USCLC National Cutaneous Lymphoma Registry Research Protocol

Sponsor:
United States Cutaneous Lymphoma Consortium (USCLC)

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I. Background

Cutaneous lymphomas are an extremely heterogeneous group of non-Hodgkin lymphomas (NHLs) that primarily manifest in the skin.[1,2] The WHO-EORTC have classified the primary cutaneous lymphomas (PCLs) into cutaneous T and B cell lymphomas[3,4] (Appendix I). Cutaneous lymphomas account for 19% of cases of extranodal lymphomas[5] with the age-adjusted incidence based on SEER data being 9.6 cases per million for cutaneous T cell lymphomas (CTCLs)[6] and 3.9 cases per million for cutaneous B cell lymphomas (CBCL).[7] The most common cutaneous lymphoma is mycosis fungoides (MF) which makes up 53-73% of the patients with CTCL.[5,6] Although the majority of patients do not have evidence by traditional screening methods of extra-cutaneous disease at the time of presentation [and hence fit the classic definition of primary cutaneous lymphoma (PCL)], those patients with certain clinical or histologic subtypes of cutaneous lymphoma commonly have, or will, develop nodal, visceral and/or blood involvement. Standard therapy generally does not offer a cure for these cancers and treatment, at its best, suppresses clinical disease and helps to slow or prevent progression. The prognosis and survival of patients vary not only on the type of cutaneous lymphoma but on the stage and various prognostic factors that are present, the latter which have been slow to identify and are not well validated.[1,8]

There is a tremendous need to improve the treatment and outcome of patients with cutaneous lymphoma and a collaborative, cooperative, multidisciplinary effort is necessary to do so. This goal necessarily starts with a means of collecting information on patients with all types of cutaneous lymphoma using a standardized lexicon and methodology. The diagnosis, evaluation, staging and response criteria for all types of cutaneous lymphoma have recently been either amended or developed by the United States Consortium for Cutaneous Lymphomas (USCLC) and its international cutaneous lymphoma partners, the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC) and published or submitted for publication.[1,9-12] The USCLC is a dedicated group of physicians of various specialties (dermatologists, oncologists, radiation oncologists and pathologists) who collectively evaluate and treat the majority of cutaneous lymphoma patients in the United States and who have established the creation of a national registry for cutaneous lymphoma as the primary goal for the society. The USCLC Registry is a unique initiative at the grass roots level of patient care that will advance the prognosis, survival and quality of life of patients with all types of cutaneous lymphoma.

II. Purpose of the Study

A. Primary: To establish a long term, secure and easily accessible electronic online registry platform for the collection of data on patients with cutaneous lymphoma in the United States

B. Secondary
   1. To determine the incidence and geographic locations of patients with the various subtypes of cutaneous lymphoma in the US
   2. To determine and validate factors for each type of cutaneous lymphoma that may affect prognosis including those related to:
      a. Staging
      b. Pathologic and molecular features of skin, lymph nodes, bone marrow or internal organs
      c. Radiologic characteristics including various types of imaging
      d. Blood tumor burden or blood markers of significance
   3. To determine the efficacy of various treatments or interventions (monotherapies or in combination) for patients with each subtype of cutaneous lymphoma
   4. To enable patients with the various subtypes of cutaneous lymphoma to input data on the effect of their disease and treatment(s) on their and their families' quality of life
   5. To enhance the communication between patients with cutaneous lymphoma and the physicians directing their care

C. Tertiary
   1. To compare and contrast treatment algorithms between study sites
   2. To develop and validate new quality of life metrics for patients with cutaneous lymphoma
   3. To develop meaningful outcome measures that are of value to physician and patient alike
   4. To provide a platform for clinical trials of patients with cutaneous lymphoma to facilitate collaborative research with other national and international organizations
   5. To encourage development of a virtual tissue bank and studies on potential biomarkers of each PCL by encouraging collection of blood/tissue at sites who are participating in the clinical registry
   6. To educate physicians, by their participation in this registry, with best current approaches and treatments of these PCLs and to encourage participation in research studies of same

III. Design and Procedures

A. Platform/Security: All data will be stored on the Answers Ahead platform. Answers Ahead is a HIPAA compliant web based application that uses SSL encryption. All data within Answers Ahead is securely stored on at least three servers for maximum redundancy. Answers Ahead's servers are stored at NAP of the Americas in Miami, FL. This 750,000 square foot TIER-IV data center features N+2 power and cooling infrastructure, category 5 hurricane resistance with approximately 19 million pounds of concrete roof ballast and 7-inch thick, steel-reinforced concrete exterior panels. Armed security guards monitor access to the facility. Servers are stored within a locked cabinet and a limited number of authorized Answers Ahead employees and contractors have access to the physical servers.

   Passwords to access the Registry will be automatically generated by the Answers Ahead platform after confirmation that informed consent form (ICF) has been appropriately authorized by a given subject and emailed to patients and physicians by secure email. Patients will only be identified by their study number within the Registry but may have other identifiers at each site that helps to identify them outside the Registry. Security is in place to shut down access to medical information if a hacker breaches any layer of security.

B. Web portal:
   A. Physicians entering data will access the Registry site through a portal on the USCLC.org website.
   B. Patients entering data may access the patient Registry site through a portal on the USCLC website or through a link provided in the Cutaneous Lymphoma Foundation website

C. Participating sites:
   1. Academic sites with experience in PCLs whose participating physicians see at least 50 new patients per year will be the sites included in the initial phase of the registry.
   2. The total number of participating sites is open ended and may include academic and non-academic sites. Participating sites must meet minimal criteria for capability to diagnose patients with all types of cutaneous lymphoma and to handle all regulatory requirements in order to enter patient data in the Registry. All sites will hold an applicable Office for Human Research Protections (OHRP)-approved assurance.
   3. Each site will have signed a site agreement that will establish ownership and use of data by sites and the USCLC.
   4. Each site will have Institutional Review Board (IRB) approval for the central protocol and an ICF to use at that site.

D. Subject Population:

1. Potential subjects who meet clinical and histologic criteria for a subtype of PCL (standards determined by the USLCL Registry Committee and updated annually) will be identified by participating physicians/investigators at each site, either in their respective clinics or from their site's database or electronic medical record. It is estimated that there are approximately 3000 new cases of PCL per year. Subjects will include all ages, races and sexes who meet the diagnostic criteria.
2. A copy of the diagnostic biopsy report and diagnostic slides must be kept at the primary site. Biopsy slides of the diagnostic biopsy must be available for review by the USCLC Pathology Committee as needed.
3. Each participating site must have a copy of each subject's diagnostic biopsy report uploaded with identifiers removed and only study number attached to the Registry site for review by the Registry Committee. In addition, each biopsy for diagnostic purposes must have been assessed and signed off by a pathologist experienced in cutaneous lymphoma either at their site or in consultation by one of the members of the USCLC Registry Pathology Task Force. In addition, to further confirm the diagnosis, each type of PCL has been determined to have absolute negative and absolute positive clinical and histologic criteria (set by the USCLC Registry Committee and updated as new information becomes available) that if either an absolute negative or the lack of an absolute positive criterium is entered upon initial entry of the subject data, this will trigger a stop from further data entry until review by the lead investigator or Registry Committee.
4. The primary subjects to be consented for the study are those with cutaneous lymphoma seen for the first time by the site investigator/physician and in whom diagnosis was made within the past 6 months. However, participating investigators are encouraged to enter any subject with cutaneous lymphoma that meets the study criteria, including those currently or previously being followed, or those who are deceased and have a waiver of consent. Minors will be considered for inclusion in this protocol only if informed consent can be obtained from their parent or legal guardian and an appropriate minor ICF signed. Female patients of child-bearing potential or who are pregnant or lactating are not excluded from this protocol as the study procedures do not represent any medical risk to the woman or fetus. Except where otherwise granted consent waiver for inclusion, subjects must review and sign the IRB-approved ICF for their site.
5. Incarcerated individuals will be excluded from this protocol.

E. Study Procedures:

1. Consenting process (except in cases where consent is waived):
   a. Academic site consenting:

All participating subjects will be consented before any data is collected. The ICF that is approved by the central IRB will be the template used at each site with modifications as necessary to meet site IRB specifications. However, the data sharing portions of the consent form must remain the same at all institutions. The original of the fully executed consent form should be kept on file at the site. A copy will be sent to the USCLC to confirm it is fully executed after which it will be destroyed by the USCLC.

b. Private practice physician consenting:
Non-academic site physicians who do not have an IRB of record may participate by either having the designated central IRB approve the protocol for their site in which case they would be responsible for the costs of this or instead have their patients participate in the online consenting process which when successfully completed, will give permission for his or her physician to input data on that patient.

c. Once a fully authorized ICF has been collected, each site should internally determine a means of identifying the subject outside the Registry. Subjects' names will be recorded on their consent forms which will be kept securely at the site where consented as part of enrollment tracking and to prevent duplicate entry in cases where any such question has been raised.

d. Registry numbers:
Once it has been determined that the subject has been properly consented and meets all criteria for the Registry, Answers Ahead, the data platform manager, will assign each subject a Registry Study Number that is unique for each subject in the Registry and that is distinct from the site study number or identifiers. The Registry Study Number consists of an institution code, a physician code, and a subject code (example: 0002-03-00125 for site 2, physician 3 at that site and patient 125 at that site). The numerical identifier for each subject is unique across all sites in the Registry. The key linking the subject's name, other identifying information and Registry Study Number will be kept by the institution where informed consent was obtained. Within the Registry, the Registry Study Number will be directly linked to the subject's clinical data.

2. Data collection:
Subjects who meet inclusion/exclusion criteria who are seen at participating academic centers or private practice sites and who have signed an IRB approved ICF (or whose inclusion involves approved IRB waiver) will be eligible to have their data uploaded into the Registry by their participating physician or designee. The following information on subjects will be collected for the Registry:

a. Date of birth, race and sex
b. The subject's current zip code and zip code of greatest time period of residence for the purpose of information on potential geographical factors and to help prevent duplicate entries
c. Clinical, pathologic, radiologic, and laboratory test results from clinic records, hospital charts, study records and outside records sent to participating physicians that are collected or retained within the patient's medical record as part of ongoing patient care.
d. Any treatments, and their response or side effects, used in clinic or in clinical trials to manage patients' disease
e. Any photographs collected as part of clinical care
f. Any photomicrographs of slides from biopsies of skin or other tissue performed as part of the diagnosis and continued care of the patient
g. Any information subjects voluntarily submit to the Registry through the patient online section of the Registry
h. Any data specifically asked of patients as part of their participation in a Registry based clinical trial
i. Any data collected as part of a cooperative clinical trial using Registry data

3. Data entry: Access to data entry will be through the USCLC website portal. All data entry is online only.

4. Plan for protection of subject privacy:

   a. The registry platform creates unique user ID and passwords, does not allow two or more individuals to have the same combination of ID and password and does not allow IDs or passwords to be re-used. Unauthorized attempts to access the system is directed and notification sent to the appropriate personnel. The system limits the duration of a continued controlled session on the basis of time or activity. All access to the registry occurs over an encrypted channel and access to Answers Ahead servers and data is controlled by a combination of role-based security and discretionary access controls to ensure that data is only accessed by authorized personnel using the principle of least-privilege.

   b. Only the subjects' Registry study number will be used when entering data or in sharing data. The key to the identifying information and Registry Study Number will be kept in a secure place at each site.

5. Data use/securing confidentiality of Protected Health Information (PHI): Participating USCLC members will be able to enter information as well as query data on their own subjects at all times. Access privileges within the system will be restricted by site and according to the user's role, ensuring

USCLC members of the security and confidentiality of their data. The USCLC has guidelines for the use of aggregate data including publications prior to any analysis or publication.

6. Ownership of data: The de-identified data entered into the Registry belongs to the USCLC but the identified data belongs to each user/site that consented the patient. Each user/site may use the data he/she enters as his/her own database and can at all times access this dataset. Once data is entered into the Registry, it may not be withdrawn from aggregate use by the USCLC. However, the USCLC may not use data other than that collected prospectively by sites without specific site agreement.

7. Data sharing:
    a. The USCLC may share collective limited data sets with agencies, groups or individuals outside the USCLC. Proposals must be presented in writing to the USCLC Registry Committee who will determine if the proposal's purpose is in line with USCLC objectives and goals.
    b. The USCLC may wish to do cooperative studies with entities outside the USCLC in order to advance knowledge of cutaneous lymphoma. The protocols for these studies and any costs related to the USCLC for seeing that the study is conducted in accordance with the specifics of the protocol must first be approved by the USCLC Registry Committee. The protocol for the study will then be submitted to the participating sites' respective IRBs for further approval. Any data provided to entities outside the USCLC will not include direct identifiers and will be done under a data use/data transfer agreement between the entity and the USCLC. Subjects are queried in the consent form whether they approve the sharing of their data under these conditions and only those subjects approving this will have their data shared in cooperative studies.
8. Future studies:
    Any USCLC member, sponsor, institution, company, or foundation may propose a research study using the Registry data to the USCLC Registry Committee. The USCLC has guidelines for the standardized process to submit potential study proposals to the Registry Committee for review. Approval for any proposal will be based on the scientific acumen, the alignment of goals with that of the USCLC and coverage of costs by the USCLC for conducting or participating in the study.

IV. Risks

Risks to subjects will be limited to a potential risk of loss of confidentiality, which we will attempt to minimize by de-identifying any data slated for analysis and maintaining the code linking the subject name and Study Registry Number only at the site.

V. Benefits

There are no direct benefits to subjects. Information regarding prognosis and response to treatment will be generated which will potentially improve subject outcomes in the future. In addition, subjects will have the ability to enter their own conclusions about the therapies used and the overall effect of these and their cancer on their quality of life which will be communicated to the physician treating them. The hope is that this will enhance patient-physician communication.

VI. Costs to the Subject

There are no costs to subjects participating in this registry study.

VII. Statistical Analysis

A. Regular analysis of the following is planned as part of the ongoing data collection and review of the registry.

1. Relative frequency of each subtype of PCL at each site
2. Geographic location of each patient with PCL and where patients are being treated relative to home location
3. The initial treatment(s) for each stage of each subtype of PCL and response to treatment, survival and if deceased, cause of death
4. The correlation of clinical, histological, radiological and/or blood tumor burden in relationship to outcome (freedom from progression, objective response to treatment, survival) especially for those with the more aggressive cutaneous lymphomas
5. The correlation of patient and physician input on response to treatment for each subtype of PCL
6. The correlation of severity of disease by patient and physician

B. Statistical methods:

1. For continuous variables, descriptive statistics such as mean, standard deviation, and range for demographics and subject staging characteristics at baseline will be obtained.

2. Categorical variables (e.g., race, gender, etc) will be reported as frequency and percentages. For categorical variables, chi-squared test of Fisher's exact test will be used as deemed appropriate.

3. Standard Kaplan-Meier curves will be generated for stage, individual variables, therapy/response to therapy and survival.

4. Response to treatment will be compared by different choice of treatments using t-test or the method of analysis of variance (ANOVA) when comparing more than two groups. If the variable does not follow normal distribution, the comparison will be performed using non-parametric tests such as Mann-Whitney test or Kruskal-Wallis test.

5. Cluster analyses will be performed to determine the number and different types of cutaneous lymphoma dependent on the significant correlated variables, such as geographical location, clinical variables and responses to therapy and prognosis.

VIII. Data Management

Each site will be responsible for all regulatory issues related to data collection, entry and storage at their site but will inform the Central Administrative Site designated by the USCLC of their initial and annual IRB approvals and any specific violations or deviations from standard procedures at their site. Only in the case of a specific collaborative study protocol using the Registry data that has been approved with specific requirements of study participants will the designated Central Administrative Site be required to take specific action to insure compliance with the protocol. Answers Ahead will provide reports on each site periodically to the USCLC that will indicate what data has been entered and what is lacking.

IX. Data Storage and Confidentiality

Study records that identify the subject will be kept confidential as required by law. Except when required by law, subjects will not be identified by name, social security number, address, telephone number or any other direct personal identifier in study records disclosed outside of participating institutions. Each site must retain records of their subjects according to site specific IRB requirements.

X. SAFETY AND UNANTICIPATED PROBLEMS

A. Unanticipated problems including deviations, violations and adverse events must be reported, as required by site IRB regulation, by each site to their site IRB
   1. Potential problems include, but are not limited to, a consent form not signed prior to uploading data into the Registry, the wrong version of a consent form utilized, a fully executed consent form not kept on file, a misinterpretation of a type of cutaneous lymphoma, or a breach of confidentiality at the site.

2. Qualifying unanticipated problems should be reported to local site IRB.

B. For this registry, adverse events or experiences are those which are:
   1. Unexpected in terms of nature, severity, or frequency.
   2. At least possibly related to the procedures involved in the Registry research.
   3. Any event that indicates that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.
   4. Sites should immediately notify their IRB of any adverse events or experiences as required locally.

C. Deviations are inadvertent acts (from the perspective of the PI and study staff) in which the protocol is not followed. Sites should notify their IRBs immediately upon the discovery of a protocol deviation

D. Violations are intentional acts (from the perspective of the PI and study staff) in which the protocol is not followed. Each site must notify their site IRB immediately upon the commission of a protocol violation or to prospectively submit a planned violation as required by the site institutional IRB.

XI: Compliance

To help to insure compliance with the protocol, the Registry Committee will provide copies of the following for each participating site:

A. The protocol, study objectives, eligibility requirements, study procedures, enrollment and withdrawal processes
B. Good Clinical Practice guidelines and related regulatory documentation requirements (Appendix II)
C. Key study team roles and responsibilities
D. Subject coding and enrollment
E. Protocol compliance
F. Clinical study record keeping, document retention, and administrative requirements

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Appendix I: WHO/EORTC Classification of Cutaneous Lymphomas

Cutaneous T-cell and NK-cell lymphomas
- Mycosis fungoides
- MF variants and subtypes
  - Folliculotropic MF
  - Pagetoid reticulosis
  - Granulomatous slack skin
- Sézary syndrome
- Adult T-cell leukemia/lymphoma
- Primary cutaneous CD30+ lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified
- Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
- Cutaneous γ/δ T-cell lymphoma
- Primary cutaneous CD4+ small/medium-sized pleomorphic lymphoproliferative disease (provisional)
- Primary cutaneous acral CD8+ T cell lymphoma (provisional)

Cutaneous B-cell lymphomas
- Primary cutaneous marginal zone B-cell lymphoma
- Primary cutaneous follicle center lymphoma
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Primary cutaneous diffuse large B-cell lymphoma, other
  - Intravascular large B-cell lymphoma
  - EBV+Diffuse large B-cell lymphoma of the Elderly
- Lymphomatoid granulomatosis

Precursor hematologic neoplasm
- Blastic plasmacytoid dendritic cell neoplasm

*As modified from Willemze 2005[1], Campos 2008[2] and personal communication, Rein Willemze June, 2015

Appendix II: Standards of Procedures in Participation of a Multicenter Study sponsored by the USCLC

I. Each site will have to complete a Site Agreement with the USCLC and obtain IRB approval before the start of enrollment. Failure to adhere to required regulatory procedures may result in temporary accrual suspension or study termination at the site in question. All participating multicenter site physicians must be current members of the USCLC.

II. Investigator Responsibility

A. Institutional Review Board (IRB) / Ethics Committee (EC) Approval
No patient will be enrolled in the study until site has successfully obtained IRB approval by their own IRBs. Copies of all submissions to and correspondence (approvals and disapprovals) from the IRB must be maintained on file at the study site.

III. Informed Consent –The specific requirements for a valid authorization are**:**

- The information
- Who may use or disclose the information
- Who may receive the information
- Purpose of the use or disclosure
- Expiration date or event
- Individual's signature and date
- Right to revoke authorization
    - You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.
    - Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at your institution. If you do decide to withdraw, we ask that you contact Dr. [PI] in writing and let [him/her] know that you are withdrawing from the study.
    - Refuse to sign authorization.

IV. Protection of Human Subjects: This study will be conducted according to Good Clinical Practices (GCP), the rules and regulations of the IRB at each participating institution, and in accordance with state and federal agencies.

V. Records and Reports
    I. Good Clinical Practice Guidelines require that investigators maintain information in the patient's medical records, laboratory reports, clinic charts, etc. that corroborates data recorded in the Registry. All participating Investigators must establish and maintain records and reports. The Investigator must maintain the signed Informed Consent Forms, CRFs, study documentation and source documents for either at least 6 years after study completion or termination or per local IRB policy whichever is longest. Study records involving pediatric research participants must be maintained until the youngest child on study is 21 years old, or for six years following completion of the study, whichever is longer, or per local IRB policy whichever is longest.