Academic Clinical Trials Program Guidelines & Instructions

Effective dates:
September 6, 2023 – June 30, 2024

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Application Compliance

- It is highly recommended to access the LLS Research Portal at https://lls.fluxx.io and begin the application process well in advance of any deadlines. In addition, each stage of the application process (letter of intent/full application) should be completed well before the deadline.

- The Academic Clinical Trials Program (ACT) is designed to support investigator-initiated clinical trials. Note that **discovery or translational work is not a fit for ACT** and will not be competitive. These types of applications are best suited for our Discovery Grant (formerly known as our Blood Cancer Discoveries Grant program) and Translational Research Programs. Potential Principal Investigators with earlier stage research activities are encouraged to apply to those programs.

- All components of the application must be present in the order indicated in these guidelines.

- Character limits include spaces. Character and other length limits are strictly enforced on the web form and the uploaded project description template. Font must be black Arial 11 pt. including figure legends, which should be text boxes separate from the figure itself. ***If character limits and font restrictions are not adhered to, or the preset margins are altered, the application may be administratively disqualified.***

- Line spacing is preset in the Word document. ***Do not change the setting. Pasting text from another document into the template may result in a change in the line spacing.*** Check the line spacing in the template before pasting, and if there is a change after pasting, return the line spacing to the original setting. Any modifications in line spacing, particularly if the change allows for more text to fit into the page, ***may result in administrative disqualification of your application.***

- Do **not** attach documents to the application that are not specifically called for. ***The application could be administratively disqualified if this rule is violated.***

- **The PI and/or Co-PI** may apply to more than one grant program during an application cycle if the aims do not substantially overlap with the aims of any other application across all programs. **You may not be on a different project within the same grant program**.

- **The Project/Core Leaders, Collaborators or Key Personnel** may be on different projects or programs provided the aims differ.

- All such duplicate grant proposal submissions with substantially overlapping aims are subject to administrative disqualification, and such proposals will not be reviewed further or considered for funding. Contact researchprograms@lls.org with any questions about this policy or to discuss with LLS scientific staff any questions concerning potential overlap between applications.

Completion of several steps in the process initiates emails sent from the LLS Research Portal. LLS staff may also send emails during the application process. Spam filters should be monitored for these emails. Contact researchprograms@lls.org if expected emails are not received by the times indicated in these guidelines or if you have any questions not clarified in this document.

Introduction

The Leukemia and Lymphoma Society (LLS) recognizes the scientific and clinical merit of research developed and conducted by independent investigators affiliated with academic institutions. Such investigator-initiated trials (IITs) play an important role in developing experimental agents to address unmet medical needs, expanding the use of approved therapeutics, and improving the use of novel treatment regimens in real-world clinical settings. To support this important aspect of research, the LLS created the Academic Clinical Trials Program (ACT) in 2022-23, and now presents a second request for applications.

LLS is a national voluntary health agency dedicated to the conquest of blood cancer and relevant premalignant conditions. LLS supports research, patient aid, community service programs, advocacy, and public and professional education.

Program Description

LLS created the Academic Clinical Trials Program (ACT) to support completion of investigator initialed clinical trials (IITs) that address unmet medical needs in blood cancer. In this program, disease areas of interest include hematologic malignancies and related pre-malignant conditions. LLS is seeking **truly novel advances** and not simply incremental advances of approved therapeutics. Novel biologic or chemical experimental agents, either as single agents or in combination, are eligible. These awards will fund clinical trials, up to $1M USD over a period of up to three years.

In this funding cycle, LLS has a particular interest in funding meritorious projects addressing follicular lymphoma. This funding will be provided in a collaborative partnership with the **Follicular Lymphoma Foundation**. The maximum amount for a co-funded award will not exceed $1 M USD. See **Cure FL Appendix** for details.

The primary focus will be Phase 1 or 2 trials with novel experimental agents. Repurposing of approved therapies into novel indications will also be considered. Investigators conducting existing trials and expansion of existing trials are welcome to apply. Investigation of corporate-owned assets is allowed. If a corporate asset is studied, a clear path to market must be obtained and demonstrated. Proposals may include correlative studies including but not limited to biomarker identification, mechanism of action, and/or patient selection.

Examples of projects of potential interest include:

- Novel immunotherapy approaches (cells, biologics, small molecules) relevant to blood cancers.
- Cell therapies and biologics targeting tumor antigens or tumor microenvironment.
- Treatment approaches in premalignant conditions for the prevention of disease.
- Personalized medicine approaches for blood cancers, including novel companion diagnostics.
- Clinical protocols that move cell therapies/bispecific antibodies to first line therapy.
- Enhanced safety and/or efficacy of stem cell transplantation.
- LLS has a special opportunity to co-fund proposals addressing follicular lymphoma. Please see the **Cure FL Appendix** for details.

Applicants must submit a proposed clinical research plan and a proposed budget with justification for its relationship to the clinical research plan. Both plan and budget are subject to modification

by LLS upon review. The submitted budget should reflect the actual needs of the project and cannot exceed $1M USD for the period of up to three (3) years of the grant. This budget ceiling includes all costs associated with the grant including indirect costs (often referred to as Institutional Overhead), which will be capped at 15% of the total award. Applicants may claim less than 15% for the indirect costs and apply those costs to the direct costs.

Maximum Duration	*Maximum Indirect Costs*	*Maximum Total Award*
Up to 3 years*	15% of Amount Requested (not to exceed $150,000)	Up to $1M

*The duration of award and budget requested (including salary and fringe benefit expenses) must reflect the actual timeline and work being proposed in the research plan.

Award Management

Prior to executing the funding agreement, the grantee and LLS will agree upon a budget that is based on the amount requested in the application, which may be modified by LLS. Additionally, a payment schedule, a bi-annual progress meeting schedule, and research milestones will be agreed upon and specified in the funding agreement. Milestones may be based on clinical progress, patient accrual, interim and final analyses, abstract and/or publication submissions, and/or other research progress metrics. A Gantt chart and milestones for the program are required at the full application phase.

It is anticipated that LLS will award up to 20% of the total agreed-upon budget at grant launch. Subsequent payments will be tied to research milestones. LLS, in its sole discretion, reserves the right to cease payments and terminate the award if LLS determines that insufficient progress toward a milestone is made within the specified timeframe.

LLS recognizes that clinical research can be unpredictable. The final budget will serve as a guideline that can be adjusted based on resource needs as the trial progresses. Any request to increase funding after submission of the application must be in writing to researchprograms@lls.org and is subject to the availability of funds.

Funded Institution's Acceptance of the Terms and Conditions

Applicants who are offered an ACT award will be sent a funding agreement. The funded institution's representatives must agree to these terms and conditions and return the signed agreement by the deadline. Currently, the NIH does not accept LLS's contract terms.

Who Can Apply

Citizenship

The program welcomes applications worldwide from appropriate academic institutions and investigators of any nationality.

Degree

Applicants must hold a medical degree (MD or ex-US equivalent). Other advanced degrees (OD, PharmD, PhD) will be considered. Non-independent investigators such as clinical fellows, residents, postdoctoral fellows, instructors, etc. are not eligible.

Leadership and Staffing

The Application will require one Principal Investigator (PI) who is responsible for the preparation and submission of the proposal including budget, the conduct of the research programs, and adherence with all stipulations made by LLS in this document, the LLS Policies & Procedures document, and in the funding agreement, if funded.

The Principal Investigator (PI):

- MUST be a person (companies or institutions are not eligible).
- MUST be an independent investigator, with demonstrated experience and training to be able to organize, manage and implement the clinical trial to meet milestones and timelines, and to protect the rights and welfare of the human subject participants.
- MUST be an established investigator, defined as a researcher with 3 or more years in an independent faculty appointment.
- May only submit one ACT application per program cycle; and cannot serve as a PI or Co-PI on more than ONE ACT application per cycle. If applying to another LLS program, the goals of each proposal must be substantially different.
- CAN serve as a Collaborator on other applications provided the aims differ.

Not eligible to apply for a grant in this program:

- Clinical fellows, residents, postdoctoral fellows, or instructors are not eligible.

A Co-Principal Investigator (Co-PI):

- MUST be a person (companies or institutions are not eligible)
- MUST be an independent investigator with an independent appointment, with demonstrated experience and training to organize, manage, and implement their portion of the clinical trial and/or project to meet milestones and timelines.
- If the PI has the necessary track record in blood cancer research, a Co-PI with complementary experience may strengthen the proposal but is not required.
- May be named as PI or Co-PI on one application per ACT program cycle.
- CAN serve as a Collaborator on other applications provided the aims differ.
- MUST be designated at the LOI phase.

The Application allows for 1-2 Co-PIs which should be selected during the Letter of Intent phase in the Fluxx webform.

Scientific Staff/Collaborators/Other Key Personnel

- MUST be a person (companies or institutions are not eligible).
- May strengthen the work proposed but is not required.
- May provide expert insight, guidance, or feedback on research progress.
- May be included on different projects or programs provided the aims differ.

Relevance

The proposed clinical research must be focused on developing innovative treatments in blood cancer or associated pre-malignant conditions. Additional correlative studies to determine mechanism of action, biomarker identification and/or patient selection are allowed.

Applications that do not meet the relevance requirement will be disqualified without full review.

Review Process & Applicant Notification

The deadline to submit all Letters of Intent (LOI) is October 25, 2023, at 3 PM ET. Letters of Intent are reviewed after the LOI deadline. Applicants will be notified via an automated email whether they are invited to submit a full application, or whether their LOI is declined. If the applicant is invited to submit a full application, immediate access to the full application phase is enabled in the LLS Research Portal. If you have not received an email regarding your LOI approval by November 29, 2023, contact researchprograms@lls.org.

The deadline to submit all full applications is January 23, 2024, at 3 PM ET. Full applications will only be accepted via the LLS Research Portal (https://lls.fluxx.io).

Key Dates

Phase	Date
Call For Proposals	September 6, 2023
Letter of Intent due	October 25, 2023
Full Application due	January 23, 2024, 3:00 PM ET
Panel Review Meeting	Late March 2024
Award Notification	May 2024
Award Start Date	July 1, 2024

**LLS's non-negotiable funding agreement terms & conditions are available on www.lls.org.*

All submission deadlines will be enforced. Please note that all times are Eastern Time (ET). If any date falls on a weekend or US holiday, the deadline becomes the next business day.

It is highly recommended that submissions are done *prior* to the deadlines. Internet traffic may be slow near the deadlines, which may result in difficulties in submissions. In addition, LLS's response time to questions may be delayed by the high volume received near the deadlines. Therefore, it is imperative that any submissions or questions be posed to LLS well ahead of any deadlines.

Review Criteria

An application receives a Priority Score based on a 9-point rating scale (1=most meritorious; 9=least meritorious) using these criteria:

- **Significance:** The proposed research has the potential to make a significant impact toward the treatment or prevention of blood cancer(s) and/or relevant premalignant conditions. Please consider novelty of the experimental agent, and/or novelty of the clinical approach of an approved therapeutic. Diseases with high unmet needs will be favored.

- **Rationale**: The scientific and/or clinical rationale is sound and is based upon a body of high quality and relevant data.

- **Plan/Impact**: The project plan includes a clinical trial, which is well planned to achieve a meaningful outcome. Correlative studies are relevant to the clinical development of the experimental agent and/or the approved therapeutic. The potential impact of the study on

blood cancer, and the timeframe in which patients might realize a benefit is meaningful. Proposed project milestones are appropriate in their relationship to the research plan.

- **Feasibility**: The proposed clinical trial and correlative studies are feasible and achievable within the project timeline. Adequate resources are proposed and available. Please consider:
    - qualifications of the Principal Investigator and Co-Principal Investigators
    - provisions for the protection of clinical trial participants
    - availability and quality of the resources and environment. This includes access to patient populations and patient samples (where applicable)
    - the overall manufacturing plan, and its robustness and feasibility to meet needs of the study (for cell-based or biologic products, if applicable)
    - contingency plans for unanticipated clinical and/or manufacturing challenges
    - a demonstrated and clear path to market for corporate-owned assets
    - if applicable, committed additional funding from the applicant's institution and/or the sponsor that enhance the proposal in its goal to benefit blood cancer patients

- **Clarity:** The proposal demonstrates clarity of thought and presentation of the plan

- **DEI**: The applicant demonstrates understanding of any health disparities associated with the indication; and the applicant presents an appropriate rationale and plan for the proposed trial study population based on current knowledge of the groups at risk for the target indication, including underserved populations. The rationale and plan for the study population align with the objectives of the trial.

- **Patient Involvement Plan**: Patient participation plans are included in the proposal. Patient engagement activities are appropriately planned and resourced to achieve meaningful engagement. The patients' needs (both unmet medical needs and first-hand experiences) are reflected in the design of the clinical trial.

Full Applications will be reviewed after the January 23, 2024 submission deadline by the ACT Subcommittee of the Medical & Scientific Affairs Committee. If an application does not meet the program goals, scope, or guidelines, it may be administratively disqualified. Applications are assigned an initial score by the primary and secondary reviewers. Only applications that fall above a scoring level determined by the committee chair will be discussed in detail for final ranking by the entire committee.

ACT applications will be rank ordered based on their Overall Priority Score (1-9, which reflects the average of all the reviewers' priority scores).

Once ranked, priority scores and funding recommendations of the ACT Subcommittee will be presented to the Medical & Scientific Affairs Committee and LLS's National Board of Directors for final determination of awardees. LLS will determine the number of awards funded, based on scientific merit and the approved budget for the program.

Any applicant selected for funding will be notified by the date indicated in the "Key Dates" section. Please do not call or email LLS to determine whether the application has been received, when it will be reviewed, or to obtain the results of the review. Please check the LLS Research Portal for the status of your application. All priority scores are confidential in that they are available to LLS's Medical & Scientific Affairs Committee, its Research Subcommittee, LLS's National Board of Directors, and administrative personnel only.

Feedback will only be provided for applications discussed by the full review committee.

General Application Instructions

All submissions must use the LLS Research Portal, Fluxx, at https://lls.fluxx.io/. It is recommended that you familiarize yourself with this portal well in advance of any deadlines.

Registration

Both the applicant and institution must be registered in the LLS Research Portal. If you have applied to LLS in the past, you do not need to create a new registration. Simply log in with your username and password. If you forgot your password, click the "reset or create password" link and enter your email address. The system will send your username and a link to update your password. Once updated, you can begin the LOI. If you are a first-time user to the LLS Research Portal, please complete the intake form located at this link: Account Creation Request so an account can be created for you. Only LLS staff members have administrative permission to create new accounts.

Institutional Designation

Applicants should create their profile from the standpoint of where they will perform their research described in the application. The applicant must indicate the name of the institution as well as the name of the signing officials for that institution.

If your institution is not displayed as an option under this field of the application, you may contact researchprograms@lls.org to have it registered in the system. Please provide the official's full name and email address.

Data Entry

Both the LOI and the full application may be accessed and changed multiple times as needed prior to the submission deadline. However, neither the LOI nor the full application can be changed once the respective deadlines have passed or the final application has been submitted. Moreover, some fields may not be modified in the full application following submission of the LOI.

Forms and Format

Applicants will provide information on the LLS Research Portal and a downloadable template at the LOI and full application phases. The applicant's name should be typed in the upper right corner of each page of the template. All information must be typed in English using commonly accepted grammar and punctuation. Some information will be captured when applicants populate fields on the LLS Research Portal. Fields in bold are required. Character limits include spaces. Character and other length limits are strictly enforced on the web form and the uploaded project description template.

Font must be black Arial 11 pt. including figure legends, which should be text boxes separate from the figure itself. *If character limits, font restrictions, margins and/or page limitations are not adhered to, the application may be administratively disqualified***.**

Contacting LLS

Questions that are not clarified in this document or the LLS Research Portal should be addressed to researchprograms@lls.org.

Beginning an Application

The application will be completed in two phases: Letter of Intent and Full Application.
Below are step-by-step instructions for applying:

1) Read the Guidelines & Instructions in full and familiarize yourself with the LLS Research Portal.

2) Log into the LLS Research Portal, and under "Information" in the left navigation bar, select Academic Clinical Trial Program. Click "Apply to ACT!" to begin the application process (well ahead of the deadline).

3) Click "Edit" and follow the instructions for each web form field. Bold font indicates required information.
   - Character limits include spaces. Character and other length limits are strictly enforced on the web form and the uploaded project description template. If character limits are not adhered to, the application may be disqualified.
   - You may save your work and return to it at any time by clicking "Save." Clicking "Submit" will lock your application and prevent further modification at that stage. Contact researchprograms@lls.org if you submit in error (must be before the deadline).

4) Once your LOI is submitted, you will receive an automated confirmation email within two business days from the LLS Research Portal. Consider that these emails may end up in your spam filter.

5) If your LOI is selected, you will have access to the full application. Click on your request, found in *New* or *Pending*, to continue with your application.

6) Please carefully follow the instructions on the LLS Research Portal and this document. Full applications require completion of both the web form and the application template, which should be downloaded from the *Project or Supporting Documentation* section of the LLS Research Portal. **Failure to follow all application instructions may result in administrative disqualification of your application.**

7) Submit your full application to the LLS Research Portal prior to the full application deadline. **We strongly recommend submitting well before the deadline, as site traffic on the day of and days leading up to the deadline will be heavy.**
   - Contact researchprograms@lls.org with any questions about the application phases that are not addressed in the LLS Research Portal, the FAQ, or this document.

8) To create a fair process to all applicants, these Guidelines & Instructions and information on the LLS Research Portal must be followed. ***Do not ask for exceptions to these policies, including but not limited to exceptions to deadlines or making corrections to your document past the deadline.***

Carefully check every page of your application prior to submission. You are ultimately responsible for this submission, even if someone else submits your final application.

If you have any technical difficulties with the LLS Research Portal, please contact researchprograms@lls.org.

Detailed Letter of Intent Phase Instructions

Each applicant must submit the LOI by **October 25, 2023, at 3:00pm ET** via the LLS Research Portal (https://lls.fluxx.io). The applicant should carefully craft the information requested in the LOI as this information is automatically populated into the full application and is subject to the "Changes" clause listed below. There are two main aspects to the Letter of Intent Phase: all Fluxx webform fields and the "Previous Studies/Preliminary Data/Trial Summary" (2 page maximum) downloadable template for completion.

The LOI for ACT will be reviewed after the deadline. If the LOI is approved, the applicant will be notified by an automated email from the LLS Research Portal stating that they may proceed to the full application phase. Applicants may also check the status of their LOI on the LLS Research Portal.

Organization Information

(If the institution or officials are not listed, please contact researchprograms@lls.org with the name and email address for the official you need added)

Institution: Indicate the name of the institution where the research will be performed.

Principal Investigator: The Principal Investigator is the applicant.

Institutional Signing Official (ISO): The ISO is the institutional representative responsible for signing and agreeing to the accuracy of the application and the terms and conditions of the award, should the application be selected for funding.

Financial Officer: The Financial Officer is the institutional representative responsible for the financial administration of externally funded research.

Additional Access (Admin/Assistant): Access may be given to personnel to assist in the application process. This is the institutional representative responsible for the day-to-day administration of externally funded research (or the Research Administrator).

Technology/Transfer Official (TTO): The TTO is the institutional representative responsible for overseeing Intellectual Property.

Clinical Trial Sponsor: the name of the sponsor who takes responsibility for and initiates the clinical investigation. The Sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

Zip Code of the Institution: Enter the zip code of the institution if located within the United States. You will need to click on the zip code from the drop-down menu to ensure it is captured in the zip code field. If not located within the US, this can be left blank.

Co-PI: Each designated Co-PI has a specific role and associated responsibilities in the proposed project. Up to 2 Co-PI's are allowed for an application. The designated Co-PI(s) cannot be changed after the Letter of Intent phase.

Project Information

Project Title: Provide a title adhering to the 100-character limitation (which includes spaces).

Project Summary (Public): Provide a short summary (approximately 2-4 sentences) in lay language. Charts and graphs cannot be included in the project summary section of the LLS Research Portal.

Lay Description (Public): Briefly describe the proposed research in lay language. Include a description of the proposed treatment, the patient population to be studied, the clinical problem/research question that will be addressed, and how the results will be measured. Describe the potential impact to patients and the timeframe in which the patient benefits might be realized. Clearly state how your study will progress into a solution for a problem in the treatment or prevention of a blood cancer or pre-blood cancer condition.

The Lay Description is essential for LLS to continue successful fundraising to support our current and future grantees, including the later years of ***your*** award, should it be funded. Thus, we require a well-written Lay Description, with sufficient detail and suitable language for non-scientists. Do not include confidential information, as the Lay Description (and Project Summary) will be shared with others. The Lay Description has a maximum of 3,000 characters, including spaces. Scientific/Greek characters or symbols must not be used.

Brief Biography (for the PI only): Provide a brief, professional biography introducing the applicant to a lay audience. Approximately 1,000 characters including spaces.

Structured Clinical Abstract: Briefly describe the overall proposed project in **8,000** characters (including spaces) or less using technical language in the following sections:

a. **Background and Preliminary Data**: Describe the background and overall purpose of your proposed clinical trial. Include the current standard of care. Include a brief description of the preliminary data on which the study is based. (Maximum 2,500 characters)

b. **Goals and Objectives**: Provide a succinct project overview. State the clinical problem and research question(s) to be studied. Summarize your study design, including the proposed treatment(s), patients to be studied, and endpoints. Describe potential benefits and risks to patients. Briefly summarize correlative studies: design, approach to analyzing your findings, and describe what you expect to find or achieve. (Maximum 2,500 characters)

c. **Expected Outcomes and Clinical Significance**: Describe the potential impact of your study on blood cancers, and the patient's experience. Describe the timeframe in which the benefits may be realized. (Maximum 1,500 characters)

d. **Role of the Co-PIs (Optional):** If applicable, describe the role, responsibilities, and anticipated time commitment of each Co-PI, i.e., which research activities depend fully on the Co-PI and how. (Maximum 1,500 characters)

Once the LOI has been submitted, the Structured Clinical Abstract may not be changed without approval. If awarded, sections a-c will serve as a scientific abstract.

Key Scientific Terms: Please check the appropriate or relevant option(s) in the following categories. You may check multiple options, but please be thoughtful when selecting your answers:

- Major Disease Key Words
- Specific Disease Key Words
- Other Key Terms (Optional)

Amount Requested: Enter the total amount of funding requested over the life of the grant. (Maximum $1,000,000). The amount requested on the LLS Research Portal should match the budget section of the full application template. Please note that LLS does not follow NIH guidelines for budgets. Please adhere to the LLS rules as outlined in this document.

Proposed Start Date: The start date for ACT grants is July 1, 2024.

Proposed End Date: The end date for ACT grants will be determined at launch.

IRB Status: Indicate the IRB status of the trial. Include the IRB approval date, or the scheduled/anticipated IRB review date.

Clinical Development Status: Indicate whether the treatment is in active clinical development in other clinical trials outside of this application. If yes, describe the indication and clinical stage, and whether the compound has been on or is on clinical hold. If no, please explain.

Previous Submission: Indicate whether you have previously submitted a similar proposal (or one similar) to LLS and indicate the date of any prior submission.

Key Personnel or Collaborators Information: Include collaborators or key personnel (internal or external to your institution) that will help strengthen your application. Please include their name(s) and institution(s). *This section helps LLS identify conflicts with reviewer assignments.*

Previous Studies/Preliminary Data/Trial Summary: Upload the Previous Studies/Preliminary Data/Trial Summary (2 page maximum) to the "Project and Supporting Documentation" section of the web form in PDF format. Text, figures, and references must be written single spaced in Arial size 11 font. **Note**: When uploading this template to Fluxx, please ensure you choose the correct file name from the drop-down menu which should read "Previous Studies/Preliminary Data/Trial Summary." If the wrong file name is chosen, you will not be able to submit your LOI. References are not required at the LOI phase. However, if you do provide them, please ensure the two-page limit is adhered to.

LOI Save, Review, and Submit Instructions

Validation will automatically occur after clicking the "Save" button. Validation is a safety measure for the applicant to ensure that all required fields are complete. If required fields are empty or incomplete, the system notifies the applicant of fields that require information.

After clicking "Save" you will be directed to review your LOI. Please ensure all information is accurate, and then click the "Submit" button to submit your LOI to LLS.

Each applicant must submit the LOI by **October 25, 2023, at 3:00 pm ET** via the LLS Research Portal. After clicking the "Submit" button, the applicant will receive an automated email within 2 business days stating that your information was successfully submitted. If you do not receive the

email confirmation within two business day, contact researchprogram@lls.org.
Signatures of the applicant and institution officials are not required for submission of the LOI.

Changes
Information collected in the Letter of Intent Phase will automatically populate fields in the full application. Once submitted, changes may only be made after receiving prior approval from LLS.

The applicant must email researchprograms@lls.org requesting any change and identifying the elements to be changed. Any changes made without the prior approval of LLS may result in the disqualification of the application.

Detailed Full Application Phase Instructions

Each applicant must submit a full application by **January 23, 2024, at 3:00 pm ET** via the LLS Research Portal. Some sections of the full application will be automatically captured on the LLS Research Portal from the Letter of Intent Phase. Other pieces of information will be captured in the application template that must be downloaded, completed, and then uploaded by the applicant as a **single PDF**. The applicant may not modify any information from the submitted LOI as this is subject to the "Changes" section listed above and may result in disqualification of the application.

Failure to submit as a single PDF in the order below may result in disqualification of the application.

Three sections are required in the uploaded PDF:

Section 1: Graphical Abstracts (1 page maximum)
Please provide two graphical abstracts, which provide reviewers with quick overviews of your clinical trial and project. You may wish to illustrate key aspects such as the clinical trial design, and/or clinical development plan. For novel experimental agents you may wish to illustrate the biologic mechanism of action or treatment approach, like a graphical abstract in a Cancer Cell paper.

Section 2: Project Description (14 page maximum)
Download and complete the project description template, including all required signatures, and upload to the "Project or Supporting Documentation" section of the web form. Margins are preset and must not be changed. Text, figures, and references must be written single spaced in Arial size 11 font.

Only one application PDF is accepted at the full application phase (Project Description Template combined with biosketch(es) and all applicable appendix documents). Do not delete the LOI "Previous Studies/Preliminary Data/Trial Summary" PDF file.

The template consists of the following required elements:

a. **Project Description (14 page maximum, including figures)**
The following information should be provided in this order. The approximate length listed for each section in the sequence is a recommendation and not a strict limit for each section. It is up to the applicant to utilize more or less space for individual parts based off the specifics of their application.
- Title and Study Goal (approximately ½ page)
- Rationale and Risk/Benefit (approximately 1 page)

- Previous Studies/Preliminary Data (approximately 3 pages). *Note: For the Previous Studies/Preliminary Data and Clinical Trial Summary sections, insertion of HTML links or clinicaltrials.gov website links is allowed.*
- Clinical Trial Summary. (approximately 2 pages). *Note: A Clinical Protocol Synopsis may be placed in the Appendix.*
- Assays/Methodologies/Manufacturing Plan Summary (2 pages)
- Patient Involvement Plan (approximately 2 pages)
- Interaction with Other Investigators (approximately ½ page)
- Resources and Environment (facilities, clinical site(s), clinical operations, data management, regulatory support, additional committed funds) (approximately 1 page)
- References Cited (approximately 1 page)
- Gantt chart and trial specific milestones (approximately 1 page)

Please do not upload manuscripts, IRB documents, or complete trial protocols.

b. Description of Model Systems and Reagents

Provide information on the models, drugs, and reagents described in your project description. This will be an easily assessable resource for reviewers to understand what is described in more detail in the text and figures.

c. Budget

The Budget and Budget Justification should provide itemized detail for each major category for all years of the project. The budget can be summarized in year one and extrapolated for the remaining two years. All totals and subtotals should be completed on the form. The aggregate costs over the two to three (2 to 3) years cannot exceed $1,000,000, including indirect costs.

Permissible Direct Costs include the following with the specified limitations:

- Personnel Expenses including salary, wage, or stipend with fringe benefits. **Direct costs for the salary and fringe benefit expenses are limited to the actual costs for the proposed work.**
- Supplies & Materials requests should be itemized by category.
- Equipment Purchase requests must identify each item of equipment with an acquisition cost of more than $4,000.
- Travel Expense requests cannot exceed $2,000 per year of the award.
- Patient Care Costs (Inpatient/Outpatient)
- Subcontract Costs
- Other Direct Cost requests

Permissible Indirect Costs (often referred to as Institutional Overhead, IDC, M&A, G&A, or pooled costs) are those costs incurred for common or joint objectives that cannot be readily identified with a particular project (general maintenance, utilities, library, etc.) as defined in the Office of Management and Budget, Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards. ***Indirect costs are limited to 15% of the total costs requested.*** For institutions that do not choose to use these funds for indirect costs, LLS allows the funds to be applied to other project costs.

Impermissible Costs include membership dues, tuition, books, journals, and publication costs.

d. Budget Justification: (2 page maximum)

e. Additional Funds (1 page maximum)
If a trial is receiving additional funds from the PIs institution and/or a sponsor, the applicant must provide the total funding committed from each source and detail what the funds will be used for. Additionally, if a corporate asset is being provided, any letters of support from the corporation must be included in the proper section of the application.

f. Signature Page
This form must be completed, including the indicated signatures.

Section 3: Appendix

The following sections must be attached in this order to the end of the template (from Section 2) to create a single PDF. ***No other information may be provided in this section*.**

a. Principal Investigator's NIH Biosketch (This document is not required for Senior Staff/Collaborators but is required for any Co-Principal Investigator(s)).
Use the most recent NIH biosketch format found on the NIH website. Publications submitted and under review should be indicated on the biosketch. An eRA Commons Username is not required.

b. Principal Investigator's NIH Other Support Document (This document is not required for Senior Staff/Collaborators but is required for any Co-Principal Investigator(s) identified in the application).
Use the most recent NIH Other Support Document format found on the NIH website. Must contain all current and pending support from any source. **In addition, specific aims must be listed for current and pending grants that may overlap or appear to overlap with the LLS application.** This includes any grants or portions of grants submitted to any organization, including LLS.

If funding decisions about potentially overlapping, pending grants become available following submission of an LLS application, LLS must be notified within five (5) business days of the applicant's receipt of that information.

LLS recognizes that some investigations, particularly those involving clinical trials, may require multiple funding sources, so overlap of specific aims with another grant may be appropriate and acceptable. The need for and details about such overlap should be clearly explained in the application. However, LLS will consider an applicant's other current grant support in its funding decisions. This may result in LLS funding only part of the grant or none of the grant, depending on the level of overlap. In addition, LLS reserves the right to adjust the level of funding of an awarded grant should another overlapping or potentially overlapping grant that was pending at the time of application submission be awarded to the applicant.

Failure to abide by LLS's rules on disclosure of current or pending support may jeopardize the funding of the current application and may affect future LLS funding decisions.

c. Co-Principal Investigator's NIH Biosketch (if applicable)
Use the most recent NIH biosketch format found on the NIH website. Publications submitted and under review should be indicated on the biosketch. An eRA Commons Username is not required.

d. Co-Principal Investigator's NIH Other Support Document (ifapplicable)
Use the most recent NIH Other Support Document format found on the NIH website. This form must contain all current and pending support from any source. **In addition, specific aims must be listed for current and pending grants that may overlap or appear to overlap with the LLS application.** This includes any grants or portions of grants submitted to any organization, including LLS.

e. Collaboration/Support Letters
Required if reagents critical for the research are to be obtained from non-commercial and/or commercial sources and are not currently available in your lab.

f. Clinical Protocol Synopsis (optional; not to exceed 8 pages)
Attach a Clinical Protocol Synopsis. It should summarize the necessary elements of the trial. DO NOT include the full clinical trial protocol.

g. Assurances (Required)
All assurances that are applicable to your research must be accompanied by a signed letter from the ***appropriate institutional official***, including assurances that are pending. Do not send letters signed by yourself nor from anyone outside of the designated institutional offices.

***Any application without these letters attached will not be reviewed*.**

Full approval for any IRBs that are necessary for the research must be obtained by the award start date.

Description of Assurances

Human Subjects: The applicant must indicate if human materials or subjects will be involved in the proposed research. The status (approved, pending, or exempt) of the Institutional Review Board (IRB or equivalent oversight entity) approval must be provided. The Human Subject Assurance Number (OHRP) must be included. If the research project has received IRB approval, the date must be provided, and documentation must be included in the single PDF of the application.

Projects for which IRB approval is required, but for which IRB approval has not yet been obtained, must include the scheduled IRB review date. The application may be submitted with IRB approval pending but an award will not be made without documented IRB approval. It is recommended that the applicant notify LLS before the grant review if the IRB status has changed.

If a project is exempt from IRB review, the certificate of exemption must be included in the single PDF of the application.

Laboratory Animals: The applicant must indicate if laboratory animals will be involved in the proposed research. The status and date of Institutional Animal Care and Use Committee (IACUC or equivalent oversight entity) approval must be provided. The Animal Welfare Assurance number must be included. Documentation of institutional approval must be included in the single PDF of the application. The application may be submitted with IACUC approval pending but an award will not be made without documented IACUC approval if it was pending at the time of application submission. It is recommended that the applicant notify LLS before the grant review if the IACUC status has changed.

Recombinant DNA: The applicant must indicate if the proposed research involves the use of recombinant DNA. Documentation of institutional approval must be included in the single PDF of the application.

Biohazard Statement: The applicant must indicate if the proposed research involves the use of biohazards. If the applicant indicates affirmatively, then an institutional statement of assurances regarding potential biohazards and safeguards must be included in the single PDF of the application.

Note: Your institution is required to have assurance procedures in place, so please check with them if you are unsure how to obtain your assurance approval documentation.

No attachments besides those listed above can be included in the Appendix.

Applications that include additional documents besides those requested may be administratively disqualified.

Uploading the project document and final submission

All final application documents must be combined into a single PDF in the order listed above. Failure to submit as a single PDF in the order above may result in disqualification of the application. Upload the full application components, as a single PDF, in the "Project and Supporting Documentation" section on the web form. The file upload should be labeled, "ACT Project Description/Application" which you can choose from the document upload drop-down menu. **Do not delete the LOI "Previous Studies/Preliminary Data/Trial Summary" PDF file.**

Fluxx Webform Updates

- **Budgeting Information:** Enter the budgeting information as required on the web form.
- **Applicant Assurance:** Check the box to accept the terms as stated on the web form field.

Save and Review

Validation will automatically occur after clicking the "Save" button. Validation is a safety measure for the applicant to ensure that all required fields are complete. If required fields are empty or incomplete, the system notifies the applicant of fields that require information.

Submission & Confirmation

After clicking the "Submit" button, you will receive an automated email **within 2 business days** stating that your information was successfully submitted. **If you do not receive the email confirmation of submission, contact LLS at** researchprograms@lls.org. Only one application document and one Letter of Intent request document should be present. If extra documents remain after submission and before the deadline, email researchprograms@lls.org and let us know which documents to remove.

Carefully check your PDF prior to submission. If you notice problems with your PDF after you have submitted, email researchprograms@lls.org, and we will help you upload the correct document if you are unable to delete the incorrect document. ***This email must be received, with the correct document, prior to the deadline; there are no exceptions to this rule.***

The applicant is ultimately responsible for the submission, regardless of who actually is

uploading information on the LLS Research Portal. Every year, LLS has a small number of people that notice problems with their application after the deadline. The solution to this problem is very simple and in the hands of the applicant:

- **Check your application prior to final submission.**
- **Submit well ahead of the deadline.**
- **We are not responsible if any applicants are unable to submit by the deadline if our system indicates that:**
  a. **the application procedure was started less than 24 hours before the deadline.** or
  b. **a previously started application file was then only picked up again less than 3 hours before the deadline.**

Once the deadline has passed, only the following updates may be made:

- Regulatory approvals
- Significant updates to clinical trials:
  - IRB updates
  - Opening of the trial
  - Patient enrollment
  - Opening of new clinical sites
  - Efficacy and/or safety updates
- Updates regarding any transfers to a newinstitution

If you plan to withdraw your application at any time during the application cycle, please inform LLS staff of your decision by writing to researchprograms@lls.org.

APPENDIX TO THE LLS-FLF UNITED TO CURE FL (CURATIVE RESEARCH TO ELIMINATE FOLLICULAR LYMPHOMA) AWARD REQUEST FOR PROPOSALS

The Follicular Lymphoma Foundation (FLF) was established in 2019 as an international effort on a mission to identify new treatments and cures for follicular lymphoma (FL).

The Follicular Lymphoma Foundation and LLS are partnering to seek research projects to accelerate the development of therapeutic candidates **with the potential to cure FL at first relapse, either as monotherapy or in a combination approach.**

Through *The LLS-FLF United to CURE FL Award,* FLF and LLS intend to award **up to four research grants**, each providing funding as outlined in the **LLS ACT** (up to $1 million over 2-3 years) or the **LLS TRP** (up to $750,000 over 3 years). These grants would support research projects **focused on FL**, led by Ph.D. level and/or M.D. level investigators.

FLF and LLS encourage investigators with promising ideas to apply.

Background:

While outcomes for patients with FL have improved substantially over the last 40 years, there remains a very high level of unmet need in the FL Patient population. Nearly all patients will experience relapse and often multiple relapses, over the course of their disease. A subset of patients experiences early disease progression or transformation to aggressive disease, with 5-year survival rates as low as 50%. Even patients with more favorable survival rates endure significant challenges - the psychological toll of an incurable, relapsing disease, increasing toxicities of therapies designated for later relapses, and ongoing risk of transformation to aggressive lymphoma.

FL has rarely been the central focus for drug development: historically most drugs available to treat FL were first evaluated for other lymphomas. Putting FL front and center will catalyze focused development of therapies for this underserved patient population.

Ultimately, the goal is to make curative therapies available to FL patients as soon as possible.

Scientific Focus:

Proposals shall focus on accelerating the development of immune system engaging therapies, including cellular (e.g., CAR-T) and humoral (e.g. bispecific molecules) approaches, and/or targeted therapy for FL.

In the long term, rational sequencing of these two classes is likely to be curative in a larger fraction of patients than either single approach. However, combination therapy for FL may not be an appropriate pursuit until more is known about optimal patient selection, mechanisms of resistance, and duration of effect of each distinct class.

As such, programs that advance each therapeutic strategy separately with line of sight to a future combination approach may offer the greatest value to patients in both the near and long term.

1. Immunotherapy: Immunotherapy is very effective against FL in terms of high response rates and durability. Although such therapies are believed to hold great promise for a curative effect, no plateau in relapse-free survival curves is yet apparent.

1.1. Cellular immunotherapy: CAR-T, and others.

Anti-CD19 targeted CAR-T has demonstrated efficacy against relapsed or refractory (r/r) FL. As an example, a 95% overall response rate and 81% complete response in r/r FL patients treated with axi-cel (Yescarta ® , ZUMA-5 study), and with limited but compelling follow up data show many maintaining that response in this study and others. The FDA has approved 4 CAR-T therapies; three of the four are indicated or in NDA for r/r or transformed FL. New CAR technologies are advancing this modality, including the optimization of costimulatory and other CAR domains. However, CAR-T therapies are limited by many factors, such as a small menu of known tumor antigens presented on the cell surface, T cell exhaustion, etc., and others as yet unknown.

For cell therapy, better ways to engineer, grow and target T cells will improve safety, long term efficacy and accessibility. Other immune cells such as NK cells may play a therapeutic role. A more detailed understanding of the host immune system in patients with FL and their lymphoma microenvironment would enhance the development and use of immunotherapies.

1.2. Bi-specific T cell engagers (bispecific antibodies and related constructs):

Bispecific antibodies and related constructs targeting CD20 on B cells and CD3 on T cells are active in patients with r/r FL, with mosunetuzumab FDA approved in later lines of therapy, and other agents in late-stage development, either alone or in combination in earlier lines of therapy. Permutations with different structures, different B and T cell targets, additional co-stimulatory targets, etc are under active investigation. Optimization of many factors regarding BITES could advance outcomes of patients with FL.

As for cellular immunotherapy, understanding and modifying the host immune response and microenvironment are likely to improve outcomes with these agents as well.

2. **Targeted therapy:** epigenetic regulators, and others.

Accumulating data indicates the important roles of epigenetic mutations commonly found in FL. Tazemetostat, FDA approved in 2020 for r/r FL, has shown a 68-82% overall response rate in r/r FL patients with an EZH2 mutation, a lower response rate for wild-type EZH2, but relatively short durations in both groups. HDAC inhibitors have induced overall response rates of 47% - 64%. However, complete response rates and response durations have been low in both classes, and expansion of the epigenetic toolkit has been hampered in part by the difficulty in targeting loss of function mutations. Proposed research investigating targeted therapy is not limited to epigenetic regulators, and other classes of targeted therapies may be proposed if supported by strong biological rationale.

While targeted drugs administered as monotherapies are less likely to achieve curative impact, they still can play an important role in the FL armament. Given the high frequency of FL epimutations, and evidence for their role in tumor evasion of immune surveillance, epigenetic reprogramming could potentially prime, amplify or sustain an immunotherapeutic effect. This class may also be capable of targeting the underlying precursor population, referred to as the common progenitor cell population.

Key considerations for proposals:

- Projects should involve an early phase clinical trial focused on FL that meets criteria for the LLS ACT program.
- Any biologically validated target(s) or novel cell or antibody-based engineering process may be proposed. Regarding targeted therapy development, there is particular interest in epigenetic mechanisms.
- Designs that explore and exploit resistance pathways, e.g antigen escape, T cell exhaustion, etc to current or novel approaches are encouraged.
- Given high industry activity in this space, proposals must articulate how and why philanthropic funding will accelerate the timeline of impactful therapeutic development.

Note that FLF finds it an acceptable strategy to leverage awarded funding in conjunction with additional funding entities, opportunities, or partnerships to achieve described outcomes. Should an applicant choose to pursue an alternative funding pathway, it should be clearly described within the proposed research plan.

Alongside the scientific peer review panel, all applications will be subject to a Patient Review panel. Patients will review the lay summary and description. The potential clinical impact and timeframe of such impact is often of interest to the Patient Review panel.

Please ensure applications include aims with clear milestones (at six-month intervals, starting at month six), extending through the full proposed timeframe.