to Blood Advances as separate, simultaneous publications. If the reviews are not prepared as separate publications, details about the reviews will be included with the guideline reports as supplements.

Authorship, sponsorship, and acknowledgements of such publications will be in accordance with academic standards and customs and requirements of the journal of publication. ASH authorship criteria for the guidelines are presented as Appendix B.

Dissemination and Implementation
To support understanding and implementation of the guidelines, the panel will be asked to write recommendations and remarks that are clear and actionable.

The chair and panelists will strategize a dissemination and implementation plan that will enhance access, for clinician and patients, to the guideline and support understanding and implementation of the guidelines recommendations. While a formal strategy will be written around the time of public comment, panelists will also be asked to flag recommendations in development for which there are implementation barriers (e.g., insufficient clinician awareness or education, lacking information systems support).
Revision

After publication, ASH will maintain these guidelines through regular revision. The need for revision will be determined through a process that includes annual monitoring for new evidence, expert review, and committee decision-making. When ASH agrees to undertake a revision, a new guideline panel or panels will be appointed, which may include members of the original panel. The new panel will prioritize new and old questions, then follow other usual steps of the ASH guideline development process.
### Timeline

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<th>2021</th>
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<tr>
<td></td>
<td>Jul</td>
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<tr>
<td>ASH vets and appoints panel leadership (chairs and ex officio members).</td>
<td>Aug</td>
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<tr>
<td>Panel leadership hold teleconferences to refine the scope.</td>
<td>Sep</td>
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<tr>
<td>ASH selects and contracts with methodology team.</td>
<td>Oct</td>
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<td>ASH vets and appoints guideline panel.</td>
<td>Nov</td>
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<td>Jan</td>
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<tr>
<td>ASH vets and appoints guideline panel.</td>
<td>Feb</td>
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<td>Ash staff, methods team, and panel leadership provide orientation to the guideline panels.</td>
<td>Mar</td>
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<td>The panels prioritize clinical questions including outcomes.</td>
<td>Apr</td>
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<tr>
<td>Methods team develops protocols for systematic reviews. Panel reviews.</td>
<td>May</td>
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<tr>
<td>Methods team systematically reviews available evidence.</td>
<td>Jun</td>
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<tr>
<td>Guideline panel reviews the results of the systematic reviews.</td>
<td>Jul</td>
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<tr>
<td>Guideline panels form recommendations.</td>
<td>Aug</td>
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<tr>
<td>ASH staff make recommendations and evidence tables available for public comment.</td>
<td>Sep</td>
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<tr>
<td>Guideline panels review public comments and consider revisions.</td>
<td>Oct</td>
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<tr>
<td>Authors from the guideline panels and the methodology team write manuscript reports of the guidelines for submission to <em>Blood Advances</em>.</td>
<td>Nov</td>
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<tr>
<td>ASH committees and officers approve publication of the guidelines under the imprimatur of ASH.</td>
<td>Dec</td>
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<tr>
<td>Authors submit the reports to <em>Blood Advances</em>.</td>
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<td><em>Blood Advances</em> reviews, accepts, produces, and publishes final reports.</td>
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References


Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren; Fertility Preservation in

