
ACCELERATE: AN INTERNATIONAL, OBSERVATIONAL REGISTRY FOR PATIENTS WITH CASTLEMAN DISEASE

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ACCELERATE is an acronym for “Advancing Castleman Care with an Electronic Longitudinal registry, E-Repository, And Treatment/Effectiveness research.”

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STUDY SUMMARY

Title	ACCELERATE: AN INTERNATIONAL, OBSERVATIONAL REGISTRY FOR PATIENTS WITH CASTLEMAN DISEASE
Short Title	Castleman Registry
IRB Number	824758
Protocol Number	N/A
Methodology	Observational
Study Duration	Open-ended
Study Center(s)	Physician directed patient enrolment in 24 sites in Europe (EU), Latin America (LA), and Asia-Pacific (AP). Patient self-enrolment in North America and rest of world outside of the above mentioned sites, according to local regulations.
Objectives	Primary: - To collect real-world demographic, clinical, laboratory, Patient Reported Outcome (PRO), and treatment data on patients with Castleman disease. Secondary: - Carefully define clinical features and biomarkers associated with Castleman disease to inform diagnostic criteria and identify subgroups of patients - Inventory Castleman disease treatments and assess their effectiveness and safety profiles - Collect data on survival of Castleman disease patients and quality of life metrics - Inventory the types and locations of clinical tissue samples that may be available for future research.
Number of Patients	We expect to enroll 600 Castleman disease patients in the first five years.
Main Inclusion and Exclusion Criteria	To be eligible for the registry, patients must satisfy all of the following inclusion criteria: - Person of any age; - A reference pathology report suggesting “Castleman disease” (not limited to cutaneous involvement only) can be located and uploaded; - Have the ability to understand and complete an informed consent process where applicable per local regulations
Intervention	This is a non-interventional registry of patients with Castleman disease.
Statistical Methodology	The registry is designed to generate data for informational purposes. As a result, reporting will be descriptive and no formal hypotheses are to be tested. The statistical analysis plan for this registry will include analyses of demographics and baseline disease characteristics, treatment effectiveness data, biologic parameters, safety data, and comparability between treatment groups.
Data and Safety Monitoring Plan	The registry will be governed by an ACCELERATE Steering Committee (ASC) and Certification & Access Subcommittee (CAS). The ASC will be responsible for the data quality management and the ongoing safety of patients.

Background and Study Rationale

1 Introduction

This document is a research protocol for a human research study. This study will be conducted in full accordance with the provisions set forth in the protocol as well as with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the HIPAA Privacy Rule.

The University of Pennsylvania (“UPenn” or “Sponsoring Institution”), in collaborative partnership with the Castleman Disease Collaborative Network (CDCN) and Janssen Pharmaceutica NV, will establish ACCELERATE, a prospective, international, observational, web-based registry of pathologically confirmed Castleman disease.

1.1 Background and Relevant Literature

Castleman disease describes a group of rare and heterogeneous disorders that share common lymph node histological features and heterogeneous clinical characteristics. Unicentric Castleman disease (UCD) occurs in a single lymph node and is typically asymptomatic.¹ Multicentric Castleman disease (MCD) involves multiple enlarged lymph nodes, systemic inflammatory symptoms, proliferation of reactive lymphocytes, multiple-organ system dysfunction, and death, if improperly treated, due to excessive release of proinflammatory cytokines, such as Interleukin-6.²

The 10-year overall survival rate was approximately 40% in a 2012 series of 60 MCD cases, up from 13% in a 1993 series of 38 patients.^{3, 4}

1.2 Etiology and Epidemiology

Human Herpes Virus-8 (HHV-8) is the well-established cause for MCD in HIV-positive patients and in some HIV-negative patients that are immunocompromised (e.g., post organ transplantation).⁵ In these HHV-8-associated MCD cases, immunodeficiency enables HHV-8 to escape from host immune control, lytically replicate in lymph node plasmablasts, and signal the release of viral IL-6, human IL-6, and several other proinflammatory proteins.⁶ There is also a group of HIV-negative and HHV-8-negative MCD patients, in which the disease is referred to as idiopathic MCD (iMCD). The etiology of iMCD proinflammatory hypercytokinemia is not known and may be viral, inflammatory, or neoplastic.⁷

The proinflammatory hypercytokinemia in MCD causes:

- Production of acute-phase reactants
- Proliferation of polyclonal lymphocytes and enlargement of lymph nodes
- Synthesis of polyclonal immunoglobulins, which can cause auto-antibody production;
- Cytopenia, such as anemia, which may lead to fatigue; thrombocytopenia, which may cause abnormal bruising and bleeding; and leukopenia, which may contribute to an increased risk of infection
- Increased synthesis of hepcidin by the liver, which can cause anemia
- Fluid overload (e.g., edema, ascites, pleural effusions, anasarca) and capillary leak syndrome due to excessive vascular endothelial growth factor (VEGF) secretion and hypoalbuminemia, which can cause acute kidney injury

The incidence of UCD and MCD has not been established; a recent study estimates 4,353 new cases of Castleman disease per year in the US, which has been approximated to include 1,000 new cases of MCD.⁸ Estimates have not been performed on European data sets, but there is no evidence to suggest that the incidence differs between populations globally. iMCD can occur at any age, but it typically affects individuals in the fourth and fifth decades of life and it is slightly more common in males than females.^{1, 3} Better understanding of epidemiology, prognostic factors, and outcomes are needed.

1.3 Clinical, Laboratory, and Pathologic Features of Castleman disease

UCD is typically asymptomatic and curative with lymph-node resection. UCD patients can sometimes demonstrate symptoms beyond localized lymph-node enlargement. Occasionally the lymph node can be in a location that does not allow resection. Also, these patients can develop paraneoplastic pemphigus and bronchiolitis obliterans organizing pneumonia, which are both life-threatening.

The clinical spectrum of MCD (both HHV-8-associated MCD and iMCD) ranges from waxing and waning mild lymphadenopathy with B-symptoms (e.g., fevers, fatigue, weight loss, night sweats) to more severe cases involving intense inflammation; hepatosplenomegaly; vascular leak syndrome with anasarca, pleural effusions, and ascites; organ failure; and even death.³ Acute episodes can display significant clinical overlap with acute viral illnesses and autoimmune diseases.² Skin involvement in the form of cherry hemangiomas often occurs. Clinical differences can be observed between ethnic groups. Patients of Asian descent often display large violaceous skin lesions and interstitial pneumonitis,^{9, 10} and Polynesian patients demonstrate a mild clinical course despite significant biochemical derangements.¹¹

Laboratory abnormalities commonly include anemia, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, IL-6, VEGF, and fibrinogen; positive anti-nuclear antibody (ANA), anti-erythrocyte autoantibodies, and anti-platelet antibodies; proteinuria, hypoalbuminemia, polyclonal plasmacytosis, polyclonal hypergammaglobulinemia (HGG), and thrombocytosis or thrombocytopenia.¹² Kawabata et al. described a group of iMCD patients in Japan with TAFRO features (thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly), which demonstrate milder lymphadenopathy, mixed or hyaline vascular (HV) histopathology, severe thrombocytopenia, normal or mildly elevated levels of IL-6 and VEGF, the presence of autoantibodies, severe anasarca, and normal immunoglobulin levels.¹³ These same features have also been observed in iMCD patients throughout the world.

There are also a host of neoplastic, infectious, and autoimmune diseases reported to co-occur with iMCD, for which it is difficult to differentiate or determine a causative relationship from limited case reports since there is no official diagnostic criterion. The differential diagnosis of Castleman disease may include autoimmune lymphoproliferative syndrome (ALPS), multiple myeloma, Epstein-Barr infection, monoclonal gammopathy of undetermined significance (MGUS), AL amyloidosis, B-cell non-Hodgkin's lymphoma (including Waldenström macroglobulinaemia), chronic lymphocytic leukemia, and connective tissue disorders. An initial diagnostic workup to exclude other possible diseases may include complete blood count with differential and peripheral blood smear; ESR; CRP; ANA; bone marrow aspirate and biopsy; lymph node biopsy, including testing for HHV-8 via LANA-1 staining or PCR; clinical chemistry tests, including blood urea nitrogen (BUN), serum creatinine, serum electrolytes, serum calcium and serum albumin, serum β 2-microglobulin and lactate dehydrogenase; serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) and immunofixation; routine urinalysis, 24-hour urine collection for electrophoresis and immunofixation; measurement of serum free light chains; and cytogenetics (metaphase karyotype and FISH).

Once diagnosed, all Castleman disease cases should be subclassified based on centricity (unicentric vs multicentric), HHV-8 status, and lymph-node histological morphology (HV, plasma cell [PC], mixed [M], plasmablastic). HV is characterized by widened mantle zones composed of concentric rings of small lymphocytes in an "onion skin" pattern around small atrophic germinal centers with penetrating hyalinized vessels and dysplastic follicular dendritic cells (FDC).¹⁴ In PC, the germinal centers are hyperplastic rather than atrophic, the interfollicular region contains sheets of plasma cells and vascular proliferations, the FDC network is normal, and there is preserved lymph-node architecture.¹⁵ The mixed variant displays features of both HV and PC. The plasmablastic variant is only found in HHV-8-associated MCD.

1.4 Current Treatments for Castleman disease

Surgical excision of the enlarged lymph node is curative in most cases of UCD.¹ B-cells are the host for HHV-8, and off-label use of rituximab for B-cell depletion is the best studied therapy that is generally effective in HHV-8-associated MCD. Antivirals and/or cytotoxic chemotherapy with liposomal doxorubicin have been added in patients with severe symptoms or concurrent Kaposi sarcoma cases.¹⁶

The only approved treatment for iMCD is through blockade of IL-6 signaling with monoclonal antibodies (mAbs): Siltuximab, an anti-IL-6 monoclonal antibody (mAb) that is approved to treat HIV-negative and HHV-8-negative MCD by the USA FDA Food & Drug Administration (Apr 2014), the European Commission (May 2014), and Health Canada (Dec 2014), demonstrated durable tumor and symptomatic response at a significantly higher rate compared with placebo in the first randomized Phase II study in MCD (34% vs. 0%; $p=0.0012$).^{17, 18} Tocilizumab, an anti-IL-6 receptor mAb that is approved to treat MCD in Japan, has demonstrated effectiveness at inducing and maintaining remission in a small study, mainly involving iMCD patients.¹⁰

Three main off-label treatment strategies have been employed in iMCD, but their effectiveness and safety have not been prospectively studied⁷:

- **Anti-inflammatory and immunosuppressive therapies:** Corticosteroids can improve symptoms during acute exacerbations of iMCD, but most patients relapse during steroid tapering.^{19, 20} Immunosuppressive therapies, particularly cyclosporine A, are being used more frequently as some physicians are treating iMCD more like a systemic inflammatory disease.^{21, 22}
- **Cytotoxic chemotherapy:** Cytotoxic lymphoma-based chemotherapies (e.g., cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) induce responses in a large portion of the most severely ill iMCD patients by eliminating a large portion of IL-6-secreting cells, but relapses are common and side effects are significant.^{23, 24}
- **Immunomodulation:** The mAb, rituximab, is frequently used in iMCD, but appears to be only partially effective and typically does not provide long-term disease control.²⁵⁻²⁷ Select other immunomodulatory agents with reported activity include: bortezomib, a proteasome inhibitor that targets plasma cells, has been noted to lower IL-6 levels and induce remission in four reported cases of iMCD;²⁸⁻³⁰ thalidomide, an immunomodulator that inhibits TNF- α , IL-1, IL-6, IL-12, and VEGF and stimulates T-cells potentially via cereblon inhibition, has demonstrated effectiveness at inducing remission, decreasing IL-6 levels, and lowering CRP in iMCD;³¹⁻³³ and anakinra, an IL-1 receptor antagonist, which has also been reported to induce remission in a pediatric case of iMCD and in a patient who did not respond to anti-IL-6 therapy.^{34, 35}

1.5 Overall Rationale for the Registry

While progress has been made in patient outcomes over the last 20 years, there is a lack of data relating to clinical features, laboratory data, comorbidities, treatment effectiveness, safety profiles, and outcomes for Castleman disease. There are also many gaps in our understanding of disease pathogenesis. Gathering objective demographic, clinical, laboratory, patient reported outcomes (PRO), and treatment data will help to advance patient care. The Scientific Advisory Board (SAB) of the CDCN identified building a natural history registry as the top priority to answer many of these unknowns in 2012.

When the European Medicines Agency (EMA) approved siltuximab for use in Europe in 2014, they imposed a post approval measure ("PAM") on the makers of siltuximab (Janssen Pharmaceutica NV) to carry out a disease registry study of patients that are on siltuximab or siltuximab eligible, which would include anyone with HIV-negative, HHV-8-negative multicentric Castleman disease regardless of treatment or anyone on siltuximab through off-label use. The EMA required that Janssen Pharmaceutica NV enroll either 100 patients or remain open for 5 years whichever is greater through this disease registry.

In an effort to improve understanding of CD and also meet the EMA's PAM, the CDCN, UPenn, and Janssen Pharmaceutica NV joined together to establish plans for ACCELERATE, a prospective, international, observational, web-based registry of pathology-confirmed Castleman disease. ACCELERATE will use an innovative registry study design to integrate data from medical records, patients, and physicians. The resulting data analyses will provide information about the natural history of the disease, aid in evaluating the effectiveness and safety profile of treatments, and provide insights into the pathogenesis of the disease. These data, in turn, may lead to improvements in its diagnosis and treatment, and they will be shared with the Castleman disease community through the CDCN website, information sheets, peer-led publications, and international scientific presentations. The EMA reviewed an initial protocol submitted in December 2014 and concluded on April 23, 2015 that "the design of the registry is considered acceptable." Tabulated data from the registry will be submitted by Janssen Pharmaceutica NV to the EMA every six months to fulfill the

EMA's PAM requirement. No specific requirements were imposed by the EMA for specific data elements, such as treatment efficacy or safety data, to be collected.

These three collaborative partners and Principal Investigator (PI), Dr. David Fajgenbaum, are uniquely qualified to carry out this project. The CDCN is the only organization solely dedicated to advancing research and care for Castleman disease patients and will provide scientific guidance. UPenn is an academic institution at the forefront of Castleman disease and orphan disease research. Janssen Pharmaceutica NV is the manufacturer of the first-ever and only FDA, EU, and Canadian-approved therapy for HIV-negative and HHV-8-negative MCD (idiopathic or "iMCD"). Dr. Fajgenbaum is considered an authority on Castleman disease, and has engaged with hundreds of Castleman disease patients, physicians, and researchers over the last five years. He has assembled the world's 28 Castleman disease experts on the CDCN Scientific Advisory Board, organized the four largest-to-date MCD research meetings and two largest patient summits, and build a 300+ database of treating physicians and interested researchers around the world.

2 Study Objectives

2.1 Primary Objective

- Collect real-world demographic, clinical, laboratory, PRO, and treatment data on patients with Castleman disease.

2.2 Secondary Objectives

- Carefully define clinical features and biomarkers associated with Castleman disease to inform diagnostic criteria and identify subgroups of patients
- Inventory Castleman disease treatments and assess their effectiveness and safety profiles
- Collect data on survival of Castleman disease patients and quality of life metrics
- Inventory the types and locations of clinical tissue samples that may be available for future research

This registry is designed to generate data from medical records, physician surveys, and patient surveys for informational purposes and to serve as a resource for future analyses. Thus, the results will be presented descriptively and no formal hypotheses will be pre-specified.

3 Organization of Study Protocol Document

Overview of Two Arms of Registry

The registry will enroll patients and collect data through two different sets of procedures.

- “Patient-powered arm” (PPA) - Patients located anywhere in the United States of America (USA), Canada, or rest of world (except for patients enrolled through the physician-directed arm below) will be able to enroll themselves directly into the registry via the PPA and consent to medical record data written in English being extracted by the ACCELERATE Registry Team (ART) at UPenn and, when available, electronic medical record data automatically being sent to and integrated into the ACCELERATE registry. Also, per location, additional data may be collected through ongoing medical record updates and physician and patient surveys. Family members of deceased patients will also be able to enroll their deceased family members with Castleman disease into the registry, per local regulation.
- “Physician-directed arm” (PDA) - Physicians (“Participating Physicians”) at 24 study sites in EU, LA, and AP have been selected to serve as the 24 lead investigators for the PDA. These Participating Physicians and site staff will consent and enroll patients and perform data entry in English. Additional data may also be collected through patient surveys, per local regulation. The ART will serve as the Global Data Coordinating Center for all data collected through the PPA and the PDA. As Global Data Coordinating Center, the ART will be responsible for executing the Statistical Plan, monitoring data collecting and safety, reporting, and managing data access and migrations.

Data Collection Between Regions

	Patient-Powered Arm	Physician-Directed Arm
IRB/IEC	Central IRB approval at UPenn. IRB/IEC approval not required at patient’s physician’s institutions	Each of the 24 registry sites in EU, LA, and AP gain IEC approval as applicable for the registry
Patient Enrollment/ Consent	Patient or family member of deceased patient directly enrolls through web-based portal	Participating Physicians at the registry sites enroll patient
Process for Medical Record Delivery	ART contacts institutions for medical records; Patients may also send their records in English directly to ART by fax, email, or mail; and/or, when available, electronic medical record data will be automatically sent to and integrated into the registry (see Section 24)	If patient was previously seen by another physician or institution, the Participating Physician will request these records be sent to him/her for data entry
Primary Data Source	Medical records and prospective clinical notes extracted by ART at UPenn and/or, when available, electronic medical record data automatically sent to and integrated into the registry	Medical records entered by site staff at registry site and prospective data entry by site staff based on clinic visits and hospitalizations
Additional Data Sources (optional)	Physician surveys and patient surveys, if allowed by local regulation	Patient surveys, if allowed by local regulation
Biospecimens	Lymph node and/or bone marrow slides (and/or tissue blocks to generate slides) may be sent to ART to be scanned and uploaded to assist with grading likelihood of accurate diagnosis, if allowed by local regulations	Lymph node and/or bone marrow slides may be scanned and uploaded to the database by the Participating Physician to assist with grading likelihood of accurate diagnosis, if allowed by local regulations

Organization of Study Protocol Document

Herein, this registry protocol document is broken up into three parts.

- Part A of this document describes the protocol for enrollment and data collection for the Patient-Powered Arm (PPA).
- Part B of this document describes the protocol for the Physician-Directed Arm (PDA).
- Part C of this document describes the UPenn study team's role as the Global Data Coordinating Center for the PPA and PDA.

PART A: Patient-Powered Arm (PPA)

4 Investigational Plan for PPA

4.1 General Design for PPA

The proposed study is a non-interventional, observational, multi-national, multicenter, prospective, natural history study registry of patients with pathology-confirmed Castleman disease. The ACCELERATE Registry database will collect data from the following sources:

- Patient medical records
- Physician surveys via a physician portal
- Patient surveys via a patient portal

All patients must give their informed consent to participate in this registry before any data collection is performed. Patients will enroll themselves directly into the registry and consent to medical record data extraction by the ACCELERATE Registry Team (ART) and/or, when available, compatible electronic medical record data automatically sent to and integrated into the registry via an online consent process. After the patient signs the electronic consent to participate in the study, the patient will also provide a signature to allow release of medical records to the study team (see Section 11.2). Patients will need to upload a reference pathology report suggesting "Castleman disease" or the ART must be able to locate and upload such a pathology report in order to enter the baseline data collection stage. Family members of deceased Castleman disease patients may authorize the enrollment of deceased patients into the study (see Section 10.6).

During the baseline stage, patient medical records will be collected and retrospective baseline data extracted into a Pulse InfoFrame database by the ART. Patients and physicians will also be able to provide additional data via surveys. Following the baseline data collection stage, patients will enter the prospective data collection stage where observational methodology will be used to collect prospective clinical, laboratory, PRO, and treatment data (efficacy, safety) for all patients whenever available. At least every 12 months, data from clinical visit notes, medical records from hospitalizations, physician and patient surveys, and/or, when available, compatible electronic medical record data will be automatically added to the database.

A panel of international experts on the Certification/Access Subcommittee (CAS) will meet periodically throughout the duration of the registry to review every patient's data to grade the likelihood of the patient's diagnosis with Castleman disease. When available, the CAS will also be able to review participants' unstained lymph node and/or bone marrow slides to assist with grading, if acquired by the ART and permitted by local regulations. The CAS will not exclude patients from the database, but will provide a grade for the likelihood of correct diagnosis with Castleman disease.

4.2 Data to be Collected

Data elements to be collected and entered into the registry database include elements that fall under the below categories, as available through routine clinical practice.

4.2.1 Categories of registry data elements

- Contact information and socio-demographics
- Diagnoses, Family History, and Anthropometric

- Pathology
- Laboratory
- Clinical features
- Radiographic
- Hospitalizations
- Surgeries and procedures
- Co-morbid conditions
- Flares, treatments, and adverse events
- Survival/Outcomes
- Clinical research participation and biospecimens
- Physician reported data
- Patient reported outcomes data

4.2.2 GUID and PHI Elements Collected

Data collected through ACCELERATE will be coded by the ART so that direct patient identifiers are not exposed to future researchers. A Global Unique Identifier (GUID), a computer-generated alphanumeric code that is unique to each research participant, will be generated for each patient through complimentary software provided by the National Institute of Health. The following information is needed to generate an encrypted GUID:

- Complete legal given first, middle and last names of patient at birth
- Date of birth
- Name of city/municipality in which patient was born
- Country of birth
- Physical sex of patient

The GUID enables data from a coded patient to be integrated; tracked over time; and linked across projects, databases and biobanks. The CDCN is in the process of launching several translational research studies and building a biobank for storing tissue samples. All of these projects will use the GUID to track participants. Researchers will be able to request coded data, which may include indirect identifiers but no direct identifiers, from multiple data sources and identify common patients through the GUID.

For patients who additionally give permission to be re-contacted at a later date, their preferred method of contact will also be stored in a protective fashion. This may include phone number (cell, work, or home), fax number, home or business address, or electronic mail address.

Additional Protected Health Information (PHI) that will be collected for the registry includes:

- All elements of dates directly related to an individual, including birth date, admission date, discharge date, diagnosis date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
- The last four digits of Social Security numbers to assist with acquiring medical records;
- Full Social Security numbers to assist with acquiring medical records and to check death records (will be an option for selection in the informed consent process);
- Medical record numbers to assist with acquiring medical records.

Direct identifiers that are flagged as PHI, which will be marked as an attribute on the table, will not be available to data export functionality. These data containing direct identifiers will only be visible to the PI, ART, and Certification & Access Subcommittee (CAS), who have all been trained in procedures of patient confidentiality. No direct identifiers will be available as data output from the registry to future researchers. Limited indirect identifiers will be shared. The purpose of maintaining this PHI will be to facilitate the entry of follow-up data into the registry.

4.3 Study Measures

There is no standard for assessing activity of Castleman disease or response to therapy in routine clinical practice. The registry will attempt to comprehensively document common symptoms, radiologic responses, and biological parameters in accordance with patients' routine care, and response may be evaluated using these data. Key clinical features, including lymphadenopathy, constitutional symptoms (Sweats, fever (>100.5), weight loss, fatigue (> 2 CTCAE score)), large spleen and/or liver, fluid overload (edema, anasarca, ascites, effusions), eruptive cherry hemangiomas or violaceous papules on the skin, and interstitial pneumonitis, will be assessed for all patients. The primary data source will be the medical records of each enrolled patient, which will be collected and entered into the electronic case report form (eCRF) by the ART at baseline and from clinic notes prospectively. Also, when available, compatible electronic medical record data will be automatically sent to and integrated into the registry (see section 24). Patients will also be able to complete the below questionnaires via a patient portal on the ACCELERATE website. Reminders to enter data into the portals every 3 months will be emailed to each participant with easy link to their own data collection page. Two reminders will be sent to the participant. The first reminder will be sent automatically 2 weeks before the survey due date, and if necessary, the second reminder will be sent automatically on the survey due. The ART will then follow-up with the participant via email, phone, or mail as needed. At each data entry time-point, participants will be asked for their most recent phone number, email and physical address.

Optional Patient surveys

The multicentric Castleman Disease Symptom Scale (MCD-SS)³⁶ will be used to assess 16 patient reported symptoms (see Attachment in Section 32.3). Scores range from 0 to 5. The MCD-SS will be completed by patients at the following time points:

- *At the time of enrollment to establish a baseline score*
- *Every three months after enrollment*

European Quality of Life-5 dimensions (EQ5D-5) (see Attachment in Section 32.3) will be used to provide insight into the health-related quality of life impact of CD across five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The EQ5D-5 will be completed by patients at the following time points:

- *At the time of enrollment*
- *Every three months after enrollment*

A self-reported flare (SRF) assessment (see Attachment in Section 32.3) will be used to record patients' personal perspectives and accounts of disease activity as well as collect dates of flare activity. To limit self-report error, a participant flare definition describing an autoimmune illness with symptom fluctuations, which has been used previously for systemic lupus erythematosus flare self-reporting, will be provided.³⁷ An exacerbation is defined as: The appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom that had been stable for at least the previous 30 days and which persisted for a minimum of 24 hours.³⁸ The SRF will be completed by patients at the following time points:

- *At the time of enrollment*
- *Every three months after enrollment*

Patients will also be asked to complete surveys to confirm information collected from medical record data. These surveys will be tailored based on information contained in the patient's medical record. Categories of questions may include dates and reasons for hospitalizations, past medical history, current and past medications (an online log of medications with dates will be provided for them), and dates of recent doctors visits. For example, "have you been hospitalized for any reason over the last 3 months (or since last completing this questionnaire)?" Patients may be shown a timeline displaying when their hospitalizations, flares, and treatment regimens began and ended. The tailored survey will be completed by patients at the following time points:

- *At the time of enrollment*
- *Every three months after enrollment*

4.4 Study Endpoints

4.4.1 Primary Study Endpoints

This registry is designed to generate data for informational purposes and as a resource for future analyses. Thus, the results will be presented descriptively and no formal hypotheses will be pre-specified or endpoints assessed.

5 Study Population and Duration of Participation for PPA

5.1 Duration of Study Participation

This is an open-ended study. The registry will exist for at least 5 years after the first patient is enrolled. Patients can leave at any time.

5.2 Total Number of Patients and Sites

Prospective enrollment will be an ongoing effort for at least five years, without a fixed end date or target patient number. We expect to enroll approximately 450 patients into the registry from the PPA (mostly in North America) in the first five years. With concurrent enrollment in the PDA, we anticipate our total patient numbers at approximately 120 per year and 600 over the course of the first five years. UPenn is the only location involved in the PPA, but no patients will be enrolled through UPenn clinical staff. All patients will enroll into the PPA through the ACCELERATE website.

5.3 Inclusion Criteria

To be eligible for the registry, patients must satisfy all of the following inclusion criteria:

- Person of any age
- Have a reference pathology report suggesting “Castleman disease” not limited to cutaneous involvement only that can be uploaded
- Be able to provide electronic informed consent, as per local regulations

Deceased patients may also be enrolled when a reference pathology report suggesting “Castleman disease” can be supplied or when the ART is able to locate and upload such a pathology report.

5.4 Exclusion Criteria

Because this registry is designed to provide as wide a picture of routine clinical practice as possible, inclusion criteria are set deliberately wide and there are no exclusion criteria.

5.5 Patient Recruitment

Patients will be recruited to enroll themselves directly into the registry, regardless of what center their treating physician is located at. Castleman disease patients and the family members of deceased patients will be notified about the existence of ACCELERATE and recruited to enroll via the ACCELERATE registry website on www.CDCN.org/ACCELERATE through:

- Advertisements in the Castleman Disease Collaborative Network (CDCN) e-newsletter, website, and social media;
- Emails to patient members of the CDCN and patients who contact the CDCN through the website or by email;
- Outreach to the CDCN physician database and the authors of published case reports to ask them to provide information about ACCELERATE to their patients about participation;
- Mailings to academic hematology divisions and private practices, and to share information with patients; and
- Emails to other patient advocacy groups (e.g., International Castleman’s Disease Organization, EURORDIS, NORD, PatientsLikeMe).

See Section 32.2 for text. All posting will be done in collaboration with the CDCN and posting will be done through CDCN media services (communications, marketing Facebook, Twitter, etc).

The ART will also use the Penn Data Store to identify and recruit Castleman disease patients. A list of patients in the Penn Medicine network with Castleman disease will be generated by the Penn Data Store, and the ART will call or send letters to these individuals inviting them to participate. A request of information will be submitted to the Data Analytics Center.

5.6 Vulnerable Populations

The registry will involve children and may involve pregnant women, although pregnant women are not specifically targeted for this research. As there are no interventions, nor compensation related to this observational registry, study procedures will not affect the condition of children or pregnant women and do not require additional protections for these populations. A supplemental form related to protection of vulnerable populations has been completed for children.

6 Study Procedures for PPA

There are 3 stages of data collection planned for the registry:

- Baseline: All patients will have historical data and current patient status captured from a review of medical notes and survey questions.
- Prospective Data Collection Stage: This stage will capture clinical, laboratory, treatment, and safety data every 12 months. Any changes since the last data collection point and interim lab values will be captured. Patient- and physician-reported data will be captured via surveys every 3 months.
- End-of-Registry: Final prospective data collection, including survival.

The Data Collection Schedule in Section 11.8 summarizes the frequency and timing of data to be collected.

6.1 Enrollment and Baseline Data Collection Stage

Patients will enroll themselves directly into the web-based registry and complete an electronic consent process or telephone consent to participate in the registry. The patient will provide a signature to complete an authorization for release of medical information, as shown in section 11.2. Depending on institutional requirements, a local authorization for release of medical information may be completed in place of that shown in section 11.2. When necessary, a member of the ART will be named as the witness for authorization for release of medical information. As long as a pathology report suggestive of Castleman disease is available for the patient and the patient consents, the patient will be enrolled. All patients will be assigned a Global Unique Identifier (GUID), which will be entered with all data (see Section 4.3.2 for details).

Upon receipt of consent and completion of authorization forms, the ART will request and obtain copies of medical records (paper-based or electronic). If a complete list of providers has not been provided, baseline records will be obtained and specialists or other health caretakers who are named in these records will be contacted. Radiographic images (x-rays, MRI's etc.) will be obtained by mail and scanned into the database. Also, when available, compatible electronic medical record data will be automatically sent to and integrated into the registry (see section 24). Patients will also be able to mail, fax, or email medical records to the ART. Collection of medical record information will be tracked using a REDCap database. Baseline data collection will involve abstraction of data elements from medical record into an eCRF by the ART with close supervision by the PI. The PI and CDCN Scientific Advisory Board developed the inventory of data elements to be extracted based on an extensive literature review, medical record abstraction of cases, and expert experience. We expect to add, subtract or modify these data elements during the course of the registry based on periodic data audits. The types and locations of all stored Castleman disease tissue samples from clinical procedures, which may be available for future research, will also be stored in the registry ("e-repository") using a LabVantage database. Patients and physicians will also be invited to complete surveys through online portals at baseline (described in Section 4.3).

If consented, patients may be re-contacted for additional information.

6.2 *Observational Phase*

6.2.1 *Prospective Data Collection Stage*

The prospective data collection stage is defined as the period from baseline to patient withdrawal or completion of the registry. Data collection during the prospective data collection stage will occur every 12 months. The ART will contact clinics and hospitals and request records of every clinic visit and hospitalization for the patient. The ART will review medical records. Patients will be asked via survey every 3 months about recent hospitalizations, which will prompt the ART to obtain those medical records. At each data collection point, the ART will review medical records obtained since the previous data collection and record the relevant data in the eCRF. Data for biological parameters that are obtained as part of the patient's usual standard care will be collected and evaluated when available. Also, when available, compatible electronic medical record data will be automatically sent to and integrated into the registry (see Section 24). The prospective data collection stage will also involve physicians and patients completing surveys every 3 months (described in Section 4.3). Treatment response and identification of any possible adverse events (AEs) will be assessed at each data collection point as well.

We will perform periodic record collection at least every 12 months to follow the course of the disease. If the ART does not receive a medical record or clinical note within 12 months, the ART will contact the patient for additional information. If the ART is not able to get in contact with the patient, patient family members and loved ones will be contacted for additional information. If the ART is still unable to get in contact with the patient, the steps described in Section 6.4 will be taken to obtain vital status information. The consent form specifically allows record collection for the lifespan of the patient, and any post-mortem medical records. Prospective data collection will continue until the registry is complete or the patient is withdrawn from the registry, irrespective of the treatments prescribed by their physicians.

The ART may also seek out stained and/or unstained lymph node and/or bone marrow slides from patients' previously performed clinical procedures to be sent to UPenn and uploaded to a secure online system to assist the CAS with diagnostic grading. The CAS will review these slides as part of their grading of the quality and likelihood of diagnosis. Lymph node and/or bone marrow slides collected for the registry that are determined to be unnecessary (e.g., extra unstained slides) by the CAS may also be used for future research studies (e.g., immunohistochemistry, genomic studies) along with correlative clinical data from ACCELERATE, if consented by the patient.

6.3 *End of Enrollment and End of Data Collection in the Registry*

The registry will exist for at least 5 years after the first patient is enrolled, but the termination date for the registry has not been determined. Patients will continue to be observed in this registry until one year after the last patient is enrolled. The Sponsoring Institution reserves the right to terminate the registry at any time for any reason at the sole discretion of the Sponsoring Institution. Patients will be followed for the entire prospective data collection stage until the registry is closed.

6.4 *Patient Withdrawal*

Patients may withdraw from the study at any time without impact to their care. Patients will be able to withdraw by sending a letter to the address listed on the consent form. Patients that are lost to follow-up or withdraw from the registry will be censored on the last date that the patient is known to be alive or lost to follow-up.

If a patient withdraws from the registry, the reason for withdrawal, if available, is to be documented in the eCRF and the End-of-Registry Form(s) should be completed. If a patient is lost to follow-up, every reasonable effort should be made by the site staff to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up should be documented. For these participants, where applicable, vital status registries e.g., National Death Index in the United States, will be screened to obtain vital status information annually. Any data collected prior to loss to follow up will be available for inclusion in all analyses. Survival data will be collected for all patients annually after enrollment or at the close of the registry, whichever occurs first, except for those patients who withdraw their consent beforehand.

7 Safety and Adverse Events for PPA

There are three tiers related to safety and reporting for the PPA:

1. Unanticipated problems (as defined in section 7.1.7) involving risks to patients and others will be monitored for all patients throughout the study. Since the study procedures are not greater than minimal risk and are limited to existing data and no study interventions are employed, no risk of physical harm is expected from participation in the registry. The greatest risk is breach of confidentiality. If any unanticipated problems related to the research involving risks to patients or others happen during the course of this study, these will be reported to the IRB in accordance with University of Pennsylvania IRB requirements. Unanticipated problems that do not involve risks to patients or others but arise will be summarized in a narrative or other format and submitted to the IRB at the time of continuing review.

2. Though not considered to be adverse events of the registry (because the registry is non-interventional), safety events will be collected for all Castleman disease treatments in the registry, when specifically noted as a safety event in the medical record (see Section 7.2). There will be text on the ACCELERATE website advising physicians who observe adverse events and serious adverse events to report these through existing safety reporting procedures per local regulations. The ART will not contact physicians regarding safety reporting in the PPA. Physicians will only be contacted regarding safety reporting in the PDA.

3. Since Janssen Pharmaceutica NV produces a Castleman disease therapy and is a collaborative partner for this registry, safety reporting procedures not typically performed for observational registries will be performed for all Janssen Pharmaceutica NV drugs, including siltuximab. All safety events attributed in the medical records to the use of Janssen Pharmaceutica NV products will be collected as part of (2) and will also be reported to Janssen Pharmaceutica NV to comply with the company's pharmacovigilance practices for the duration of Janssen Pharmaceutica NV's financial sponsorship, which is anticipated to last for five years. See section 7.5.2. This is not a requirement imposed by the EMA as part of the PAM.

7.1 Definitions

The below definitions are provided in relation to the second tier of reporting.

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

It should be noted that disease progression can be expected in this patient population, therefore disease progression is generally not considered as an adverse event, unless reported as such by the investigator.

7.1.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended and occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function.

An adverse drug reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected or at least a possibility; i.e., the relationship cannot be ruled out. All Castleman disease adverse events judged by either the reporting Participating Physician or the Sponsoring Institution as having a reasonable causal relationship to a medicinal product qualify as adverse drug reactions.

7.1.3 Serious Adverse Event or Serious Adverse Drug Reaction

Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above, such as important medical events that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above (e.g. suspected transmission of an infectious agent by a medicinal product is considered a serious adverse event). Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the Principal Investigator to have a significant clinical impact.

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event and that must be provided. Pre-planned hospitalization for documented preexisting conditions that do not worsen during the conduct of the program (e.g., a patient goes into the hospital for a pre-planned hip replacement) do not meet the criteria for reporting as a serious adverse event.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events. It should be noted that disease progression can be expected in this patient population, therefore disease progression is generally not considered as a serious adverse event, unless reported as such by the investigator.

Serious Adverse Drug Reaction

Adverse drug reactions are classified as serious or non-serious. A serious adverse drug reaction (SADR) is any ADR that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

7.1.4 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the appropriate Summary of Product Characteristics (SmPC).

7.1.5 Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely, by the definitions listed below.

7.1.6 Product Quality Complaint

A product quality complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product after it is released for distribution.

7.1.7 Unanticipated problems

An unanticipated problem, in general, includes any incident, experience, or outcome that meets all of the following criteria: 1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the patient population being studied; 2) related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and, 3) suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 Recording of Adverse Events

All adverse events associated with participation in the registry will be recorded for all participants (see tier 1 in section 7). Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

This is a non-interventional registry, and no specific safety tests will be collected unless available as part of routine clinical practice. Evaluations of safety and tolerability will be documented according to the time points provided in the Data Collection Schedule. Only results available per routine clinical practice will be collected.

The following procedures shall be used for both the background data collection and prospective data collection stages as they both involve retrospective data entry from medical charts. All ADRs, pregnancies, and special situations documented in the source data following exposure to Castleman disease treatments are to be recorded in the CRF, regardless of seriousness (see tier 2 in section 7). For an adverse event to be recorded in the CRF, there should be information in the source data (medical records) and/or retrospective study database that confirms that the event is specifically indicated or clearly implied (verbally or documented) as at least possibly related to the use of the Castleman disease treatment. Adverse drug reactions should be collected from the first documented use of the Castleman disease treatments within the protocol-defined data collection period until 30 days after the last documented use of the Castleman disease treatments within the data collection period.

7.3 Relationship of AE to Treatment and Severity Criteria

The Principal Investigator and designated study staff will not make attributions regarding possible adverse events in the PPA. Per section 7.2, the study staff will only record the event in the CRF if the source data specifically indicates or clearly implies the event is possibly related to the use of the Castleman disease treatment.

An adverse event is considered not associated with the use of the treatment if the attribution is not related or doubtful by the definitions listed below:

- **Not related:** An adverse event that is not related to the use of the drug.
- **Doubtful:** An adverse event for which an alternative explanation is more likely, e.g. concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible:** An adverse event that might be due to the use of the drug. An alternative explanation, e.g. concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

- **Probable:** An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely, e.g. concomitant drug(s), concomitant disease(s).
- **Very likely:** An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

An assessment of severity grade will be made using the following general categorical descriptors:

- **Mild:** Awareness of symptoms that are easily tolerated causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** Sufficient discomfort is present to cause interference with normal activity.
- **Severe:** Extreme distress causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

7.4 Special Reporting Situations

As Janssen Pharmaceutica NV is a financial sponsor for this registry, a collaborative partner, and the manufacturers of an FDA- and EMA-approved treatment for multicentric Castleman disease (siltuximab), Janssen Pharmaceutica NV may need to evaluate safety events of interest for Janssen Pharmaceutica NV medicinal products. These include, but are not limited to:

- Overdose of a Janssen Pharmaceutica NV medicinal product
- Exposure to a Janssen Pharmaceutica NV medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen Pharmaceutica NV medicinal product
- Inadvertent or accidental exposure to a Janssen Pharmaceutica NV medicinal product
- Any failure of expected pharmacologic action (i.e., lack of effect) of a Janssen Pharmaceutica NV medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen Pharmaceutica NV medicinal product;
- Medication error involving a financial sponsor product (with or without patient/patient exposure to the financial sponsor medicinal product, e.g., name confusion)
- Pregnancy exposure

These safety events may not meet the definition of an adverse event; however, from a Janssen Pharmaceutica NV perspective, they are treated in the same manner as adverse events. Therefore, special reporting situations, which are explicitly stated in the medical records, should be recorded in the eCRF and any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the eCRF.

7.5 Reporting of Adverse Events and Unanticipated Problems

The Principal Investigator will promptly notify the Penn IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to patients or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days. See tier 1 in section 7.

There will not be enrolled Participating Physicians or any sites in the PPA. The patient's physician will be instructed on the ACCELERATE website to independently report all AEs in accordance with local regulation. In the US, adverse event reporting by physicians or patients is voluntary, and they are encouraged to employ the US FDA Adverse Event Reporting System (FAERS; <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>). Patients may also voluntarily report adverse events in FAERS.

A product quality complaint (PQC) may have an impact on the safety and effectiveness of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the financial sponsor, and are mandated by regulatory agencies

worldwide. The ART will report PQCs to Janssen Pharmaceutica NV, which has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the financial sponsor or its affiliates will be conducted in accordance with those procedures.

All initial PQCs involving a Janssen Pharmaceutica NV product must be reported to Janssen Pharmaceutica NV within 24 hours after being made aware of the event. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding PQCs for a Janssen Pharmaceutica NV product are listed on the contact information page(s), which is/are provided separately. If the defect for a Janssen Pharmaceutica NV product is combined with a serious adverse event, the personnel must report the PQC to Janssen Pharmaceutica NV according to the serious adverse event reporting timelines.

7.5.1 Follow-up Report

This is a non-interventional registry, and no specific safety tests will be collected unless available as part of routine clinical practice. If there are any events reported specifically related to research participation (e.g. breach of confidentiality or uneasiness with study questionnaires) appropriate follow-up will be carried out until resolution of the reported event. Evaluations of safety and tolerability of siltuximab will be collected from medical records according to the time points provided in the Data Collection Schedule, but no additional AE follow up will be performed for patients in the PPA of the registry

7.5.2 Safety reporting: notifying the financial sponsor

UPenn is the Sponsoring Institution of the registry. Janssen Pharmaceutica NV is the financial sponsor for this registry, a collaborative partner, and the manufacturers of an FDA- and EMA-approved treatment for HIV-negative and HHV-8-negative multicentric Castleman disease (siltuximab, SYLVANT®).

The safety data received for the PPA will be managed by UPenn. In fulfillment of tier 3 in section 7, UPenn will notify Janssen Pharmaceutica NV within 24 hours of becoming aware of any Janssen Pharmaceutica NV product-related AE/SAE from a medical record. UPenn will ensure that only AE/SAE cases related to Janssen Pharmaceutica NV products entered in the eCRF will be reported to Janssen Pharmaceutica NV. On a monthly basis UPenn will provide Janssen Pharmaceutica NV with the database extract including information about all AEs and SAEs for Janssen Pharmaceutica NV products.

The ART will perform a safety database reconciliation between Janssen Pharmaceutica NV's global safety database and the ACCELERATE registry database. Janssen Pharmaceutica NV will provide an extract (as an excel file) from its safety database, SCEPTRE, which will list all the SAEs registered so that UPenn can perform the reconciliation against the medical database. In case of any inconsistency related to the safety data extract, UPenn will add a query to the corresponding eCRF and/or send a data update request to Janssen Pharmaceutica NV Safety Management.

7.5.3 Data and Safety Monitoring Plan

See Section 21 in Part C regarding ART as Global Data Coordination Center.

8 Study Administration, Data Handling and Record Keeping for PPA

8.1 Confidentiality

8.1.1 Country-Specific Regulations

For patients enrolling through the PPA in the USA, information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require patient authorization informing the patient of the following:

- The PHI collected as part of the study
- The purpose of the use/disclosure
- Who may use or disclose PHI
- Who may receive PHI

- The duration of the authorization (if it does not expire, this should be indicated)
- The right to revoke the authorization
- A statement that once information is shared outside of the covered entity it may no longer be protected by HIPAA

In the event that a patient revokes authorization to collect or use PHI, the Principal Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect vital status (i.e. that the patient is alive) annually after withdrawal.

For patients enrolling through the PPA in Canada, information about study patients will be kept confidential and managed according to the requirements of the legislation applicable to the personal health information of the individuals who consent to participate in the study (Personal Health Information Protection Act or “PHIPA”).

For patients enrolling through the PPA from outside of the USA and Canada, information about study patients will be kept confidential, but our data acquisition and handling may not cover all required privacy practices in that particular country. We will state this in the consent for patients enrolling from outside of the USA and Canada. If necessary, the protocol may need to be amended per local regulation.

8.1.2 Confidentiality Practices for the PPA

A number of precautions will be taken to assure the confidentiality of patients. Immediately after enrollment, each patient will be assigned a GUID, which will be used to identify the participant's database records. This unique identifier will be generated from patient identifiers, but will not contain any patient identifiers such as the patient's initials or significant dates. Collection of medical record information will be tracked using a REDCap database. All paper documents (e.g. original medical record documents) will be stored within locked filing cabinets located in the Hospital of the University of Pennsylvania (HUP). Some of the medical records may be transferred to a secure, HIPAA compliant, off-site records management storage facility. When compatible electronic medical record data is available to be automatically sent to and integrated into the registry, the precautions listed in section 24 will be taken. A Pulse Infotrame database will employ multiple security features to limit access to any PHI to study team members only. Data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The computerized database will tag all PHI data and not permit the viewing of such data except by authorized parties. Strict control over data viewing based on role-based permissions will be enforced. Study personnel, including the ART, whose responsibilities require access to personal data agree to keep the identity of registry patients confidential. Data containing direct identifiers will not be available for export to anyone outside of the ART at any time. For future review by the CAS, stained lymph node and/or bone marrow slides will be uploaded to a web-based hosting provider, separate from the Pulse Infotrame database. To ensure confidentiality, all slides will be completely de-identified by the ART prior to upload. Qualified Researchers, who apply for access to the database, will have a limited dataset with direct identifiers removed transmitted securely using downloaded Excel compatible file formats or single SAS data files.

8.2 Data Collection and Management

The ART will collect and manage data in accordance with the below outline and flowchart in Section 11.6.

1. Enrollment: The patient will enroll into the registry through the ACCELERATE website. The patient will provide electronic informed consent and complete enrollment questionnaires that includes their authorization for the ART to access medical records and, when available, for electronic medical record data to be automatically sent to and integrated into the registry. A GUID will be created for each patient.
2. Baseline Data Collection:
 - a. The ART will contact the patient's hospital and physician to request medical records be faxed, emailed, or mailed to the ART study location at UPenn. If applicable, the clinic or

institution will invoice the ART for the cost of collecting the medical records. Alternatively, patients may send copies of medical records by fax, mail, or email to the ART study location at UPenn. If the records are not delivered to the ART study location at UPenn, the ART will check with the medical records department at UPenn to see if they were incorrectly sent there and will follow up with the clinics and hospitals. If there is a problem with the release form, the ART will re-contact the patient. Collection of medical record information will be tracked using a REDCap database.

- b. Patients and those patients' treating physicians, which are self-identified by the patient through initial registration or identified through medical record review, will also be invited to access the online portals and complete optional surveys.
 - c. Patients will also be able to send medical records in English directly to the ART by fax, email, or mail. This may need to be done more frequently for patients outside of the USA and Canada, as the general release form may not be sufficient for some physicians to release records.
 - d. When available, electronic medical record data will be automatically sent to and integrated into the registry (see section 24).
- 3. Prospective Data Collection
 - a. The ART will contact the patient's hospital and physician to request medical records be faxed, emailed, or mailed to the ART study location at UPenn every 12 months.
 - b. If no information is obtained for a 12-month period, the ART will contact the patient to update their status. If the patient cannot be located, the ART will contact family members and, in the event the patient still cannot be located, will check vital status through a national death registry.
 - c. Patients will also be able to send medical records in English directly to the ART by fax, email, or mail.
 - d. Patients and those patients' treating physicians will also be emailed every 3 months to access the online portals and complete optional surveys.
 - e. When available, electronic medical record data will be automatically sent to and integrated into the registry (see section 24).
 - f. The ART will contact the patient's hospital to request that unstained lymph node and/or bone marrow slides or tissue blocks be sent to UPenn, when available. The ART will de-identify and scan these slides for future review by the CAS.
- 4. Extract data
 - a. Medical records obtained from baseline data collection and from prospective data collection will be extracted into the eCRF in the same fashion. Electronic data capture will be used for this registry. Guidelines for eCRF completion will be provided and reviewed with registry personnel before the start of the registry. All eCRF entries, corrections, and alterations must be made by the ART. The ART must verify that all data entries in the eCRFs are accurate and correct. If necessary, queries will be generated in the eCRF. The ART must adjust the eCRF (if applicable) and complete the query.
 - b. Adverse events will be recorded and the ART will scan and lock paper records in safe storage.
 - c. When available, data from electronic medical records will be integrated automatically into the ACCELERATE registry prospectively, so no data extraction will be needed for those data (see Section 24).
- 5. Withdrawal
 - a. A patient may withdraw for any reason. If this occurs, the ART will record the reason in the eCRF and complete an end of registry form. If agreed at the time of withdrawal, the ART will contact the patient annually or check vital status through a national death registry annually.
- 6. Secure physical and electronic document storage
 - a. Primary records, such as original copies of electronic informed consent forms, will be stored in a locked filing cabinet and will only be available to study team members. As the files will have personally identifiable information, the documents will be stored in files labeled only with a name and will not be linked to GUID. Electronic copies of these

documents will be created and stored securely. These primary records will not be available to any future recipients of registry-repository data without a separate IRB approval.

See Section 23 in Part C for data management that will be performed for both the PPA and PDA as part of the Global Data Coordinating Center's responsibilities.

8.3 Computer System

The Pulse Inframe computer system is described in Section 24 as management of the system is a major responsibility of the Global Data Coordinating Center. It is used for both the PPA and PDA.

8.4 Data Access & Migrations

Information about Data Access & Migrations is in Section 25.

8.5 Records Retention

See Section 26.

8.6 Providing Results to Patients

See Section 27.

9 Study Monitoring, Auditing, and Inspecting for PPA

9.1 Study Monitoring Plan

See Section 28.

9.2 Auditing and Inspecting

The Principal Investigator will permit study-related monitoring, audits, and inspections by the IEC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

10 Ethical Considerations for PPA

This protocol and any amendments will be submitted to the Institutional Review Board (IRB) at UPenn, in agreement with local legal prescriptions, for formal approval of the study conduct to cover enrollment and informed consent of patients the PPA (Part A) and to cover data coordination for PDA study sites and data collection from patients and physicians as Penn will serve as a global data coordination center (Part C). This approval will be the only IRB approval obtained for the PPA, because the registry design involves patient self-enrollment, patient-reported data, and patient consent to the ART accessing medical records and clinical notes and collecting additional data from physicians. The physicians of the patients enrolled will not be required to seek IRB approval at their institutions. The decision of UPenn IRB concerning the conduct of the study will be made in writing before commencement of this study.

The ACCELERATE Steering Committee (ASC) will review and vote on all potential protocol amendments. For all protocol amendments determined by the ASC (excluding the ones that are purely administrative, with no consequences for patients, data or registry conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IRB for review and approval before implementation of the change(s).

10.1 Risks

The risks to study patients due to participation in this protocol are small. The only risk to participants is breach of confidentiality. This risk has been fully addressed as described in Section 8.1 (Confidentiality).

10.2 Benefits

It is not anticipated that patients will receive any direct benefit as a result of their participation in the ACCELERATE registry. However, this registry will generate data that may improve our knowledge and treatment of Castleman disease, which may benefit patients with Castleman disease in the future.

10.3 Risk Benefit Assessment

The potential long-term benefit of improving knowledge and treatment of Castleman disease outweigh the low risks associated with participation in this study for these patients.

10.4 Informed Consent Process / Privacy Policy Authorization

10.4.1 Country- and Registrant-Specific Differences in Informed Consent Process

The Informed Consent Process will differ based on the location of the study patient (USA, Canada, rest of world) and the type of registrant (Patient <7 years old, Patient 7-17 years old, Patient >17 years old, Parent of Patient <7 years old, Parent of Patient 7-17 years old, family member of deceased patient). See Section 11.6 for detail on how each consent process will differ based on location and type of registrant. See summary table below of the informed consent and records request processed in different countries.

	USA	Canada	Rest of world (not including PDA sites)
How the patients gives Informed Consent	Type name for consent on website (if adult patient or family of deceased patient) or verbal assent with parental permission by telephone (if minor). Click "I agree" to participation when prompted.	Type name for consent on website (if adult patient or family of deceased patient) or verbal assent with parental permission by telephone (if minor). Click "I agree" to participation when prompted.	Type name for consent on website (if adult patient or family of deceased patient) or verbal assent with parental permission by telephone (if minor). Click "I agree" to participation when prompted.
Privacy Authorization	Informed Consent also includes HIPAA text	Informed Consent also includes PHIPA Text	Informed Consent will also include text stating "our data acquisition and handling may not cover all required privacy practices in that particular country"
Records request authorization	Electronic signature	Electronic signature	Electronic signature

Based on patients' responses to location of the patient and type of registrant, a different set of tasks will be required and a consent form customized for the location and the type of registrant will appear. For example, patients residing in the USA will have required HIPAA elements in their informed consent. Patients who reside outside the USA would still get the online consent to participate in the registry, but it won't include the standard HIPAA language since it does not apply to them.

All patients will review a consent form on the ACCELERATE registry website providing sufficient information for patients to make an informed decision about their participation in this study. Patients >17 years old and family members of deceased patients will complete the consent process online. Family members of deceased patients will consent and will complete a privacy policy (HIPAA in USA, PHIPA in Canada) acknowledgment and a medical records release form acknowledgement (see Section 10.6). Parental permission will be obtained from parent/legal guardian for all underage participants and assent will be obtained as described below; however, where applicable, these procedures will be modified to comply with local regulations and requirements.

- Patients < 7 years old: the parent or legal guardian will complete the consent process online

- Patients 7-17 years old: The study will be explained to the candidate participants in detail. Parental permission and verbal assent by the participating child will be obtained by telephone and documented
- Underage participants that reach the legal age for providing informed consent will be re-consented by telephone as soon as feasible.

10.4.2 Components of Informed Consent

See Section 11.1 for components of the Informed Consent Forms, which will be customized based on location and type of registrant. The observational nature of the registry and that the registry only intends to collect information and follow their course of treatment in the clinical practice setting will be explained to potential patients. Patients will be informed that their authorization to allow the collection of the data is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care they will receive. Participants will be informed that research results will only be returned to the patient if a clinically-actionable, life-threatening disease other than Castleman disease is highly suggested from review of their data. Specifically, the consent will include:

- Global consent for the patient to participate in the registry
- Consent for the ART to contact all physicians that have cared for the patient for additional clinical data and to remind the physician to complete a survey every three months
- Consent for the ART to re-contact the patient for additional clinical data and to remind the patient to complete a survey every three months
- Consent for the ART to access and process all past and future medical records for the patient
- Consent for the ART to track the location and type of tissue samples currently stored
- Consent for the ART to have ongoing clinical notes sent to the ART
- Consent for the ART to request lymph node and/or bone marrow slides or tissue blocks be sent for central pathology review by the CAS with the understanding that tissue blocks may be depleted
- [Optional] Consent for lymph node and/or bone marrow slides collected for the registry that are determined to be unnecessary (e.g., extra unstained slides) by the CAS to be used for research studies (e.g., immunohistochemistry, genomic studies) along with correlative clinical data from ACCELERATE
- Consent for the ART to re-contact the patient in the future to request tissue samples and to present options for future research opportunities
- Consent for the transfer of coded data without direct identifiers to other entities, such as health authorities and other third parties, without violating confidentiality, to the extent permitted by the applicable law(s) or regulations
- Consent for automated transfer of data from your electronic medical records
- Consent for medical records to be transferred to a secure, HIPAA compliant, off-site records management storage facility if necessary

The ART will review the consent form in detail by telephone with the patients <17 years old and their parents. The ART will also be available by telephone to answer any questions that patients >17 years old and deceased family members may have about the registry. When necessary, Dr. Fajgenbaum or his qualified designate will use interpreters for this task. Patients will also have the ability to view the consent and review further before returning to the website to complete the consent process online or performing assent/parental permission by telephone. A combined consent-authorization document will be used. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a patient, using the IRB-approved consent form, must be completed before that patient participates in any registry-related activities. The patient must complete the consent form process electronically or verbally consent by telephone. A copy of the combined consent-authorization form will be available for the patient to print for their records. Following consent, patients will also provide their signature in an electronic signature-capture for completion of a records release authorization form to allow release of medical records to the ART (see Section 10.5).

10.4.3 Alterations to Typical Consent Process

10.4.3.1 Waiver of Written Documentation of Consent

We are requesting a waiver of documentation of consent and an alternation to the privacy policy (HIPAA in USA, PHIPA in Canada) authorization, not requiring a signature, because this study is minimal risk to patients (see Section 10.1) and the activities required for participation are very similar to activities that people often do outside of the research context without signing a document.

Instead of obtaining written documentation of consent, a combined informed consent-HIPAA (or PHIPA in Canada) authorization will be displayed on the registry website. Potential patients >17 years old and family members of deceased patients will have the ability to review the details of the study and call the ART to ask questions about the registry. After complete review, patients will type their name and click “I agree” to indicate that they have read and understand the terms of the registry and agree to participate. Potential patients 7-17 years old and parents of patients under 18 years old will be required to perform a verbal consent by telephone.

10.5 Medical Records Release Authorization Form

Following informed consent, the patient will complete a survey (Section 11.5) to identify caregiver and hospital contact information. Using an electronic signature-capture, the patient will provide a signature to be used for a records release authorization form (see Section 11.2). The patient will be informed that they may need to provide a written signature by mail or asked to complete a HIPAA authorization form for specific institutions. Depending on specific institutional requirements, the form in section 11.2 or an institutional release authorization form will be completed and sent to all providers and hospitals listed in the survey as well as all other current and former providers and hospitals. When applicable, a member of the ART will serve as the witness to the authorization form. Participants may be asked to provide additional identification (e.g. copy of driver’s license) depending on institutional requirements. Depending on country of residence, the medical records request authorization form will include HIPAA language (USA), PHIPA language (Canada), or, for individuals outside of the USA and Canada, the records request form will state that the study data acquisition and handling practices may not cover all required privacy practices in that particular country. The database will provide electronic signature capture technology. The patient will be informed that some institutions will not accept the electronic signature, and they may need to be re-contacted for a paper signature that is faxed, scanned, or mailed. Furthermore, some institutions, may not send the records and patients will need to acquire the medical records and/or tissue samples themselves and then fax, email, or mail them to the ART in English.

10.6 Permission for Use of Medical Records for Deceased Individuals

While deceased individuals technically do not qualify as “human subjects” and the requirements for informed consent do not apply to these individuals, permission for use of medical records will be obtained from family members who register and wish to provide data about their deceased family member for inclusion in the registry. As part of the registration process, family members of deceased individuals will be asked to sign a tailored authorization to allow us to collect and include the information of the deceased individual in the registry. This authorization will be compliant with the requirements for research with deceased individuals under HIPAA in the USA and PHIPA in Canada and may be tailored to local regulations. For countries outside of the USA and Canada, the records request form will state that our data acquisition and handling may not cover all required privacy practices in that particular country. The family member will also need to complete the records release form.

11 Part A Attachments

11.1 Statement of Research/ Consent Form

11.1.1 Components of Informed Consent

- Contributing medical information to an international data registry for Castleman disease called ACCELERATE
- Collection of available tissue specimens that are left-over from clinical care
- Participation in surveys online every 3 months
- Agreeing to future contact by researchers
- Optional Use of Collected Samples

For additional information, see the separate informed consent documents.

11.1.2 Pre-consent eligibility questions for ACCELERATE Castleman disease registry

- Has the patient ever had a lymph node biopsy performed and had a pathology report state that the patient's lymph node may be suggestive of or diagnostic for Castleman disease?
Yes – Proceed to Question 2
 - No
 - Message: Thank you for your interest in the ACCELERATE Castleman disease registry. A lymph node must have been resected and reviewed by a pathologist in the past in order for a diagnosis of Castleman disease to have been made. Therefore, we are requiring that every patient who enrolls in this study has had a lymph node biopsy that a pathologist has considered to be suggestive of or diagnostic for Castleman disease. Based on your response, you do not appear to be eligible to participate at this time. Please call [215-614-0689](tel:215-614-0689) if you have questions.
 - Don't know
 - Message: This registry intends to enroll all patients with Castleman disease. A lymph node must have been resected and reviewed by a pathologist in the past in order for a diagnosis of Castleman disease to have been made. Therefore, we are requiring that every patient who enrolls in this study has had a lymph node biopsy that a pathologist has considered to be suggestive of or diagnostic for Castleman disease. Please call [215-614-0689](tel:215-614-0689) if you have questions.
- Do you (the person completing this form) live in the USA, Canada, or another country outside of the USA or Canada?
 - Dropdown with USA and Canada at the top of the list and then every other country below.
 - If USA is selected, then the Statement of Research/Consent form is tailored for the USA with HIPAA authorization language.
 - If Canada is selected, then the Statement of Research/Consent form is tailored for Canada with PHIPA authorization language.
 - If a country/territory within which we have a PDA arm (France, Germany, UK, Spain, Italy, Norway, Mexico, Argentina, Brazil, Taiwan, or China) is selected, then a message will direct the user to contact one of the physicians within that country.
 - If another country is selected, then the Statement of Research/Consent form tailored for the USA is included with a message stating "Our data acquisition and handling may not cover all required privacy practices in your particular country."
 - Please select the choice that best applies to the patient (Please note: to be considered a patient with Castleman disease, a pathology report suggesting "Castleman disease" is required). Dropdown:
 - I am a child with Castleman disease and I am less than 7 years old
 - I am a child with Castleman disease and I am between 7 and 17 years old
 - I am the parent of a child less than 7 years old that has Castleman disease
 - I am the parent of a child between 7 and 17 years old that has Castleman disease
 - I am a patient older than 17 years old that has Castleman disease
 - I am a family member of a deceased patient who had Castleman disease

- vii. I am a family member of a patient that is older than 17 years old who is unable to give consent

After question #3 is answered, the appropriate response and consent option will follow based on the age of participant, location of enrollment, and the relationship of the registrant to participant.

11.2 Example Medical Records Release Authorization Form for PPA in USA

HIPAA AUTHORIZATION TO RELEASE HEALTHCARE INFORMATION

Patient's name: _____
 Patient's previous name(s): _____
 Date of Birth: _____ Last 4 of SSN: _____
 Address: _____ Area Code/Phone #: _____

I hereby authorize **University of Pennsylvania ACCELERATE Registry** to obtain comprehensive medical records and medical information in your files in paper or electronic format pertaining to medical records and history, including pathology reports, X-rays, MRI's, mental health, psychiatric information and psychotherapy notes, Human Immunodeficiency Virus (HIV), drug and alcohol abuse, sexually transmitted diseases (STDs), genetic information, and emancipated minor records.

Records will also be requested periodically at future times to update our information base. Records will remain confidential. I authorize the release of healthcare information as specified above from:

Name: [INSERT NAME OF INSTITUTION/CLINIC]

Address: [INSERT ADDRESS OF INSTITUTION/CLINIC]

I hereby request you to release this information to University of Pennsylvania ACCELERATE Registry, to the electronic health record interoperability company, Intersystems, and to the ACCELERATE Registry's database vendor, Pulse Infotrame, working on behalf of the ACCELERATE Registry at the below address:

Dr. David Fajgenbaum, MD, MBA, MSc
Assistant Professor of Medicine, Division of Translational Medicine & Human Genetics
Principal Investigator, ACCELERATE Natural History Registry
Hospital of the University of Pennsylvania (HUP), 5th Floor Silverstein, Suite 5100
3400 Spruce Street, Philadelphia, PA 19104
(Phone) 215-614-0936
(Fax) 877-991-9674

I understand that the terms of this Authorization are governed by the Health Insurance Portability and Accountability Act of 1996, and its implementing regulations, as may be amended from time to time ("HIPAA").

I understand that I have the right to revoke this Authorization in writing, at any time, sending a written request which shall be considered effective upon receipt. I understand that any revocation must include my name, address, date, and my signature. I understand that a revocation is not effective to the extent that any person or entity has already acted in reliance on my Authorization. Information obtained prior to revocation will remain in the dataset and continue to be used.

I understand that I am not required to sign this Authorization and that my provider cannot condition treatment on my execution of this Authorization. I have the right to receive a copy of this Authorization. I understand that once my information is disclosed pursuant to this Authorization, it may be re-disclosed by the recipient listed above and, in that case, may no longer be protected by HIPAA. This Authorization does not expire.

I further understand that this authorization is voluntary and that I may refuse to sign this authorization. My refusal to sign will not affect my eligibility for benefits or enrollment or payment for or coverage of services.

Signature of Individual

Printed Name

Date

Authority of Individual:

☐ Self

☐ Power of Attorney

☐ Parent of Minor

☐ Other (specify): _____

☐ Court-Appointed Guardian

A photocopy or fax of this signed Authorization shall be deemed as valid as the original.

11.3 Medical Records Release Authorization Form for PPA in Canada**AUTHORIZATION TO RELEASE HEALTHCARE INFORMATION**

Patient's name: _____
 Patient's previous name(s): _____
 Date of Birth: _____ Area Code/Phone #: _____
 Address: _____

I hereby authorize **University of Pennsylvania ACCELERATE Registry** to obtain comprehensive medical records and medical information in your files in paper or electronic format pertaining to medical records and history, including pathology reports, X-rays, MRI's, mental health, psychiatric information and psychotherapy notes, Human Immunodeficiency Virus (HIV), drug and alcohol abuse, sexually transmitted diseases (STDs), genetic information, and emancipated minor records.

Records will also be requested periodically at future times to update our information base. Records will remain confidential. I authorize the release of healthcare information as specified above from:

Name: [INSERT NAME OF INSTITUTION/CLINIC]

Address: [INSERT ADDRESS OF INSTITUTION/CLINIC]

I hereby request you to release this information to University of Pennsylvania ACCELERATE Registry, to the electronic health record interoperability company, Intersystems, and to the ACCELERATE Registry's database vendor, Pulse Infotrame, working on behalf of the ACCELERATE Registry at the below address:

Dr. David Fajgenbaum, MD, MBA, MSc
Assistant Professor of Medicine, Division of Translational Medicine & Human Genetics
Principal Investigator, ACCELERATE Natural History Registry
Hospital of the University of Pennsylvania (HUP), 5th Floor Silverstein, Suite 5100
3400 Spruce Street, Philadelphia, PA 19104
(Phone) 215-614-0936
(Fax) 877-991-9674

I understand that the terms of this Authorization are governed by the Personal Health Information Protection Act, and its implementing regulations, as may be amended from time to time ("PHIPA").

I understand that I have the right to revoke this Authorization in writing, at any time, sending a written request which shall be considered effective upon receipt. I understand that any revocation must include my name, address, date, and my signature. I understand that a revocation is not effective to the extent that any person or entity has already acted in reliance on my Authorization. Information obtained prior to revocation will remain in the dataset and continue to be used.

I understand that I am not required to sign this Authorization and that my provider cannot condition treatment on my execution of this Authorization. I have the right to receive a copy of this Authorization. I understand that once my information is disclosed pursuant to this Authorization, it may be re-disclosed by the recipient listed above and, in that case, may no longer be protected by PHIPA. This Authorization does not expire.

I further understand that this authorization is voluntary and that I may refuse to sign this authorization. My refusal to sign will not affect my eligibility for benefits or enrollment or payment for or coverage of services.

_____ Signature of Individual	_____ Printed Name	_____ Date
Authority of Individual:		
☐ Self	☐ Power of Attorney	
☐ Parent of Minor	☐ Other (specify): _____	
☐ Court-Appointed Guardian		

A photocopy or fax of this signed Authorization shall be deemed as valid as the original.

11.4 Medical Records Release Authorization Form for PPA outside of USA or Canada

AUTHORIZATION TO RELEASE HEALTHCARE INFORMATION

Patient's name: _____
 Patient's previous name(s): _____
 Date of Birth: _____ Area Code/Phone #: _____
 Address: _____

I hereby authorize **University of Pennsylvania ACCELERATE Registry** to obtain comprehensive medical records and medical information in your files in paper or electronic format pertaining to medical records and history, including pathology reports, X-rays, MRI's, mental health, psychiatric information and psychotherapy notes, Human Immunodeficiency Virus (HIV), drug and alcohol abuse, sexually transmitted diseases (STDs), genetic information, and emancipated minor records.

Records will also be requested periodically at future times to update our information base. Records will remain confidential. I authorize the release of healthcare information as specified above from:

Name: [INSERT NAME OF INSTITUTION/CLINIC]

Address: [INSERT ADDRESS OF INSTITUTION/CLINIC]

I hereby request you to release this information to University of Pennsylvania ACCELERATE Registry, to the electronic health record interoperability company, Intersystems, and to the ACCELERATE Registry's database vendor, Pulse Infotrame, working on behalf of the ACCELERATE Registry at the below address:

Dr. David Fajgenbaum, MD, MBA, MSc
Assistant Professor of Medicine, Division of Translational Medicine & Human Genetics
Principal Investigator, ACCELERATE Natural History Registry
Hospital of the University of Pennsylvania (HUP), 5th Floor Silverstein, Suite 5100
3400 Spruce Street, Philadelphia, PA 19104
(Phone) 215-614-0936
(Fax) 877-991-9674

I understand that this registry's data acquisition and handling may not cover all required privacy practices in my particular country.

I understand that I have the right to revoke this Authorization in writing, at any time, sending a written request which shall be considered effective upon receipt. I understand that any revocation must include my name, address, date, and my signature. I understand that a revocation is not effective to the extent that any person or entity has already acted in reliance on my Authorization. Information obtained prior to revocation will remain in the dataset and continue to be used.

I understand that I am not required to sign this Authorization and that my provider cannot condition treatment on my execution of this Authorization. I have the right to receive a copy of this Authorization. I understand that once my information is disclosed pursuant to this Authorization, it may be re-disclosed by the recipient listed above and, in that case, may no longer be protected by local privacy laws. This Authorization does not expire.

I further understand that this authorization is voluntary and that I may refuse to sign this authorization. My refusal to sign will not affect my eligibility for benefits or enrollment or payment for or coverage of services.

_____ Signature of Individual	_____ Printed Name	_____ Date
---	------------------------------	----------------------

Authority of Individual:

☐ Self

☐ Parent of Minor

☐ Court-Appointed Guardian

☐ Power of Attorney

☐ Other (specify): _____

A photocopy or fax of this signed Authorization shall be deemed as valid as the original.

11.5 Example Survey Questions to Identify Medical Caregiver's Contact Information

Please list the names and locations of ALL hospitals at which the patient has been treated since their Castleman disease symptoms began. Include the first date the patient was admitted and whether or not a lymph node was removed at that hospital.

Hospital Name:

Hospital City:

Hospital Country:

Ever had a lymph node removed here: Yes/No

Date of first hospitalization:

[Repeated for as many hospitalizations as the patient has had]

Please list ALL physicians that the patient has seen since Castleman disease symptoms began. Please indicate the patient's "primary" Castleman disease treating physician. Please also indicate if the patient is still seeing each physician.

Physician First Name:

Physician Last Name:

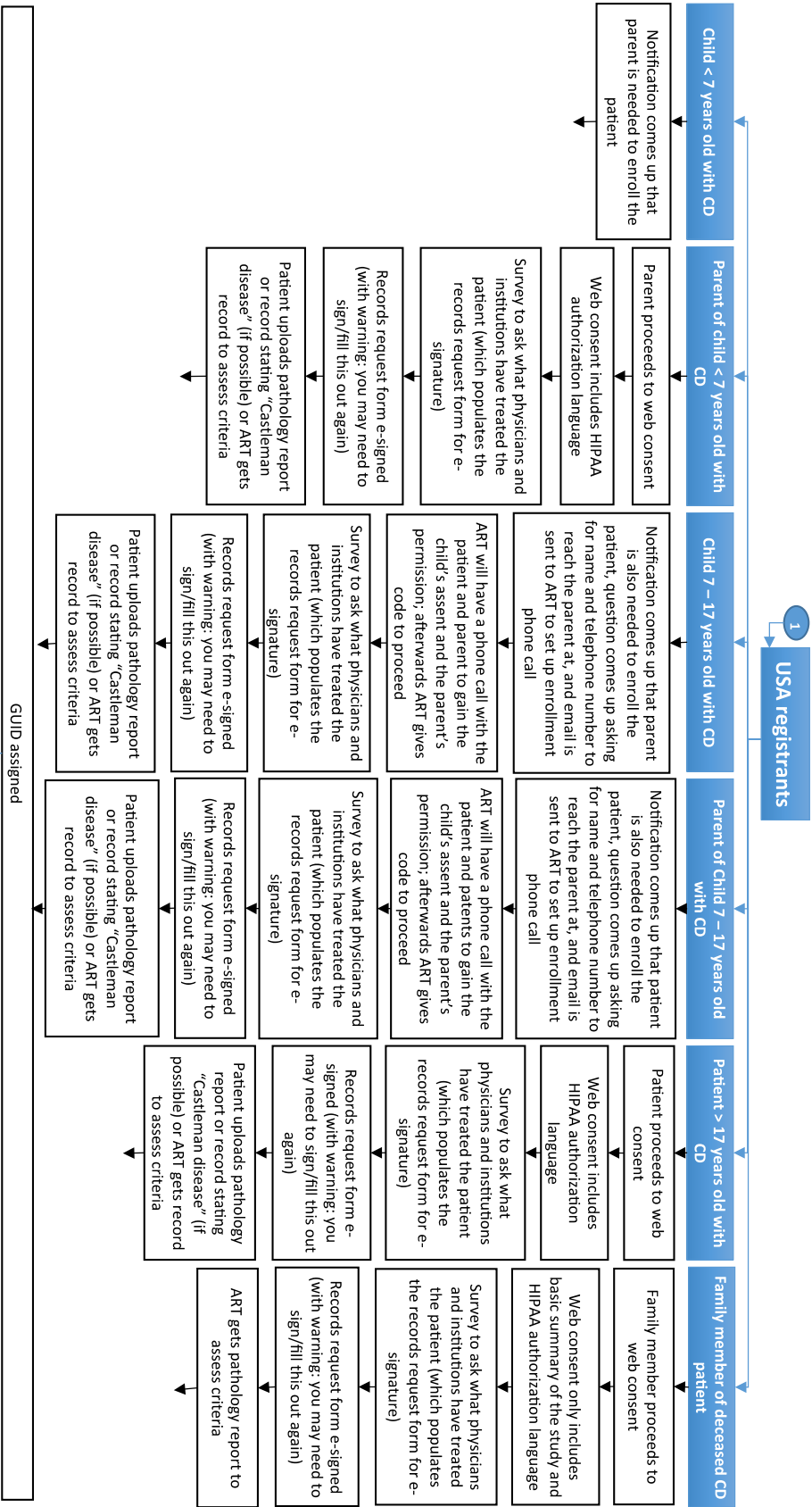
Institution:

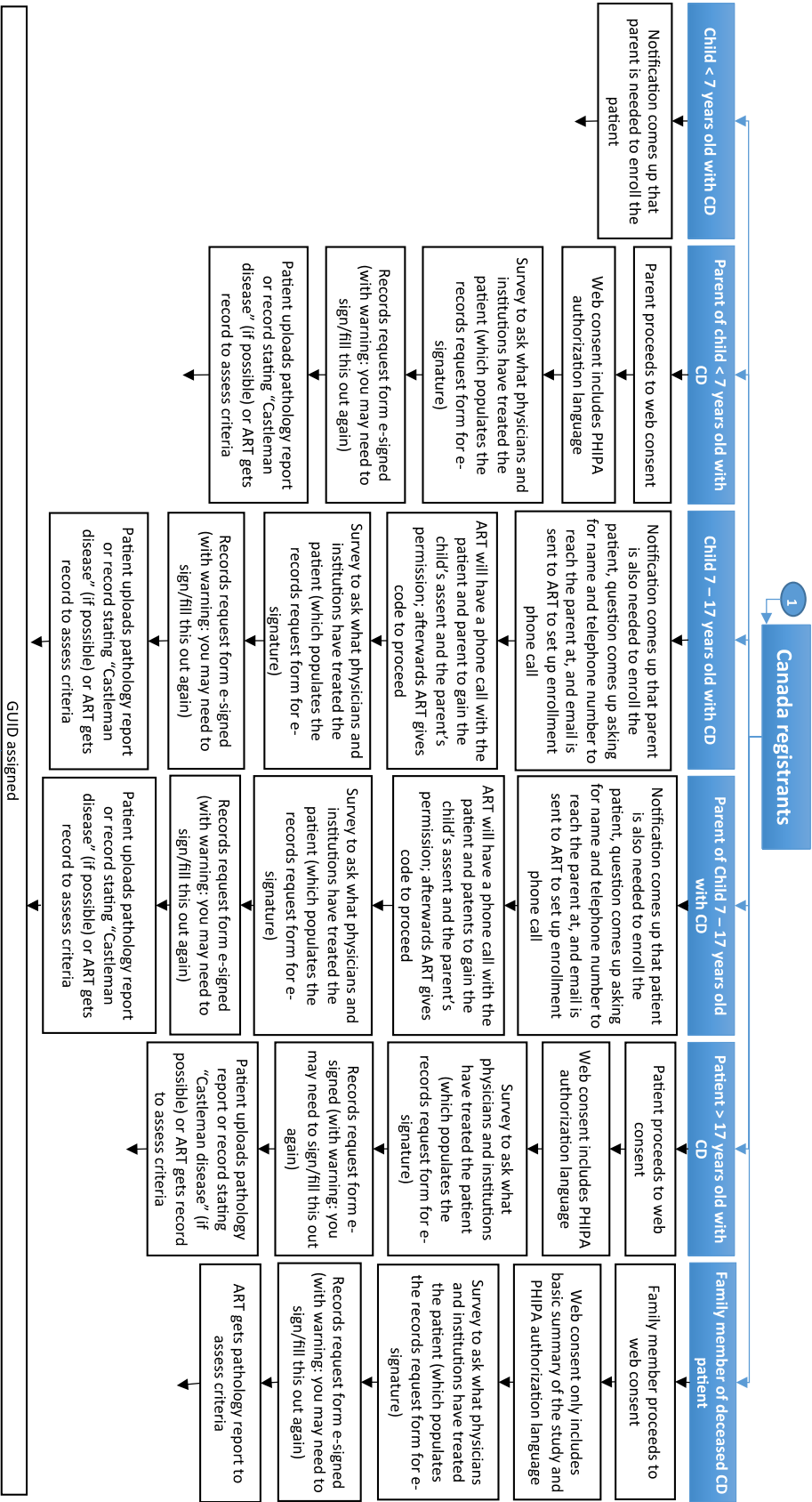
Country:

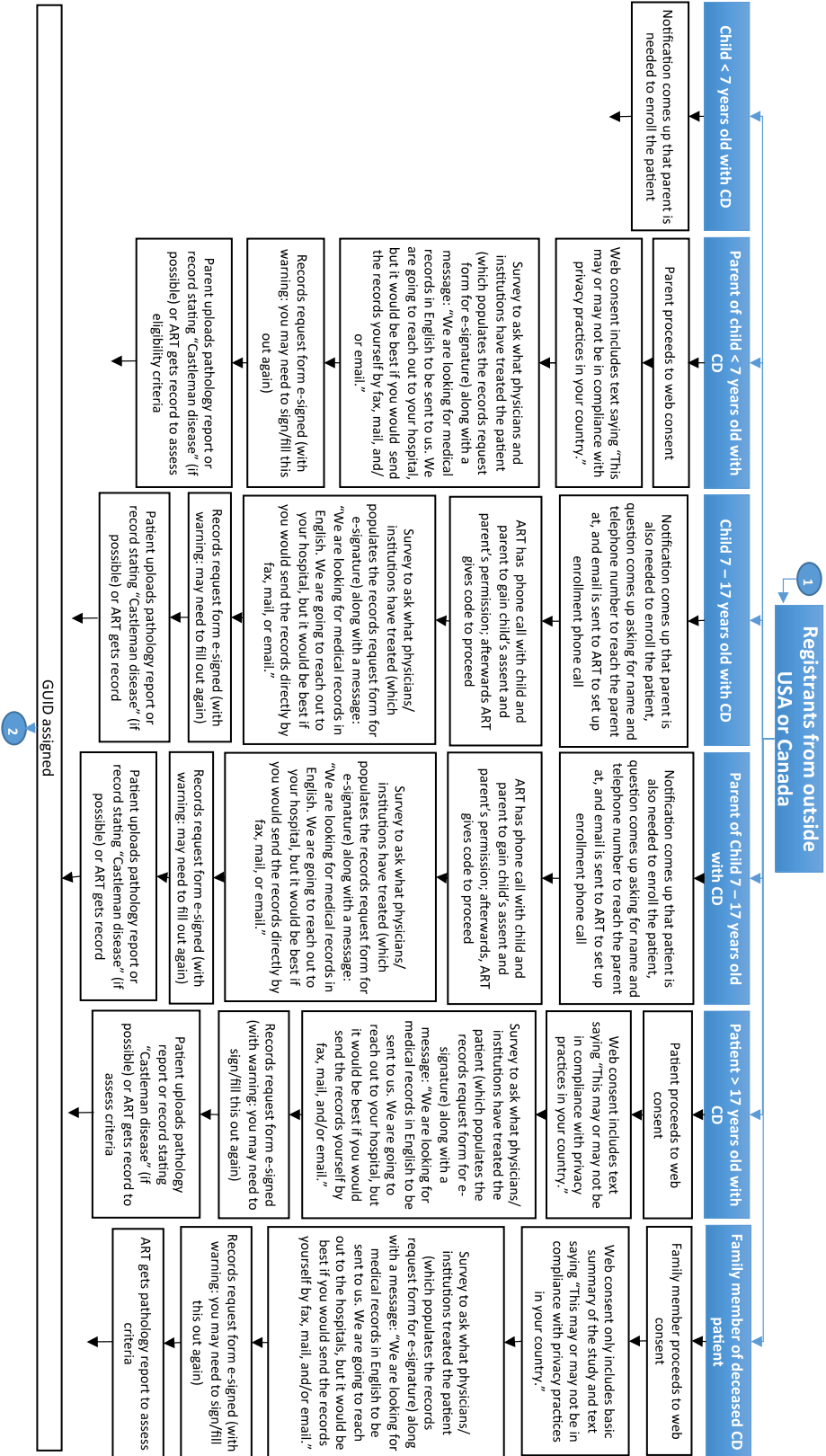
Primary Castleman Treating Physician: Yes/No

Currently Treated by: Yes/No

11.6 Study Procedures Flowchart including Informed Consent Process for each geographic region and type of registrant

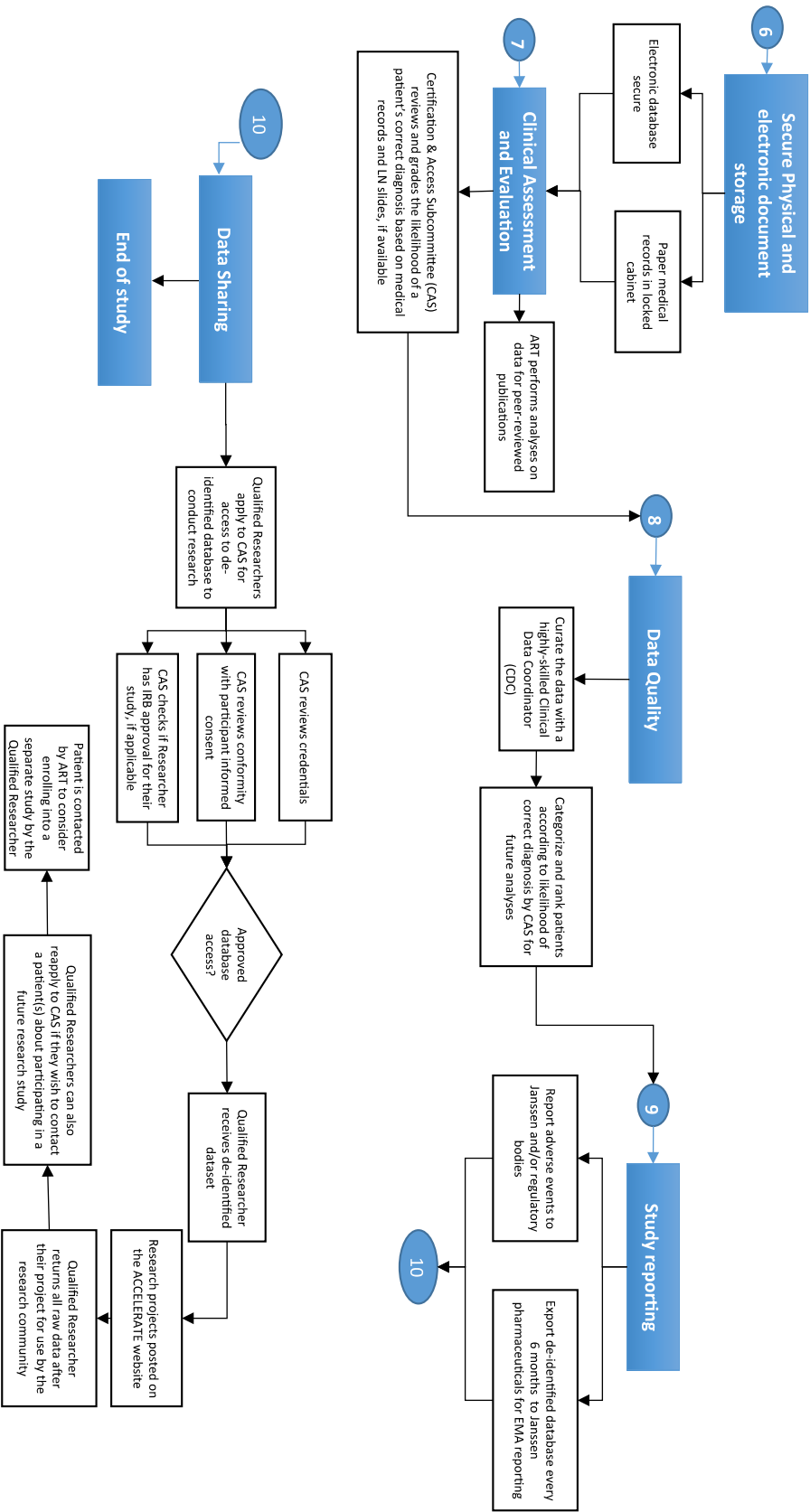






¹ This may need to be adapted per local regulations.





11.7 Telephone Scripts

The following phone script will be used when patients contact the ART to learn about the registry

Date:	Interviewer(SC name):
Protocol Name:	Protocol #:
Patient Name:	Investigator Name:
Patient Phone:	CRC Name:

Hello. This is [ART member name] from the University of Pennsylvania. Who am I speaking with?

Thank you for calling me regarding your interest in our research study. Our office is leading the establishment of an international Castleman disease research study. The study involves collecting medical records and survey data on patients with Castleman disease from around the world so that we can better understand the disease and how best to care for patients with Castleman disease.

Are you interested in participating in this study? If you are not, please know that this will not affect your clinical care in anyway.

- **If NO:** Thank you for your time and have a great day!
- **If YES:** proceed to next question.

Great, thank you for your interest. Would it be OK for me to ask you a few questions to see if you may qualify for the registry?

- **If NO:** Thank you for your time and have a great day!
- **If YES:**

1. Do you know if a pathology report from a lymph node biopsy has ever stated that you may have Castleman disease?
2. How old are you?
3. What country do you live in?

Met criteria for enrollment? ☐ No ☐ Yes

- **If NO:** Thank you for answering my questions. From what you've told me, you would not qualify for this study. Thank you again for your time and have a great day!
- **If YES:** From the information you've told me, you may qualify for the study. You can either go through the consent process to register online at www.CDCN.org/ACCELERATE or, if you prefer, I can consent you by telephone.
 - If you are a patient with Castleman disease that is 7-17 years old or the parent of a child with Castleman disease that is younger than 18 years old, then we will need to schedule a phone call so that both the pediatric patient with Castleman disease and the parent can provide parental permission and patient assent.

Would you like to schedule a time for you, or, if you are a patient with Castleman disease that is 7-17 years old or the parent of a child with Castleman disease that 7-17 years old, a time for both of you to complete the consent process by telephone? ☐ No ☐ Yes

- **If NO:** OK, you can go through the consent process to register online at www.CDCN.org/ACCELERATE. If you change your mind, please call the office at 215-614-0936. Thank you for your time and have a great day!
- **If YES:** When would you like to schedule the telephone consent? Would you like for me to call you back to schedule this?

[if you confirm that the caller's name, including spelling, is the same as noted above, you can type: "As above"]

Name:

Email Address:

Best phone # to reach you:

Best time of day to contact you:

- The telephone consent process will take about 10-15 *minutes*. Is there a day of the week that is best for you? *[write day here]*
- How about *[date, day and time]*?
- So I will speak with you on *[day, date, time]*. I will also email you a confirmation of our phone call time and the study consent form for your review.
- Do you have any questions? *[List the gist of their questions here]*.

Please call Dr. David Fajgenbaum at 215-614-0936 if you have any further questions or need more information. Thanks and have a great day!

The following phone script will be used when the ART calls patients identified through the Penn Data Store.

Date:	Interviewer(SC name):
Protocol Name:	Protocol #:
Patient Name:	Investigator Name:
Patient Phone:	CRC Name:
This is [ART member name] calling from the University of Pennsylvania. Am I speaking with [name of patient]? If yes, continue. If no, leave your name and number and ask the person to have the patient call you back. Our office is leading the establishment of an international Castleman disease research study. The study involves collecting medical records and survey data on patients with Castleman disease from around the world so that we can better understand the disease and how best to care for patients with Castleman disease. Dr. Fajgenbaum has reviewed your medical record and asked me to call you to see if you might be interested in learning more about the Castleman disease research study that he is working on. Are you interested in participating in this study? If you are not, please know that this will not affect your clinical care in anyway. • If NO: Thank you for your time and have a great day! • If YES: proceed to next question.	
Great, thank you for your interest. Would it be OK for me to ask you a few questions to see if you may qualify for the registry? • If NO: Thank you for your time and have a great day! • If YES: 1. Do you know if a pathology report from a lymph node biopsy has ever stated that you may have Castleman disease? 2. How old are you? 3. What country do you live in?	
Met criteria for enrollment? ☐ No ☐ Yes • If NO: Thank you for answering my questions. From what you've told me, you would not qualify for this study. Thank you again for your time and have a great day! • If YES: From the information you've told me, you may qualify for the study. You can either go through the consent process to register online at www.CDCN.org/ACCELERATE or, if you prefer, I can consent you by telephone. ○ If you are a patient with Castleman disease that is 7-17 years old or the parent of a child with Castleman disease that is younger than 18 years old, then we will need to schedule a phone call so that both the pediatric patient with Castleman disease and the parent can provide parental permission and patient assent.	

Date (mm/dd/yyyy): ____ / ____ / ____	Research staff name:
Name of patient contacted:	
Would you like to schedule a time for you, or, if you are a patient with Castleman disease that is 7-17 years old or the parent of a child with Castleman disease that is younger than 18 years old, a time for both of you to complete the consent process by telephone? ☐ No ☐ Yes • If NO: OK, you can go through the consent process to register online at www.CDCN.org/ACCELERATE. if you change your mind, please call the office at 215-614-0936. Thank you for your time and have a great day! • If YES: When would you like to schedule the telephone consent? Would you like for me to call you back to schedule this? <i>[if you confirm that the caller's name, including spelling, is the same as noted above, you can type: "As above"]</i> Name: Email Address: Best phone # to reach you: Best time of day to contact you: • The telephone consent process will take about 10-15 minutes. Is there a day of the week that is best for you? <i>[write day here]</i> • How about <i>[date, day and time]</i>? • So I will speak with you on <i>[day, date, time]</i>. I will also email you a confirmation of our phone call time and the study consent form for your review. • Do you have any questions? <i>[List the gist of their questions here]</i>. Please call Dr. David Fajgenbaum at 215-614-0936 if you have any further questions or need more information. Thanks and have a great day!	

11.8 Data Collection Schedule

In the PPA, prospective data collection will occur every 12 months. Also, patients may contribute patient-reported outcomes (PRO) data periodically (e.g., via electronic methods) and physicians may contribute physician-reported data.

	Baseline	Prospective Data Collection* *Occurring every 12 months	Final Data Collection/End of registry ¹
Medical History, Current CD Status, and CD Treatment			
Informed consent (ICF)/Assent & Authorization	X		
Contact information	X		
Socio-demographic & Diagnosis	X		
Family history & anthropometric	X	X	X
Review Inclusion Criteria	X		
CD Medical history ^{2,3}	X ⁴	X	X
Co-morbid conditions	X	X	X
Disease timeline	X	X	X
Treatment History	X	X	X
Clinical outcomes	X	X	X
Pathology reports & lymph slides	X	X	X
Safety Assessments			
Adverse Events	X	X	X
Other Assessments			
Patient surveys for PRO data ⁵	X	X (every 3 months)	X

¹ The End of Registry form will be the last data collection time point for an individual patient. The form will also be completed when a patient withdraws.

² Symptoms of disease and control, relief and elimination of symptoms (including current treatments) may be assessed using these parameters.

³ The location and type of tissue samples will be collected and tracked. Patients will have stained lymph node and/or bone marrow slides submitted for pathology review within that country. Where possible, the slides will be scanned and uploaded to the database.

⁴ Including dates of initial diagnosis, distribution of enlarged nodes at diagnosis, and current distribution of enlarged nodes

⁵ Patients can also choose to supply additional PRO data (e.g., via electronic methods) every three months, where permitted per local regulations.

PART B: Physician-Directed Arm (PDA)

Part B of this document describes the protocol for the Physician-Directed Arm (PDA), which will occur at 24 sites in EU, LA, and AP.

12 Investigational Plan PDA

12.1 General Design for PDA

The proposed study is a non-interventional, observational, multi-national, multicenter, prospective, natural history study registry of patients with pathology-confirmed Castleman disease. The ACCELERATE Registry database will collect data from the following sources, in accordance with local regulations:

- Patient medical records
- Patient surveys via a patient portal (where local regulation permits)

All patients must give their informed consent to participate in this registry before any data collection is performed. In the PDA, patients will enroll through Independent Ethics Committee (IEC)-approved Participating Physicians at one of 24 study sites. Patients may be existing patients of the Participating Physicians or patients may be referred to Participating Physicians from outside institutions. Patients who are deceased that had Castleman disease and were previously treated by one of the Participating Physicians may also be included in the study, per local regulations (see Section 18.5). When local regulations do not allow for deceased patients to be entered into the registry by a family member through the PDA, family members of deceased patients may enter the deceased Castleman disease patients into the PPA arm of the registry. Following consent of patients, study staff will review medical records and upload a reference pathology report suggesting “Castleman disease” in order to enter the baseline stage.

During the baseline stage, patient medical records will be collected and retrospective baseline data entered manually into a Pulse InfoFrame database by the site staff. Direct patient identifiers will not be entered into the database. Rather a GUID (see section 12.2.2) will be generated for every patient, and a log will be maintained on secure hard drive or under locked key in a secure location at each Participating Physicians site to track GUIDs for every patient enrolled at that site. Every patient will be identified in the database by the GUID. If a GUID cannot be generated due to software restrictions at the site, a unique identifier that is not linked to any patient identifiable information will be generated in its place. Just as with GUIDs, this unique identifier will be maintained in a log on a secure hard drive or under locked key in a secure location at each Participating Physicians site. Following the baseline data collection stage, Participating Physicians and site staff will perform prospective data entry. At least every 6 months, data from clinical visits and hospitalizations will be added to the database. Patients will also be able to provide additional data via surveys, per local regulation.

A panel of international experts on the Certification/Access Subcommittee (CAS) will meet periodically throughout the registry to review every patient’s data to grade the likelihood of the patient’s diagnosis with Castleman disease. The CAS will also be able to review scanned images from lymph node and/or bone marrow slides to assist with diagnostic grading, if consented by the patient, allowed by local regulations, and able to be uploaded by the Participating Physician. The CAS will not exclude patients from the database, but will provide a grade for the likelihood of correct diagnosis with Castleman disease.

12.2 Data to be Collected

Data elements to be collected and entered into the registry database include elements that fall under the below categories, as available through routine clinical practice.

12.2.1 Categories of Registry Data Elements

- Socio-demographics
- Diagnoses, Family History, and Anthropometric
- Pathology
- Laboratory
- Clinical features

- Hospitalizations
- Surgeries and procedures
- Radiographic
- Co-morbid conditions
- Disease timeline, treatments, and adverse events
- Survival/Outcomes
- Clinical research participation and biospecimens
- Patient reported outcomes (where local regulation permits)

12.2.2 GUID and Identifiable Health Information

Data collected through ACCELERATE will be coded so that direct patient identifiers are not exposed to future researchers. A Global Unique Identifier (GUID), a computer-generated alphanumeric code that is unique to each research participant, will be generated for each patient through complimentary software provided by the National Institute of Health. The Participating Physician will have access to this software and will generate each patient's GUID. The following information is needed to generate an encrypted GUID:

- Complete legal given first, middle and last names of patient at birth
- Date of birth
- Name of city/municipality in which patient was born
- Country of birth
- Physical sex of patient at birth (optional)

The GUID enables data from a coded patient to be integrated; tracked over time; and linked across projects, databases and biobanks. The CDCN is in the process of launching several translational research studies and building a biobank for storing tissue samples. All of these projects will use the GUID to track participants. Researchers will be able to request coded data, which may include indirect identifiers, from multiple data sources and identify common patients through the GUID. If a GUID cannot be generated due to software restrictions, a unique identifier that is not linked to any patient identifiable information will be generated in its place.

For patients who additionally give permission to be re-contacted at a later date, their preferred method of contact will also be stored in a protective fashion. This may include phone number (cell, work, or home), fax number, home or business address, or electronic mail address.

Additional identifiable health information that will be collected for the registry include:

- All elements of dates directly related to an individual, including birth date (only year will be entered into the database), admission date, discharge date, diagnosis date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
- Medical record numbers to assist with acquiring medical records;

Data fields that contain direct patient identifiers will be tagged in the database tables within the platform and will not be available to data download functionality. These data will only be visible to the Participating Physician, study staff, PI, ART, and Certification & Access Subcommittee (CAS), who have all been trained in procedures of patient confidentiality. Direct identifiers will not be available as data output from the registry to future researchers. The purpose of maintaining this PHI will be to facilitate the entry of follow-up data into the registry.

12.3 Study Measures

See Section 4.3 for study measures collected for both the PPA and PDA. Optional patient surveys will be included in the PDA per local regulation

12.4 Study Endpoints

12.4.1 Primary Study Endpoint

This registry is designed to generate data for informational purposes and as a resource for future analyses. Thus, the results will be presented descriptively and no formal hypotheses will be pre-specified or endpoints assessed.

13 Study Population and Duration of Participation for PDA

13.1 Duration of Study Participation

This is an open-ended study. The registry will exist for at least 5 years after first patient enrolled. Patients can leave at any time.

13.2 Total Number of Patients and Sites

The registry will be conducted at 24 investigative sites in EU, LA, and AP (PDA). UPenn will serve as the global data coordinating center for the registry. Prospective enrollment will be an ongoing effort, without a fixed end date or target patient number. We expect to enroll approximately 150 patients over the course of the first five years from the 24 PDA sites. With concurrent enrollment through the PPA, particularly in North America, we anticipate our total patient numbers at 120 per year and 600 over the course of the first five years.

13.3 Inclusion Criteria

To be eligible for the registry, patients must satisfy all of the following inclusion criteria:

- Person of any age
- Be able to provide a reference pathology report suggesting “Castleman disease” not limited to cutaneous involvement only
- Sign a participation agreement or informed consent document, as per local regulations

Deceased patients may also be enrolled when a reference pathology report suggesting “Castleman disease” can be supplied or located and uploaded by the site staff, per local regulations. When local regulation does not allow for deceased patients to be entered into the registry by a family member through the PDA, family members of deceased patients may enter the deceased Castleman disease patients into the PPA arm of the registry.

13.4 Exclusion Criteria

Because this registry is designed to provide as wide a picture of routine clinical practice as possible, inclusion criteria are set deliberately wide and there are no exclusion criteria.

13.5 Site Selection and Patient Recruitment

10 sites have been selected for patient enrollment in the EU, 5 sites have been selected for patient enrollment in LA, and 9 sites have been selected for patient enrollment in AP based on their prior ability to enroll patients in a Castleman disease study, their expected enrollment, their experience using siltuximab in the indicated patient population, and their experience conducting observational studies. These sites will apply to their institutions for IEC approval and also submit protocols to their local ethics committees, as required. UPenn will maintain copies of these approvals, distribute any protocol changes to all sites and ensure all changes are approved on an ongoing basis prior to implementation of any study activities at the participating sites.

Patients will be recruited to enroll by the pre-selected registry sites. To reduce selection bias from a participating site, all consecutive patients visiting the site that meet the inclusion criteria will be invited to enroll in the registry.

We anticipate outside referrals to the Participating Physicians at the 24 study sites based on publications and presentations about the registry as well as the following efforts, which will be implemented upon approval by the local IEC:

- Advertisements in the Castleman Disease Collaborative Network (CDCN) e-newsletter, website, and social media;
- Emails to patient members of the CDCN and patients who contact the CDCN through the website or by email;
- Outreach to the CDCN physician database and the authors of published case reports to ask them to provide information about ACCELERATE participation to their patients;
- Mailings to academic hematology divisions and private practices, and to share information with patients; and
- Emails to other patient advocacy groups (e.g., International Castleman's Disease Organization, EURORDIS, NORD, PatientsLikeMe).

See Section 32.2 for text. All posting will be done in collaboration with the CDCN and posting will be done through CDCN media services (communications, marketing Facebook, Twitter, etc). No recruitment efforts will involve any UPenn media services or social media avenues.

Study contact information will be available on the ACCELERATE website for those that may wish to inquire about participating at one of the 24 study sites.

13.6 Vulnerable Populations

The registry will involve children and may involve pregnant women, although pregnant women are not specifically targeted for this research. As there are no interventions, nor compensation related to this observational registry, study procedures will not affect the condition of children or pregnant women and do not require additional protections for these populations. A supplemental form related to protection of vulnerable populations has been completed for children.

14 Study Procedures for PDA

There are 3 stages of data collection planned for the registry:

- Enrollment and Baseline: All patients will have historical data and current patient status captured from a review of medical notes and survey questions.
- Prospective Data Collection Stage: This stage will capture clinical, laboratory, treatments, and safety data with every checkpoint, which includes when a patient is hospitalized, the patient visits his/her physician, or every six months, if a checkpoint does not occur within 6 months. At each data collection point, any changes since the last data collection point and interim lab values will be captured. Patient-reported data will be captured via surveys every 3 months, where local regulation permits.
- End-of-Registry: Final prospective data collection, including survival.

The Data Collection Schedule in Section 19.4 summarizes the frequency and timing of data to be collected.

14.1 Enrollment and Baseline Data Collection Stage

In the PDA, Participating Physicians at IEC-approved sites will consent and enroll patients in person to participate in the registry. Site staff will locate and upload a pathology report suggestive of Castleman disease as part of their registration, and Participating Physicians will assign patients a Global Unique Identifier (GUID) or other unique identifier, which will be entered with all data (see Section 12.2.2 for details).

Upon enrollment into the registry, the Participating Physician or site staff will perform baseline data collection via medical record abstraction of pertinent baseline information into an eCRF in English. The PI and CDCN Scientific Advisory Board developed the inventory of data elements to be entered based on an extensive literature review, medical record abstraction of cases, and expert experience. We expect to add, subtract or modify these data elements during the course of the registry based on periodic data audits. The types and locations of all Castleman disease tissue samples may also be entered in the registry ("e-

repository”). The Participating Physician will also collect email addresses from their patient so that they can send a link to an online portal for the patient to complete an optional survey, if consented and allowed per local regulations. Patients may be re-contacted for additional information.

14.2 Observational Phase

14.2.1 Prospective Data Collection Stage

The prospective data collection stage is defined as the period from baseline to patient withdrawal or completion of the registry. During this stage, the Participating Physician or site staff will enter additional data into the electronic Case Report Form (eCRF) when a patient is hospitalized or the patient visits his/her physician, or every 6 months, if an event does not occur. At each data collection point, the Participating Physician must review data obtained since the previous data collection and record the relevant data in the eCRF. The Participating Physician will continue to care for, test, and treat the patient in line with routine clinical practice. All procedures are standard of care, and no interventions should be introduced because of participation in the registry. If consented and allowed per local regulations, enrolled patients will be provided with a link to an online portal for the patient to complete an optional survey, which will not take more than 20 minutes to complete, every three months. The Participating Physician will collect the patient's email and enter it into the database platform. The email will be instantaneously encrypted using homomorphic encryption (Bcrypt); email addresses will not be stored as plaintext. The database platform will then send an automatic regularly-scheduled email to the patient with a request to fill out the survey.

When the time period since last data entry by a Participating Physician in the EU is >6 months, the ACCELERATE Registry Team (ART) at UPenn will contact the Participating Physician for additional information. If the Participating Physician is not able to provide additional information or get in contact with the patient, the steps described in Section 14.4 will be taken to obtain vital status information. The consent form specifically allows record collection for the lifespan of the patient, and any post-mortem medical records. Prospective data collection will continue until the registry is complete or the patient is withdrawn from the registry, irrespective of the treatments prescribed by their physicians.

If consented, the Participating Physician will also seek out stained lymph node and/or bone marrow slides from previously performed clinical procedures on select patients to be de-identified, scanned, and uploaded to the online system to assist the CAS with diagnostic grading, as allowed by local regulations.

14.2.2 Unscheduled Visits

Visits can occur at any interval that is part of routine clinical practice and are not scheduled research visits. Data from each visit will be entered into the registry database.

14.3 End of Enrollment and Data Collection in the Registry

The registry will exist for at least 5 years after the first patient is enrolled, but the termination date for the registry has not been determined. Patients will continue to be observed in this registry until one year after the last patient is enrolled. The Sponsoring Institution reserves the right to close the study site or terminate the registry at any time for any reason at the sole discretion of the Sponsoring Institution. The Participating Physician may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Patients will be followed for the entire prospective data collection stage until the registry is closed.

14.4 Patient Withdrawal

Patients may withdraw from the study at any time without impact to their care by informing the Participating Physician at the study site. Patients that are lost to follow-up or withdraw from the registry will be censored on the last date that the patient is known to be alive or lost to follow-up.

If a patient withdraws from the registry, the reason for withdrawal, if available, is to be documented in the eCRF and the End-of-Registry Form(s) should be completed. If a patient is lost to follow-up, every reasonable effort should be made by the site staff to contact the patient and determine the reason for

discontinuation/withdrawal. The measures taken to follow up should be documented. Any data collected prior to loss to follow up will be available for inclusion in all analyses. Survival data will be collected for all patients annually after enrollment or at the close of the registry, whichever occurs first, except for those patients who withdraw their consent beforehand. For patients lost to follow up, where applicable, the following steps will be taken to obtain vital status: the site staff will attempt to contact the patient, contact the patient's general practitioner, review publicly available records, and/or contact family members.

15 Safety and Adverse Events (AEs) for PDA

There are three tiers related to safety and reporting for the PDA:

1. Unanticipated problems involving risks to patients and others will be monitored for all patients throughout the study. Since the study procedures are not greater than minimal risk and are limited to existing data and no study interventions are employed, no risk of physical harm is expected from participation in the registry. The greatest risk is breach of confidentiality. If any unanticipated problems related to the research involving risks to patients or others happen during the course of this study, these will be reported to the Participating Physician's IEC in accordance with local regulations. Unanticipated problems that do not involve risks to patients or others but arise will be summarized in a narrative or other format and submitted to the IEC at the time of continuing review.

2. Though not considered to be adverse events of the registry (because the registry is non-interventional), safety events will be collected for all Castleman disease treatments in the registry. Physicians observing adverse events and serious adverse events will enter these events into the eCRF and will be instructed to report these through existing safety reporting procedures per local regulations.

3. Since Janssen Pharmaceutica NV produces a Castleman disease therapy and is a collaborative partner for this registry, safety reporting procedures not typically performed for observational registries will be performed for Janssen Pharmaceutica NV drugs, including siltuximab. All safety events attributed from clinical evaluation to the use of Janssen Pharmaceutica NV products will be collected as part of tier 2 (above) and will also be reported to Janssen Pharmaceutica NV to comply with the company's pharmacovigilance practices for the duration of Janssen Pharmaceutica NV's financial sponsorship, which is anticipated to last for five years. See section 15.5.2. This is not a requirement imposed by the EMA as part of the PAM or another regulatory body.

15.1 Definitions

The definitions for Adverse Event, Adverse Drug Reaction, Serious Adverse Event, unlisted (unexpected) Adverse Event, association with the use of drugs, unanticipated problems, and Product Quality Complaint (PQC) are provided in Section 7.1 in relation to the second tier of reporting.

15.2 Recording of Adverse Events

All adverse events associated with participation in the registry will be recorded for all participants (see tier 1 in section 15). Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

This is a non-interventional registry, and no specific safety tests will be collected unless available as part of routine clinical practice. Though not an adverse event related to participation in the study, all ADRs, pregnancies, and special situations documented in the medical records following exposure to Castleman disease treatments are to be recorded by the Participating Physician in the appropriate adverse event module of the eCRF, regardless of seriousness (see tier 2 in section 15). Evaluations of safety and tolerability will be documented according to the time points provided in the Data Collection Schedule. Only results available per routine clinical practice will be collected. Recording of adverse events will be different in the baseline data collection stage compared with the prospective data collection stage.

15.2.1 Baseline data collection stage

For data collected from medical charts for the period prior to the start of registry participation, all adverse drug reactions (ADRs), pregnancies, and special situations documented in the source data following exposure to Castleman disease treatments are to be recorded in the eCRF, regardless of seriousness. For an adverse event to be reportable in the eCRF, there should be information in the source data and/or retrospective study database that confirms that the event is specifically indicated or clearly implied (verbally or documented) as at least possibly related to the use of the Castleman disease treatment. ADRs should be collected from the first documented use of the Castleman disease treatment within the protocol-defined data collection period until 30 days after the last documented use of the Castleman disease treatment within the data collection period.

15.2.2 Prospective data collect stage

All adverse events (AE), serious adverse events (SAE), and special situations for Castleman disease treatments are to be documented in the eCRF. All adverse events and special situations following exposure to Castleman disease treatments are to be systematically recorded in the eCRF and the patient's source records, regardless of seriousness or causality. Adverse event collection should start with the first use within the registry of the Castleman disease treatment and will apply to all adverse events, regardless of seriousness, that occur within 30 days after a patient's last use of the Castleman disease treatment within the registry. All adverse events following exposure to the Castleman disease treatment should be assessed by the Participating Physician to document their opinion concerning the relationship of the event to the Castleman disease treatment; the causal relationship of the adverse event must be recorded in the eCRF. An adverse event will be considered as an ADR if there is at least a reasonable possibility of a causal relationship. Where necessary, the sponsor (and/or Participating Physician, as applicable) will report non-serious ADRs to the local health authorities following applicable requirements.

All follow-up information for SAEs that are not resolved at the end of the registry or by the time of patient withdrawal must be reported directly by the Participating Physician, within 24 hours of them becoming aware, using a Serious Adverse Event Report Form or local equivalent.

15.3 Relationship of AE to Treatment and Severity Criteria

The Participating Physician and designated study staff should use the definitions in Section 7.1 to assess the relationship of the treatment with the adverse event and assess the severity grade.

15.4 Special Reporting Situations

See Section 7.4.

15.5 Reporting of Adverse Events and Unanticipated Problems

The Participating Physicians at each site will promptly notify the IEC/IRB of all on-site unanticipated, adverse events that are related to the research activity. Other unanticipated problems related to the research involving risk to patients or others will also be reported promptly. Written reports will be filed according to local regulation.

All SAEs for patients on siltuximab should also be reported directly by the Participating Physician, within 24 hours of them becoming aware, to the local sponsor (see country-specific attachments) using a Serious Adverse Event Report Form (or local equivalent). When necessary, Janssen Pharmaceutica NV will inform the local health authorities following applicable requirements for expedited and aggregated reporting.

A product quality complaint (PQC) may have an impact on the safety and effectiveness of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the pharmaceutical manufacturer, and are mandated by regulatory agencies worldwide. Janssen Pharmaceutica NV has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by Janssen Pharmaceutica NV or its affiliates will be conducted in accordance with those procedures.

All initial PQC's involving a Janssen Pharmaceutica NV product must be reported to Janssen Pharmaceutica NV by the participating site personnel within 24 hours after being made aware of the event. The names (and corresponding telephone numbers) of the individuals who should be contacted regarding PQC's for a Janssen Pharmaceutica NV product are listed on the contact information page(s), which is/are provided separately. If the defect for a Janssen Pharmaceutica NV product is combined with a serious adverse event, the study-site personnel must report the PQC to the local Janssen Pharmaceutica NV representative according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the Janssen Pharmaceutica NV.

15.5.1 Follow-up Report

This is a non-interventional registry, and no specific safety tests will be collected unless available as part of routine clinical practice. All adverse events should be followed-up in accordance with clinical practice, regardless of seriousness. This follow-up should be recorded in the patients' source records. Evaluations of safety and tolerability will be documented according to the time points provided in the Data Collection Schedule, but no additional AE follow up will be performed for patients in the European arm of the registry.

15.5.2 Safety reporting: notifying the financial sponsor

UPenn is the Sponsoring Institution of the registry. Janssen Pharmaceutica NV is the financial sponsor for this registry, a collaborative partner, and the manufacturers of an FDA- and EMA-approved treatment for HIV-negative and HHV-8-negative multicentric Castleman disease (siltuximab, SYLVANT®). Within this study, UPenn will delegate their safety reporting responsibility related to the PDA in the PDA sites to Janssen Pharmaceutica NV, who will delegate these responsibilities to a contract research organization (CRO), Parexel.

The delegated responsibilities to fulfill tier 3 described in section 15 (reporting AEs to Janssen Pharmaceutica NV for their products for company pharmacovigilance) include:

- Training the study personnel on managing safety information according to agreed procedures;
- The retrieval and assessment of all serious adverse events originating from all clinical sites or Participating Physicians in the concerned trial;
- Submission of expedited serious single case reports to Health Authorities (by electronic means where applicable), the Ethics committee(s) and where applicable to the distribution of these to all Participating Physicians in the concerned trial;
- The preparation and submission of annual safety reports (ASR) of the concerned study;
- The submission of periodic listings of expedited serious unexpected adverse events as appropriate;
- The submission of any updated documents as required.

The PDA Registry Sites and Participating Physicians will submit to the Janssen Pharmaceutica NV Local Safety Officer (LSO) the following safety information:

- All Serious Adverse Events, pregnancy reports and product quality complaints (PQC's) involving siltuximab regardless of whether causality with the administration of siltuximab is suspected by the Participating Physician.
- The Registry Site and Participating Physician will transmit these SAE reports by facsimile in English within 24 hours of becoming aware of the event(s). Follow-up information will be transmitted within the same timelines;
- The Registry Site and Participating Physician shall notify UPenn immediately in case of a suspension of recruitment or premature stop of the registry because of a safety concern; preferably by means of a telephone contact with the Janssen Pharmaceutica NV Study Responsible Physician (SRP) or UPenn Representative, alternatively by fax within 24 hours of the decision;
- The Registry Site and Participating Physician shall provide all Adverse Events, both serious and non-serious, annually and in a final report format within 90 days after completion of the treatment.

The ART will provide the Registry Sites and Participating Physicians with the following information:

- The most recent Summary of Product Characteristics (SmPC) for siltuximab.
- ICF risk wording

- Any new information, which becomes available during the course of the Study, which may affect the overall safety profile of siltuximab.
- On a quarterly base, a list of the Study's SAEs, as previously received by UPenn from the Registry Sites and Participating Physicians, will be forwarded to the Registry Sites and Participating Physicians for reconciliation with Janssen Pharmaceutica NV's safety database.

The SAE reporting for the PDA patients will be the following:

- Participating Physician to enter SAE – following exposure to siltuximab or another Janssen Pharmaceutica NV product – in the eCRF system
- eCRF system will send alert to UPenn for follow up with Site = Start Reporting Clock
- Participating Physician to print SAE report from eCRF
- Participating Physician to fax SAE report together with Cover letter to LSO within 24 hours (hospital letters or other eCRF pages need to be attached to the fax, only the printed report).
- Participating Physician to send copy of SAE report to Janssen Pharmaceutica NV SRP and UPenn representative.
- LSO will notify Janssen Pharmaceutica NV GMS (Global Medical Safety)

All the questions associated with the SAE report forms received by the LSO for the PDA sites will be followed up by Janssen Pharmaceutica NV or Parexel. On a monthly basis, UPenn will provide Janssen Pharmaceutica NV with the database extract including information about all non-serious AEs and non-siltuximab related SAEs (siltuximab-related SAEs will be reported through a separate mechanism). Janssen Pharmaceutica NV will then further process the AE reporting to the appropriate authorities.

The ART will perform a safety database reconciliation between Janssen Pharmaceutica NV's global safety database and the ACCELERATE registry database. Janssen Pharmaceutica NV will provide an extract (as an excel file) from its safety database, SCEPTRE, which will list all the SAEs registered so that UPenn can perform the reconciliation against the medical database. In case of any inconsistency related to the safety data extract, UPenn will add a query to the corresponding eCRF and/or send a data update request to Janssen Pharmaceutica NV Safety Management.

15.5.3 Data and Safety Monitoring Plan

See Section 21.

16 Study Administration, Data Handling and Record Keeping for PDA

16.1 Confidentiality

16.1.1 Country-Specific Regulations

For patients enrolling through the PDA, information about study patients will be kept confidential and managed according to the Data Protection document (Directive 95/46/EC), International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6, and local regulations.

16.1.2 Confidentiality Practices by the Sites

A number of precautions will be taken to assure the confidentiality of patients. During the process of enrollment, each patient will be assigned a GUID by the Participating Physician, which will be used to identify the participant's database records. This unique identifier will be generated from patient identifiers, but will not contain any patient identifiers such as the patient's initials or significant dates. The patient's name and other directly identifying information will not be entered into the database. This information will be stored along with the GUID on a secure harddrive or within a locked filing cabinet located in the Participating Physician's office. All paper documents (e.g. original signed consent forms) will be stored within a locked filing cabinet located in the Participating Physician's office. All reports and communications relating to the registry will be appropriately coded, identifying patients by the GUID.

See Section 22 for the confidentiality practices taken by the ART as part of its responsibility as Global Data Coordinating Center.

16.2 Data Collection and Management Done by the Sites

Data will be collected and managed in accordance with the below outline. See flowchart in section 19.1.

1. Enrollment: The patient will be consented to enroll into the registry by the Participating Physician or site staff. The patient will sign an informed consent in-person with the Participating Physician. If the patient has been seen by other physicians and hospitalized at other institutions than the Participating Physician, the patient will complete a questionnaire that includes signing an authorization to access medical records available through the other physicians and hospitals. A GUID or other unique identifier will be created by the Participating Physician for each patient and used in place of name and other directly identifying information in the system.
2. Baseline Data Collection:
 - a. The Site Staff will gather old medical records for the patient. These medical records will be entered manually into the eCRF by the site staff.
 - b. If the patient was seen by other physicians and hospitalized at other institutions, the ART will contact the patient's hospital and physician to request medical records be faxed, emailed, or mailed to the study site. Alternatively, patients may send copies of medical records by fax, mail, or email to the study site.
 - c. During the baseline visit with the patient, the Participating Physician and/or Site Staff will enter data on the patient. Electronic data capture will be used for this registry. Guidelines for eCRF completion will be provided and reviewed with registry personnel before the start of the registry. All eCRF entries, corrections, and alterations must be made by the Participating Physician and/or Site Staff. The Participating Physician and/or Site Staff must verify that all data entries in the eCRFs are accurate and correct. If necessary, queries will be generated in the eCRF. The Participating Physician or an authorized member of the ART (at UPenn) must adjust the eCRF (if applicable) and complete the query. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in three different ways:
 - i. Site personnel can make corrections in the eCRF at their own initiative or as a response to an auto query (generated by the eCRF);
 - ii. Site personnel at the registry site can generate a query for resolution by the ART
 - iii. The Clinical Data Specialist can generate a query for resolution by the Participating Physician.
 - d. If consented and allowed by local regulations, the Participating Physician will also collect email addresses from their patient so that they can send a link to an online portal for the patient to complete an optional survey.
3. Prospective Data Collection
 - a. The Participating Physician and/or Site Staff will enter data on the patient based on clinic visits and hospitalizations that occur during routine clinical practice. Data must be entered into eCRF in English. Adverse events will be recorded and the ART will scan and lock paper records in safe storage.
 - b. If no information is entered into the registry for a six-month period, the ART (at UPenn) will contact the Participating Physician to update the status of their patient. If the patient cannot be located, the Participating Physician will contact family members and check vital status through a national death registry if available.
 - c. If consented and allowed by local regulations, a secure, automatic email will be sent to each enrolled patient with a link to an online portal for the patient to complete an optional survey every three months.
 - d. The Participating Physician may request that stained lymph node and/or bone marrow slides be de-identified scanned and uploaded through the online portal for future review by the CAS, if consented, allowed by local regulations, and feasible.
4. Withdrawal

- a. A patient may withdraw for any reason. If this occurs, the Participating Physician and/or Site Staff will record the reason and complete an end of study form. If consented, the Participating Physician and/or Site Staff will check vital status through a national death registry periodically.
- 5. Secure physical and electronic document storage
 - a. Primary records, such as original copies of signed consent forms, will be stored in a locked filing cabinet and will only be available to study investigators. The documents will be stored in files labeled only with a patient's name and therefore not linked to GUID. Electronic copies of these documents will be created and stored securely. These primary records will not be available to any future recipients of registry-repository data without a separate IEC approval.

All data management, data access, and data migrations will be done by the ART as the Global Data Coordinating Center for the registry. See Section 23 for details on data management for the PDA.

16.3 Data Access & Migrations

See Section 25.

16.4 Records Retention for PDA Sites

The Participating Physicians in the PDA will maintain all printed documents that support the data collected from each patient and all registry documents as specified by the applicable regulatory requirement(s). The Participating Physician/institution will take measures to prevent accidental or premature destruction of these documents.

If the responsible Participating Physician retires, relocates, or for other reasons withdraws from the responsibility of keeping the registry records, custody must be transferred to a person who will accept the responsibility. The new person (new custody) needs IEC approval or will inform the IEC of the transfer of responsibilities. The ART must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Participating Physician relocate or dispose of any registry documents before having obtained written approval from the Sponsoring Institution.

See Section 26 for further Records Retention information.

16.5 Providing Results to Patients

See Section 27.

17 Study Monitoring, Auditing, and Inspecting for PDA

17.1 Study Monitoring Plan

See Section 28.

17.2 Auditing and Inspecting

The Principal Investigator and Participating Physicians will permit study-related monitoring, audits, and inspections by the IEC/IRB, the financial sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The Principal Investigator and Participating Physicians will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as a Principal Investigator or Participating Physician in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

18 Ethical Considerations for PDA

This protocol and any amendments will be submitted to the Institutional Review Board (IRB) at UPenn for formal approval of the study. This approval will cover enrollment and research performed on patient data from the PPA (Part A) and cover Penn's role as a global data coordination center for the PDA protocol (Part C). The PDA protocol, which is described in Part B, will need to receive local ethical approval for each of the sites. If necessary, the protocol may need to be amended per local regulation.

This PDA arm of the registry will begin only after the Participating Physician has received all necessary approvals of the final protocol, amendments (if any), and the informed consent form, and the Sponsoring Institution has received a copy of this approval, as per local regulations. This approval letter must be dated and must clearly identify the IEC and the documents being approved. The Participating Physician (or Sponsoring Institution where required) will fulfill all other local requirements regarding project conduct (approval of protocol amendment, annual reporting) where required during the conduct of the registry and at registry completion. It is the responsibility of each Participating Physician to determine the IEC/IRB requirements and associated timelines, and for ensuring compliance with these requirements.

The following documents must be provided to the Sponsoring Institution (University of Pennsylvania) by the Participating Physician before commencement of the registry:

- Protocol and amendment(s), if any, signed and dated by the Participating Physician
- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, informed consent form, and any recruiting materials
- If appropriate, a copy of the dated and signed written DRB (Designated Regulatory Body) approval of the protocol, amendments, informed consent form, any recruiting materials. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee
- If appropriate or according to local regulation, name and address of the DRB [with a statement that it is organized and operates according to applicable laws and regulations]. If a Participating Physician or a member of the ART is a member of the DRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the registry
- Regulatory authority approval or notification, if applicable
- Where appropriate, documentation of the Participating Physician qualifications (e.g., curriculum vitae)
- Where required, completed financial disclosure form from the Participating Physician.
- Any other documentation required by local regulations
- Signed and dated trial agreement, which includes the financial agreement
- Where appropriate, documentation of Participating Physician qualifications (e.g., curriculum vitae)

A previous version of this protocol was submitted to the European Medicines Agency (EMA) on December 19, 2014. On April 23, 2015, the EMA reported that “the design of the registry is considered acceptable” to meet the EMA's requirement for Janssen Pharmaceutica NV “to conduct a Registry to collect information on patients with Castleman's disease.”

The ACCELERATE Steering Committee (ASC) will review and vote on all potential protocol amendments. For all protocol amendments determined by the ASC (excluding the ones that are purely administrative, with no consequences for patients, data or registry conduct), the amendment and applicable informed consent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s). Protocol amendments will follow the review and approval process in place as per local regulation.

18.1 Risks

The risks to study patients due to participation in this protocol are small. The only risk to participants is breach of confidentiality. This risk has been fully addressed as described in Section 22.

18.2 Benefits

It is not anticipated that patients will receive any direct benefit as a result of their participation in the ACCELERATE registry. However, this registry will generate data that may improve our knowledge and treatment of Castleman disease, which may benefit patients with Castleman disease in the future.

18.3 Risk Benefit Assessment

The potential long-term benefits of improving knowledge and treatment of Castleman disease outweigh the low risks associated with participation in this study for these patients.

18.4 Informed Consent Process / Privacy Policy Authorization

18.4.1 Country- and Registrant-Specific Differences in Informed Consent Process

The Informed Consent Process, which will meet the requirements of the Data Protection document (Directive 95/46/EC) and ICH GCP E6, will differ based on the location of the study patient (United Kingdom, Germany, France, Spain, Italy, Norway, Brazil, Mexico, Argentina, Taiwan, China) and the type of registrant (Patient <7 years old, Patient 7-17 years old, Patient >17 years old, family member of deceased patient), per local regulations. The master informed consent will be adapted to meet local regulation. When necessary, the Participating Physician will use interpreters or translators during the consent process. In addition, the patients will receive written information in their native languages describing the project. This consent form will be submitted with the protocol for review and approval by the IEC for the study.

The informed consent process will take place in-person with the Participating Physician. Potential patients will review the consent form in detail with site personnel designated to consent and have the ability to take the consent home for further review. Underage participants will be defined by local regulations in each of the selected countries. Underage participants that reach the local legal age for providing informed consent during follow-up will be re-consented as soon as feasible, i.e., at the next follow-up visit. If at the age of majority the participant is not able to provide consent due to mental incapacity the above procedures for obtaining consent will be followed.

Parental permission will be obtained from parent/legal guardian for all underage participants and assent will be obtained as described below; however, where applicable, these procedures will be modified to comply with local regulations and requirements.

- <7 years: written parental permission will be obtained and documented
- 7 to 12 years: written parental permission and verbal assent by the participating child will be obtained and documented
- 13 to 17 years: parental permission with written assent by the participating child will be obtained and documented through signature

Adult patients should appropriately record their consent by means of the patient's personally dated signature. After having obtained the consent, a second original copy of the participation agreement or informed consent form as required by local regulation must be given to the patient.

18.4.2 Components of Informed Consent

See Section 11.1 for the components of the USA and Canada versions of the Informed Consent Form, which will be adapted according to countries' specific regulations and to be an in person consent process. The observational nature of the registry and that the registry only intends to collect information and follow their course of treatment in the clinical practice setting will be explained to potential patients. Patients will be informed that their authorization to allow the collection of the data is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care they will receive. Participants will be informed that research results will only be returned to the patient if a clinically-actionable, life-threatening disease other than Castleman disease is highly suggested from review of their data. Specifically, the consent for patients in the PDA will include:

- Global consent for the patient to participate in the registry

- Consent for the ART and/or site staff to contact all physicians that have cared for the patient for additional clinical data
- Consent for the ART and/or site staff to re-contact the patient for additional clinical data and to remind the patient to complete a survey every three months
- Consent for the ART and/or site staff to access and process all past and future medical records (including post-mortem) for the patient
- Consent for the ART and/or site staff to track the location and type of tissue samples currently stored
- Consent for the site staff to have ongoing clinical notes sent to the site staff
- Consent for ART and/or site staff to request lymph node and/or bone marrow slides to de-identify scan and upload images for central pathology review by the CAS
- Consent for the ART and/or site staff to re-contact the patient in the future to request tissue samples and to present options for future research opportunities
- Consent for the transfer of coded data without direct identifiers to other entities, such as health authorities and other third parties, without violating confidentiality, to the extent permitted by the applicable law(s) or regulations
- Consent for automated transfer of data from the patient's electronic medical records

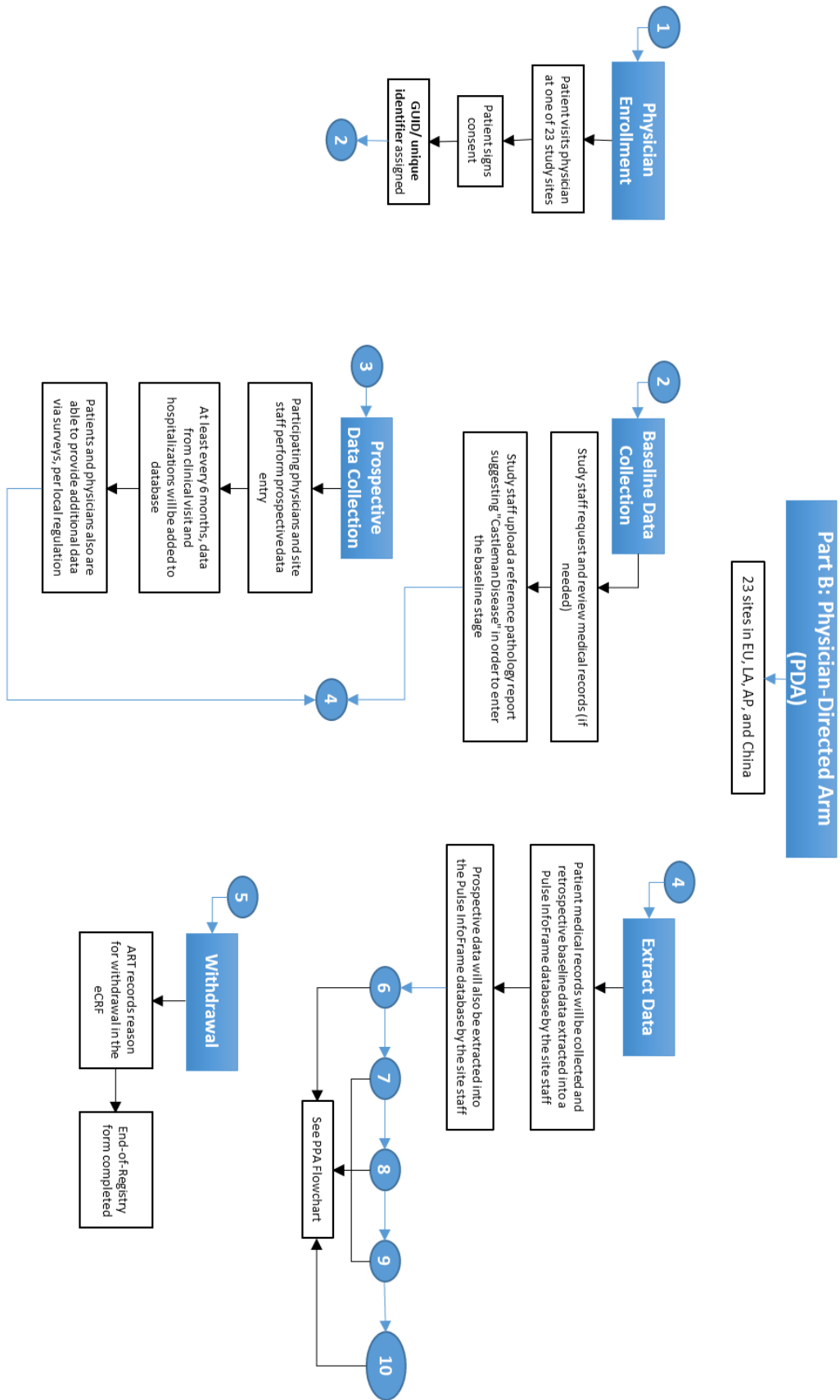
The consent form will be submitted with the protocol for review and approval by the local IEC for the study sites. The formal consent of a patient, using the IEC-approved consent form, must be completed before that patient participates in any registry-related activities. A second original copy of the combined consent-authorization form will be provided to the patient for their records. Following consent, patients will also sign a records release authorization form to allow release of medical records to the ART which will be developed by the local site as per local regulations.

18.5 Permission for Use of Medical Records for Deceased Individuals

While deceased individuals technically do not qualify as “human subjects” and the requirements for informed consent do not apply to these individuals, permission for use of medical record review and data entry will be obtained, when available, from family members who wish to provide data about their loved ones for inclusion in the registry, per local regulations. As part of the registration process, family members of deceased individuals will be asked to sign a tailored authorization to allow the registry to collect and include the information of the deceased individual in the registry. This authorization will be compliant with the requirements for research with deceased individuals under the Data Protection document (Directive 95/46/EC) in Europe and/or local regulations in EU, LA, and AP. Per local regulations, the Participating Physician may also be able to enroll deceased patients into the registry directly. When local regulation does not allow for deceased patients to be entered into the registry by a family member through the PDA, family members of deceased patients may enter the deceased Castleman disease patients into the PPA arm of the registry.

19 Part B Attachments

19.1 Study Procedures Flowchart



19.2 Informed Consent Template

See section 11.1 for components of the US and Canadian Consent forms that will be adapted per local regulation for the PDA.

19.3 Participating Physician Agreement**PARTICIPATING PHYSICIAN AGREEMENT**

I have read this protocol and agree that it contains all necessary details for carrying out this registry. I will conduct the registry as outlined herein and will complete the registry within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this registry. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the registry and the obligations of confidentiality.

Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____

Principal Investigator at Sponsoring Institution:

Name (typed or printed): _____

Institution: _____

Signature: _____ Date: _____

19.4 Schedule of Study Procedures:

Data collection in the prospective data collection stage will occur at least every 6-months as per routine clinical practice by the Participating Physician in the PDA. If data are not entered within a 6-month interval, the Participating Physician (PDA) will be contacted. Also, patients may contribute patient-reported outcomes (PRO) data periodically (e.g., via electronic methods).

	Baseline	Prospective Data Collection *	Final Data Collection/End of registry ³
*Participating Physician visit ^{1,2}			
Medical History, Current CD Status, and CD Treatment			
Informed consent & (ICF)/Assent Authorization	X		
Contact Information	X		
Socio-demographic & Diagnosis	X		
Family history & anthropometric	X	X	X
Review Inclusion Criteria	X		
CD Medical history ^{4,5}	X ⁶	X	X
Co-morbid conditions	X	X	X
Disease timeline	X	X	X
Treatment history	X	X	X
Clinical outcomes	X	X	X
Pathology reports & lymph slides	X	X	X
Safety Assessments			
Adverse Events	X	X	X
Other Assessments			
Patient surveys for PRO data ⁷	X	X (every 3 months)	X

- ¹ An Interim Checkpoint is either a hospitalization or a documented clinical visit. Data will be collected at these time points.
- ² If a Participating Physician visit does not occur within 6 months, patients will be contacted for follow up information.
- ³ The End of Registry form will be the last data collection time point for an individual patient. The form will also be completed when a patient withdraws.
- ⁴ Symptoms of disease and control, relief and elimination of symptoms (including current treatments) may be assessed using these parameters.
- ⁵ The location and type of tissue samples will be collected and tracked. Select patients will be chosen to have stained lymph node and/or bone marrow slides scanned and uploaded to the online system for central review by the CAS.
- ⁶ Including dates of initial diagnosis, distribution of enlarged nodes at diagnosis, and current distribution of enlarged nodes
- ⁷ Patients can also choose to supply additional PRO data (e.g., via electronic methods) every three months, where permitted per local regulations.

PART C: Global Data Coordinating Center

Part C describes the protocol for the UPenn study team to serve as a Global Data Coordinating Center for the PPA and PDA. As Global Data Coordinating Center, the PI and ART will be responsible for executing the Statistical Plan, monitoring data collection and safety, reporting, and managing data access and migrations.

20 Statistical Plan

20.1 Sample Size and Power Determination

The registry is designed to generate data for informative purposes. As a result, it is descriptive rather than comparative and no formal hypotheses are to be tested in this registry. Statistical methods were not used to calculate sample size. The registry will endeavor to enroll the largest number of patients feasible.

20.2 Statistical Methods

The statistical analysis plan for this registry aims to include analyses of demographics and baseline disease characteristics, treatment effectiveness data, patient reported outcome data, biologic parameters, safety data, and comparability between treatment groups.

Statistical analyses will be performed by the ART, Principal Investigator, and by Qualified Researchers, who apply to the CAS for access to coded data, which may include indirect identifiers. A general description of the statistical methods to be used to analyze the data collected in this registry by the ART is outlined below.

All continuous variables will be summarized using descriptive statistics, which will include the number of patients, mean, standard deviation, median, minimum, maximum, and 95% confidence interval. All categorical variables will be summarized using frequencies and percentages. Control of symptoms, lymph node responses, and biological parameters will be documented during the registry in accordance with patients' routine care.

20.3 Database Design

The database will be designed as a normalized hierarchical structure allowing for a specific and controlled set of measures to be recorded at irregular intervals over time and across persons. Specific records are expected for distinct types of measures, which are either acquired at different times or from different sources (e.g., hematology vs. rheumatology data, test results vs. encounter data, common vs. uncommon data elements). Data will primarily be abstracted from medical records, and it is expected that new elements

will be added to abstraction records over the life of the study. With this design, data can be extracted for analysis in one of three ways:

1. as rates and measurements within specific time periods (represented in a dashboard style interface),
2. as panel data covering multiple time periods in a given reporting format, or
3. as event history data coalescing multiple abstraction types into a single series of measures structured uniformly over time.

The data in the database, which will consist of a set of normalized tables capturing a diverse set of measurements taken over time, will be extracted with all direct identifiers removed and transferred to Janssen Pharmaceutica NV every six months for the first five years of the registry to be used only for the purposes of reporting data to the EMA. Elements in the database will be restricted to Boolean values, integers, floating point numbers, ASCII-coded English text, date, and date-time values in order to make this transfer as simple as possible. The data can be converted into fixed-length or variable-length records at their discretion. Only fields demarked for release will be extracted such that protected health information are never captured and transmitted in the transfer process.

20.4 Control of Bias and Confounding

This registry seeks to obtain data on a subset of the population of patients with Castleman disease. Many concerns exist when attempting to develop an unbiased registry sample, including biases regarding the selection of patients to be enrolled. To reduce selection bias, ACCELERATE has very wide inclusion criteria and the ART will recruit patients for the PPA through a number of avenues to ensure that a large proportion of Castleman disease patients are included. To reduce selection bias from a participating site in the PDA, all consecutive patients visiting the site that meet the inclusion criteria will be invited to enroll in the registry.

20.5 Anticipated Analyses

20.5.1 Analysis of Demographics and Baseline Disease Characteristics

All patients who complete the baseline assessment will be included in the descriptive analysis of demographic and baseline characteristic data. The aim of the initial analysis is to describe the baseline demographics and disease characteristics of Castleman disease patients. This analysis will report the frequency distribution (number and percentage of patients) for categorical variables and descriptive statistics (mean, standard deviation, median, interquartile range) for continuous variables. Baseline characteristics including demographics, comorbidities, severity of disease, diagnosis and treatment history, concomitant medications, response to prior therapy, current disease status, quality of life data, and duration of registry participation will be tabulated, as available. Baseline data collection will also be analyzed descriptively to present an overview of the state of disease progression and treatments of patients with Castleman disease, with the intent of categorizing patients according to disease characteristics, previous treatments, and other factors that may influence treatment choices.

20.5.2 Analysis of Treatment Effectiveness

There is no intervention tested in this registry. However, data on treatment regimens administered in a real-world setting will be captured. A treatment regimen is defined as a new course (which may have been initiated before enrollment) given to treat Castleman disease; this includes adjustment of any combination therapies (i.e., addition or withdrawal of specific agents within combination therapy, but not dose adjustments). The number and duration of Castleman disease treatment and surveillance periods will be summarized, as well as the treatments received and the reasons for starting and ending them.

There is no standard criterion for measuring responses to therapy in Castleman disease in routine clinical practice, although several approaches have been used in prospective clinical studies. The registry will attempt to comprehensively document common symptoms, radiologic responses, and biological parameters in accordance with patients' routine care, and the definition of response may be evaluated using these data. Clinical assessments and measures of therapeutic outcome may be explored. Demographic,

disease related, and treatment related factors may be evaluated as predictive or prognostic response parameters.

Distribution of time-to-event variables will be estimated using standard survival analysis methods, including Kaplan-Meier product-limit survival curves. The median time to event with 2-sided 95% confidence intervals will be estimated. Time to Next Therapy (TNT), measured from time of initiation of therapy to time of change of therapy, Therapy Free Interval (TFI) measured from time of last dose of last therapy to initiation of subsequent therapy, Progression Free Survival (PFS) measured from first day of a treatment regimen to time of disease progression (based on applied response criteria), and Overall Survival (OS), measured from the date of initial diagnosis of Castleman disease to the date of death (all-cause mortality), may be performed. Patients will be followed from the date of enrollment until the endpoint occurs, censoring upon registry withdrawal, death (as applicable to endpoint), or end of registry period. Survival time, measured from the start of each respective treatment to the last documented follow-up, will also be analyzed. Descriptive statistics in terms of mean, standard deviation, median, and interquartile range, in months, will be provided.

The appropriateness of comparisons between treatments will be evaluated based on the clinical and demographic characteristics of the cohorts and completeness of data. Baseline parameters and patient history will be used to identify patient characteristics that could potentially influence treatment choice and outcomes.

20.5.3 Safety Analyses

Though this study does not involve an intervention, safety information will be collected for treatments, when directly reported in medical records in the PPA and when directly attributed by the Participating Physicians in the PDA. Adverse events with onset during the registry and adverse events since baseline will be included in the descriptive analysis. For each adverse event, the percentage of patients who experienced at least one occurrence of the given event will be summarized.

Summaries, listings, datasets, or clinical narratives will be provided, as needed, for those patients who die or who experience a serious adverse event, stratified by attribution to therapy.

20.5.4 Patient Reported Outcomes Analyses

Descriptive statistics and exploratory analyses may be conducted to describe patient reported outcomes data related to Castleman disease patients allowed per local regulations.

20.5.5 Interim Analysis

Every 6 months an interim analysis will be performed. As this is not an interventional study, there are no stopping rules for efficacy and/or safety. UPenn shall provide Janssen Pharmaceutica NV with pre-defined Study Data sets with each interim analysis to generate reports to fulfill the European Medicines Agency (EMA) PAM requirement for siltuximab.

20.5.6 Ancillary Studies

Ancillary studies, which are separate from the ACCELERATE registry collaboration and utilize data elements collected during ACCELERATE, may be performed by Qualified Researchers. Sharing of data elements will allow for decreased burden on research participants who wish to participate in ancillary studies. These studies may involve more invasive procedures and will be described in separate protocols, undergo separate ethical review, and informed consent forms. Ancillary studies can be added throughout the life of the ACCELERATE registry.

21 Data and Safety Monitoring Plan

The registry will be governed by an ACCELERATE Steering Committee (ASC) and Certification & Access Subcommittee (CAS). The ACCELERATE Steering Committee will include international experts on the execution of international studies and/or management of Castleman disease with equal representation from UPenn, Janssen Pharmaceutica NV, and the CDCN. The ASC will oversee all aspects of the planning, CRF

design, data collection, data analysis, reporting, data sharing, and publishing of ACCELERATE. The ASC will also be responsible for the overall protection of research participants and other legal protections, overseeing the systems that protect the privacy and confidentiality of the research participants, and approving any changes to the protocol or inclusion of sub-studies and/or ancillary studies.

The CAS will consist of a panel of international experts on the diagnosis and treatment of Castleman disease. It will be led by a chair. Membership will be chosen by the ASC and approved by the three collaborative partners. Prior to commencing the registry, the CAS will provide input into registry design, data management, and CRF design. Once the registry begins, the CAS will monitor data quality and meet periodically to grade the likelihood of Castleman disease during the Data Verification stage. The CAS will also review applications by Qualified Researchers for access to the database and/or contacting a patient on an ongoing basis.

The Principal Investigator will also conduct a medical review every six months to identify any potential risks to research subjects and present these risks to the ASC to determine methods for protecting them during the execution of the trial. The medical review, which will be done for quality assurance purposes, will involve calculating the frequency of patients who were included and excluded from the study, patients that did not receive a confirmed diagnosis, responses to questions with “other” or “out of range,” protocol deviations, and adverse events.

22 Confidentiality Practices for the PPA and PDA

A Pulse Inframe database will employ multiple security features to limit access to any identifiable health information to study team members only. Data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. The computerized database will tag all identifiable health information and not permit the viewing of such data except by authorized parties. Strict control over data viewing based on role-based permissions will be enforced. Study personnel, including the ART, whose responsibilities require access to personal data agree to keep the identity of registry patients confidential. Data containing direct identifiers will not be available for export at any time. For future review by the CAS, stained lymph node and/or bone marrow slides will be uploaded to a web-based hosting provider, separate from the Pulse Inframe database. To ensure confidentiality, all slides will be completely de-identified by the ART or the Participating Physician prior to upload. Qualified Researchers, who apply for access to the database, will have a limited dataset with direct identifiers removed transmitted securely using downloaded Excel compatible file formats or single SAS data files. Request and receipt of medical record information and tissue samples will be tracked using secure databases (REDCap, LabVantage).

23 Data Management for the PPA and PDA

Following data collection (steps 1-5) by the ART for the PPA (see section 11.6) and the study sites for the PDA (see section 19.1), the following data management steps (steps 6-9) are taken by the ART as the Global Data Coordination Center (see section 32.5).

6. Secure physical and electronic document storage
 - a. Pulse Inframe leverages several lives of security to protect the database
 - b. The ART (PPA) and Contract Research Organization managing the documents for the PDA will maintain all documents in secure locations.
7. Clinical Assessment and Evaluation
 - a. The ART (at UPenn) will perform periodic analyses on the data, which will be included in peer-reviewed publications.
 - b. The Certification & Access Subcommittee (CAS) reviews and grades the likelihood of every patient's correct diagnosis based on medical records and LN slides, if available
8. Data Quality
 - a. (not shown) During the data entry process, automated error checking will be performed via range checks and relational checks for data consistency (Validation based fields will not permit data outside permitted ranges without secondary notification)
 - b. A highly-skilled Clinical Data Specialist will curate the database

- c. Also, the ART and Qualified Researchers, who apply for access to the database in the future, will be able to categorize and rank (for inclusion/exclusion) patients according to the grade given by the CAS before performing analyses
- 9. Study Reporting
 - a. The ART will report adverse events to Janssen Pharmaceutica NV and/or regulatory bodies in accordance with Sections 7.5 and 15.5.
 - b. The ART will export the coded database with direct identifiers removed every 6 months to Janssen Pharmaceutica NV for EMA reporting purposes.
- 10. Data Sharing
 - a. Qualified Researchers will apply to CAS for access to the coded database to conduct research.
 - b. The CAS will review credentials for the Qualified Researchers, review conformity with participants' informed consent, and check if the Qualified Researcher has IRB approval for their study, if applicable.
 - c. If approved, the Qualified Researcher will receive a file with the coded dataset with direct identifiers removed.
 - d. Research projects will be posted on the ACCELERATE website
 - e. Based on a signed Data Sharing Agreement, the Qualified Researcher will return all raw data for use by the research community after they have completed their project
 - f. Qualified Researchers can also reapply to the CAS if they wish to contact a patient(s) about participating in a separate research study being conducted by the Qualified Researcher
 - g. If approved, the patient will be contacted by a member of the ART about the research study being conducted by the Qualified Researcher

24 Computer System

Pulse Inframe hosts a secure, web-based application for building and managing online surveys, registries, and databases. The database will be password protected with strongly characterized requirements and maintained behind Pulse Inframe's firewall. It will only be accessible through secured VPN access; study members will only be able to access the data through the web-interface. All transmission to and from the database is encrypted and password protected. During CRUD (create, read, update and delete) operations – role based permissions are enforced and checked such that only those with the right to read such records are provided that right. Data will be stored indefinitely, for as long as funding is available to support the registry.

Encryption: Within the platform, we use (Advanced Encryption Standard) AES algorithms to store sensitive data. AES is the first publicly accessible and open cipher approved by the National Security Agency (NSA) for top secret information. Web traffic is only served over HTTPS with strict TLS encryption. We use external tools to verify that we are following best practices, such as Qualys SSL Labs where we consistently score an A grade for our SSL encryption setup.

Audit Logging: Every action any user performs on the platform is logged and provided in a comprehensive auditing interface. This allows an auditing user with credentials to see who viewed, updated or deleted any information stored in the system. The interface is minable and provides discrete views for all actions in case the need for retractability ensues.

Physical Security: The platform is deployed with a data center that has gone through arduous certification and external audit processes. This data center also boasts the first Tier III certified data center in Canada and represents the best in breed of security and redundancy.

Secure Login: The platform follows best practices to ensure a secure login. Strongly characterized credentials are provided and bad login attempts will lock users accounts. Timeout periods are enforced and all actions are logged. The platform only allows users from email domains for their organization.

Standards: We support the latest in international coding standards - All of the services built have been designed with the latest web-based standards and security protocols in place. We use full auditing and role based authentication methods for all credentials.

Data Integration: The ACCELERATE Registry will be capable of data migration. For example, data that comes from outside sources, such as electronic medical records can leverage our interoperability framework to be migrated. Internal sources such as patient surveys, patient history data, and laboratory values can be collected on the Registry directly.

Interoperability Framework: The Interoperability framework (Intersystems HealthShare) will exist on the same servers that house the ACCELERATE Registry, and will communicate with the provider Electronic Medical Record (EMR) through a secure Virtual Private Network (VPN). See Section 32.4. A VPN is a secure communication standard that will ensure that no external communication can affect the data being transmitted. The servers that house both the ACCELERATE Registry and HealthShare are HIPAA compliant and are housed in a secure data center.

For integration with provider EMR's to occur, a series of mapping rules will be established to match data from the patient's record to the ACCELERATE Registry within HealthShare (These mapping rules will be established during the implementation phase of the ACCELERATE Registry.) The mapping rules created will allow the ACCELERATE Registry to identify the common data fields that exist within the patient record. All data elements to be transferred will exist in an ADT (Admit, Discharge, Transfer) message located in the provider EMR. Once the data elements are identified, each data element will be validated against the data dictionary standards (type, size, upper and lower bounds, state, etc) within the ACCELERATE Registry and accepted or rejected for the transfer. If a data element is rejected, the rejection will be logged in the standardized logging system and provided in a transfer report upon completion of all validation checks. If data is rejected based on the validation checks, the CDCN user will be able to retrieve this data after reviewing the transfer report (and determining why it failed these rules). Datasets that are received by the CDCN mailbox are not deleted, but will be held for review in an audit log. The provider should not have to resend any data that is sent directly to the CDCN mailbox - whether their data was automatically matched or not.

Following the validation, all data elements will be written to the ACCELERATE Registry tables transferred via HealthShare from the provider's EMR. All fields that will be transferred to the ACCELERATE Registry will be given to data entry clerks so that they know what fields are automatically transferred. Transfer of data does not report back to the EMR as this is a one-way communication method. All values that are pulled can be reviewed for consistency within the transfer report in a web-based interface for the users.

To accomplish this, we will work with our interoperability partner to setup a legislated DIRECT secure message mailbox (such as CastlemansRegistry@Hdirect.net) so that any and all providers that have a HISP (health information service provider) certified connection can mail the patient information to that mailbox. The provider would only have to send the record to that mailbox and the HealthShare mappings will bring them into the ACCELERATE Registry as per the workflow above. The data that is transferred via the mailbox needs to correspond with the mappings, otherwise the values sent from the provider EMR will not be added to the ACCELERATE Registry and the data entry clerk will need to enter the values directly to the eCRF.

25 Data Access & Migrations

The Pulse Inframe system enables a relational database structure, so it can be used to manage multiple clinical data points and sample information.

The basic structure of this database includes three main table categories.

1. **PHI 'Master List':** Only the Principal Investigator and anticipated Study Coordinators will have full access to this table. This table includes a sequentially generated study-specific alphanumeric identifier and a separate unique random database-specific numeric identifier for each individual. If

the database user has sufficient access privileges (such as the Principal Investigator or Study Coordinator), the random identifier will be able to link PHI information to other areas of the database. Details of the enrollment and consenting process will be maintained on this table, and this Table will also serve to organize photographs and any scanned study documents with dates contain PHI.

2. Clinical Information: This table will contain coded non-PHI clinical data and will be identified by the study-specific alphanumeric identifier. It will be accessible only to individuals with clinical privileges (e.g. medical student working on a clinical outcomes or correlation project).
3. Sample storage information: This table will contain information on the type and location of stored samples identified by the study-specific alphanumeric identifier. It will be accessible to both clinical and laboratory personnel.

One of the aims of this project is to develop a centralized database for Qualified Researchers to access and conduct research. Data sharing will occur in a timely fashion, no later than the acceptance for publication of the first interim analysis of the data. Qualified Researchers who wish to apply for access to the coded database will apply to the CAS. A detailed data sharing policy will be available on the ACCELERATE website regarding the submission of formal requests with commitment to data security, review, approval and processing of such requests.

All requests will be reviewed by the CAS to ensure the qualifications of the researcher, conformity with participant informed consent, IEC/IRB approval (if applicable per local regulations) for the registry, and to provide scientific advice. If granted access, the Qualified Researcher will receive coded data, which may include indirect identifiers. A general description of all Qualified Researcher projects will be posted on the ACCELERATE website, and Qualified Researchers who receive data will be asked to return all raw data for use by the research community. Qualified Researchers that wish to contact a patient to participate in a study or contribute tissue samples will need to have a separate research protocol approved by the IRB of the researcher and re-apply to the CAS. If approved by the CAS, the ART will directly contact the patient by phone, email, or letter with this inquiry.

26 Records Retention

Janssen Pharmaceutica NV plans to fund ACCELERATE for five years from the first patient enrolled. Based on the collaborative research agreement with Janssen Pharmaceutica NV, essential documents provided by Janssen Pharmaceutica NV or its affiliates or generated for Janssen Pharmaceutica NV or its affiliates during the study must be retained for at least 2 years following issuance of the final report. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Janssen Pharmaceutica NV. The study intends to continue beyond the 5-year funding commitment by Janssen Pharmaceutica NV. It is the responsibility of the ART to inform the Participating Physician/institution as to when these documents no longer need to be retained.

If it becomes necessary for UPenn, Janssen Pharmaceutica NV, or the appropriate regulatory authority to review any documentation, the ART and/or Participating Physician will permit access to such reports.

27 Providing Results to Patients

At the time of enrollment, participants will be informed that they will be informed if a review of medical records and pathology strongly suggests that the participant may have a clinically-actionable and life-threatening disease other than Castleman disease (e.g., lymphoma). If this occurs in the PPA, the ART will inform the patient of a potential finding (without specification) and determine which physician the patient would like for us to disclose this possible finding to. In the PDA, the ART will inform the participating physician. No other research results will be disclosed to patients.

28 Study Monitoring Plan

Several processes will be put into place to ensure the accuracy and reliability of data. First, a panel of international experts will convene the Certification/Access Subcommittee (CAS) to review and classify the likelihood of a patient's correct diagnosis. When available for patients enrolled through the PPA, the ART will acquire lymph node and/or bone marrow slides or tissue blocks to be de-identified, scanned, and

uploaded to the online system to assist with further review by the CAS. Alternatively, when available, patients enrolled through the PDA will have their stained lymph node and/or bone marrow slides scanned and uploaded to the online system by the Participating Physician to assist with further review, if feasible and allowed by local regulations. The CAS will not exclude patients from the database, but will provide a grade for the likelihood of correct diagnosis with Castleman disease. Qualified researchers will be able to sort or include patients with only certain grade(s) of likelihood of correct diagnosis in their analyses. Second, Participating Physicians and registry sites have been selected based on their qualifications and experience managing Castleman disease. Third, the data will be curated by a highly-skilled Clinical Data Specialist. Fourth, protocol procedures will be reviewed with the Participating Physician and associated personnel before the start of any registry site. Fifth, data quality will be assessed at the data entry point using automated intelligent data entry forms (e.g., data element constraints, such as independent range and/or format limitations or 'relative' referential integrity limitations) and automated error checking. Finally, a pathology report suggesting Castleman disease will be needed for all patients to be included.

Since the registry is non-interventional, it is understood that some data points will be missing. Missing data will be monitored by the ART to ensure that there is not one data point that is routinely not being captured. If data are missing at random, the analyses will be performed as is, since the multivariate analyses can handle missing and/or mistimed data. Strategies for managing missing data may include limiting the analysis to patients with complete data or missing data imputation to estimate the value of the missing data.

29 Study Finances

29.1 Funding Source

This study is financed through a collaborative research agreement with Janssen Pharmaceutica NV.

29.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the UPenn [Policy on Conflicts of Interest Related to Research](#).

29.3 Patient Stipends or Payments

There are no patient payments or stipends. Participating Physicians at the 24 PDA study sites in the EU will be paid a fee for every patient that they enroll into the registry.

29.4 Contractual Arrangement

This project includes 1 collaborative research agreement and 2 subcontracts. The collaborative research agreement is between University of Pennsylvania, Janssen Pharmaceutica NV, and CDCN. The first subcontract is between University of Pennsylvania and Pulse InfoFrame, which will be providing the IT infrastructure for the registry. The second subcontract is between Janssen Pharmaceutica NV and PAREXEL, which will be assisting with site initiation in the PDA.

30 Publication Plan

Any data, generated as a result of this registry, are considered confidential and remain the sole property of UPenn and collaborative partners. The Participating Physicians at the PDA study sites agree to maintain this information in confidence and use this information only to accomplish this registry, and will not use it for other purposes without the Sponsoring Institution and collaborative partners' prior written consent. Any work created in connection with performance of the registry and contained in the data that can benefit from copyright protection (except any publication by the Participating Physician as provided for below) shall be the property of UPenn and collaborative partners (detailed in a separate agreement).

All collaborative partners and Participating Physicians are committed to open, timely, and widespread sharing and dissemination of registry findings to researchers, funders, service providers, target population, and general public. Pertinent findings will be published in peer-reviewed journals and presented at annual

meetings [e.g., American Society of Hematology (ASH), American Society of Clinical Oncology (ASCO), European Hematology Association (EHA)].

UPenn and collaborative partners shall have the right to publish such data and information without approval from the Participating Physicians in the PDA. If a Participating Physician wishes to publish information from the registry, a copy of the manuscript must be provided to the Sponsoring Institution and collaborative partners for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the Sponsoring Institution or collaborative partners in writing, the Participating Physician will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsoring Institution and collaborative partners will review these issues with the Participating Physician. The Sponsoring Institution and collaborative partners will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter registry designs and subregistry approaches, results may need to be published in a given sequence. Similarly, Participating Physicians will recognize the integrity of a multicenter registry by not publishing data derived from the individual site until the combined results from the completed registry have been published in full, within 12 months after conclusion, abandonment, or termination of the registry at all sites, or the Sponsoring Institution or collaborative partners confirm there will be no multicenter registry publication. Authorship of publications resulting from this registry will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the registry or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Upon provision of the final Study report after five years, UPenn may seek to publish, in peer-reviewed literature and through lectures, the Study Data. Upon the agreement of the Steering Committee, UPenn may also seek to publish, in peer-reviewed literature and through lectures, interim Study Data as the ASC deems appropriate. The publication or presentation review procedures set forth in the Collaboration Agreement between UPenn and Janssen shall apply whether final or interim Study Data is involved.

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32 Attachments

32.1 Specimen Preparation And Handling for the PPA and PDA

All formalin-fixed, paraffin embedded (FFPE) lymph node and bone marrow slides and tissue blocks will be sent at room temperature to:

Dr. David Fajgenbaum, MD, MBA, MSc
Assistant Professor of Medicine, Division of Translational Medicine & Human Genetics
Hospital of the University of Pennsylvania (HUP), 5th Floor Silverstein, Suite 5100
3400 Spruce Street, Philadelphia, PA 19104

Tissue sample locations and usage will be tracked using a database (e.g. LabVantage). Once received, Dr. Fajgenbaum or his staff will note in the patient's registry file that samples have been received. Then, the slides will be reviewed to see if they have already been stained with hematoxylin and eosin (H&E). If they have been stained, they will be sent to the University of Pennsylvania Pathology & Laboratory Medicine slide scanning core to be de-identified, scanned, and uploaded into an online hosting provider separate from Pulse InfoFrame. To ensure confidentiality, all slides will be completely de-identified prior to upload onto the hosting-provider. If the slides have not been stained, they will be sent to Pathology & Laboratory Medicine to be stained with H&E and then sent to the slide scanning core to be de-identified, scanned, and uploaded into the online hosting provider. Tissue blocks will be sent to Pathology & Laboratory Medicine to be cut, stained with H&E, and then sent to the slide scanning core to be de-identified, scanned, and uploaded into the online hosting provider. All slides and tissue blocks will be kept securely at room temperature in Dr. Fajgenbaum's office.

Of note, patients enrolled through the PDA will not have slides or tissue blocks sent to UPenn. When consented and possible, Participating Physicians in the PDA will de-identify, scan, and upload the slide images directly onto the online system.

32.2 Recruitment Materials

The below text will be used to describe the registry in the following ways for PPA recruitment: advertisements in the Castleman Disease Collaborative Network (CDCN) e-newsletter, website, and social media; emails to patient members of the CDCN and patients who contact the CDCN through the website or by email; and emails to other patient advocacy groups (e.g., International Castleman's Disease Organization, EURORDIS, NORD, PatientsLikeMe.

"Are you a patient with Castleman disease? A family member of a patient with Castleman disease or a family member of a deceased patient?"

The Castleman Disease Collaborative Network (CDCN) is pleased to announce that we are collaborating with Principal Investigator Dr. David Fajgenbaum and other researchers at the University of Pennsylvania (Philadelphia, PA) to build a registry to learn more about Castleman disease. Participating in this study as a patient will entail completing a consent process online or by telephone and authorizing medical records to be sent from patients' doctors and hospitals to researchers at the University of Pennsylvania. Patients will also have the option to complete a brief survey online every 3 months. Deceased Castleman disease patients may also be included if their family members register them. Through these studies, researchers hope to find new ways to detect, treat, and maybe prevent or cure this disease.

If you would like to learn more about how to contribute your medical records for this research, please visit the CDCN website at www.CDCN.org/ACCELERATE. You can also find contact information to call the research team. We greatly appreciate your support for this research."

The below text will be used to describe the registry in the following ways for PPA recruitment: outreach to the CDCN physician database and the authors of published case reports to ask them to provide information about ACCELERATE to their patients about participation; mailings to academic hematology divisions and private practices to share information with patients; and

"Do you treat any patients with Castleman disease? Have you treated any Castleman disease patients who are now deceased?"

The Castleman Disease Collaborative Network (CDCN) is pleased to announce that we are collaborating with Principal Investigator Dr. David Fajgenbaum and other researchers at the University of Pennsylvania (Philadelphia, PA) to build a registry to learn more about Castleman disease. Participating in this study as a patient will entail completing a consent process online or by telephone and authorizing medical records to be sent from patients' doctors and hospitals to researchers at the University of Pennsylvania. Patients will also have the option to complete a brief survey online every 3 months. Deceased Castleman disease patients may also be included. Through these studies, researchers hope to find new ways to detect, treat, and maybe prevent or cure this disease.

If you would like to learn more about how your patients can contribute their medical records for this research, please visit the CDCN website at www.CDCN.org/ACCELERATE. You can also find contact information to call the research team. We greatly appreciate your support for this research."

The below text may be used to describe the registry in advertisements for patients treated by physicians at the sites in the PSA.

"Are you a patient with Castleman disease?"

The Castleman Disease Collaborative Network (CDCN) is pleased to announce that we are collaborating with your physician and researchers at the University of Pennsylvania (Philadelphia, PA, USA) to build a registry to learn more about Castleman disease. We are looking for patients to enroll. Participating in this study as a patient will entail completing a consent process with your physician and authorizing that your

physician access and collect information from your medical records. Through these studies, researchers hope to find new ways to detect, treat, and maybe prevent or cure this disease.

If you would like to learn more about how to contribute to this research by registering, please talk to your doctor or visit the CDCN website at www.CDCN.org/ACCELERATE. You can also find contact information to contact the research team at the University of Pennsylvania. We greatly appreciate your support for this research.”

The below text may be used as advertisements on various CDCN Social Media Platforms such as Facebook and Twitter.

Post #1:

Get Excited!!

The ACCELERATE registry, the first Castleman's registry ever, is coming soon!

We need patients to contribute medical record data to this registry to help us better understand Castleman's.

This study is an important step to understand and beat Castleman's!

www.CDCN.org/ACCELERATE

Post #2:

We are proud to announce that ACCELERATE, the first Castleman's registry ever is now live!

We need patients to contribute medical record data to this registry to help us better understand Castleman's.

If you are interested, learn more and register now at www.CDCN.org/ACCELERATE

Post #3:

The answers to the unknowns of Castleman's are within each of us! Join the ACCELERATE registry to help us better understand Castleman's! www.CDCN.org/ACCELERATE

Post #4:

We need patients like you to join the ACCELERATE registry to help us find answers to Castleman Disease!

The answers to this disease could be in your medical records. www.CDCN.org/ACCELERATE

Post #5:

Join ACCELERATE now- the first Castleman disease registry ever! Patterns across hundreds of patients could help us to answer the unknowns of the disease. www.CDCN.org/ACCELERATE

32.3 Study Questionnaires

Multicentric Castleman Disease Symptom Scale (MCD-SS)³⁶

Multicentric Castleman's Disease Symptom Scale

When filling out this questionnaire, please consider your experiences with Castleman's Disease symptoms during the past 24 hours. Choose the response that best describes your experiences with Castleman's Disease symptoms by marking the corresponding box (☐).

Please rate the severity of the following symptoms during the past 24 hours.	Did not experience	Very Mild	Mild	Moderate	Severe	Very Severe
1. Cough	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Shortness of breath	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Loss of appetite	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Tiredness	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Fatigue	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Lack of Energy	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Feeling Weak	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Sores or rash on your skin (skin lesions)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Itching	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Numbness or Tingling	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Pain	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Fever	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Swollen lymph nodes (swollen lumps in neck area, under arms, or groin area)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Swelling or edema in other body areas (face, chest, abdomen, arms, hands, legs, or feet)	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Night Sweats	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Excessive daytime sweating	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

EQ5D-5

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

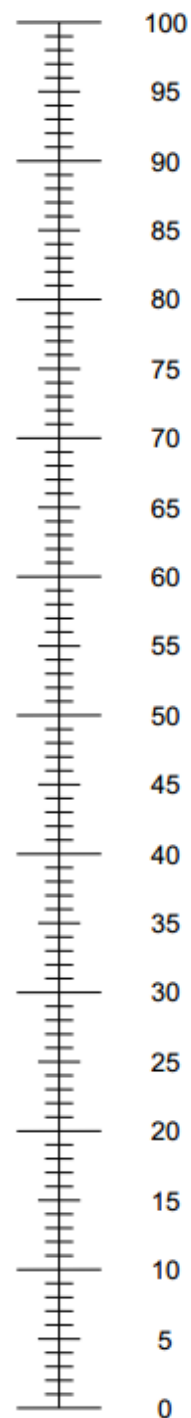
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Patient Initials: Study Number: Date: The best health
you can imagine

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The worst health
you can imagine

Self Reported Flare (SRF) questionnaire adapted for Castleman disease

An exacerbation or flare is defined as:

The appearance of a new clinical Sign / Symptom or the clinical worsening of a previous Sign / Symptoms that had been stable for at least the previous 30 days and which persisted for a minimum of 24 hours.

Poser CM et al. *Ann Neurol* 1983 :13(3); 227-231

Based on the above definition:

Please list all of the symptom exacerbations or flares that you've had in the last three months using the exacerbated symptoms form.

[Drop down list of symptom options]

- Shortness of breath
- Loss of appetite
- Tiredness/Fatigue/Lack of energy/Feeling weak (combined)
- Skin lesions
- Itching
- Numbness or tingling
- Pain
- Fever
- Swollen/enlarged lymph nodes
- Swelling or edema in other body areas
- Night Sweats
- Excessive daytime sweating
- Other, please specify:

What was the approximate date that your most recent symptom exacerbation or "flare" began?

____ / ____

What was the approximate date that your most recent symptom exacerbation or "flare" ended?

____ / ____

Could you identify any trigger to this/these events? (open ended)

How did you manage this/these events? (open ended)

Has the number of events increased or decreased with ongoing management?
Decreased

Increased

Do you regularly see a medical professional for review for your illness management?
No

Yes

In your opinion, since your diagnosis has your general health:
improved remained the same deteriorated

Additional questions regarding recent hospitalizations and current treatments

What is the highest grade or level of school the patient has completed or the highest degree the patient has received? (PPA Only)

- Eighth grade or less
- More than eighth grade, but did not graduate from high school
- Went to a business, trade, or vocational school instead of high school
- High school graduate
- Completed a GED
- Went to a business, trade, or vocational school after high school/ Went to college, but did not graduate
- Graduated from a college or university
- Professional training beyond a four-year college or university
- He/she never went to school
- He/she went to a school, but respondent doesn't know what level
- Respondent doesn't know if he/she went to school

What is the annual gross income for the household in which the patient lives (in U.S. dollars)? (PPA Only)

- Less than \$10000(USD)
- \$10000-\$14999
- \$15000-\$19999
- \$20000-\$24999
- \$25000-\$29999
- \$30000-\$34999
- \$35000-\$39999
- \$40000-\$44999
- \$45000-\$49999
- \$50000-\$54999
- \$55000-\$59999
- \$60000-\$74999
- \$75000-\$84999
- \$85000-\$99999
- \$100000-\$149999
- \$150000-\$199999
- \$200000-\$249999
- \$250000 and above
- Unknown
- Decline to Provide

What medications are you currently taking? (PPA Only)

Please list the names and locations of ALL hospitals at which the patient has been treated since their Castleman disease symptoms began. Include the first date the patient was admitted and whether or not a lymph node was removed at that hospital. (Completed by Physician in PDA and by ART in PSA).

Hospital Name:

Hospital City:

Hospital Country:

Ever had a lymph node removed here: Yes/No

Date of first hospitalization:

[Repeated for as many hospitalizations as the patient has had]

Please list ALL physicians that the patient has seen since Castleman disease symptoms began. Please indicate the patient's "primary" Castleman disease treating physician. Please also indicate if the patient is still seeing each physician. (Completed by Physician in PDA and by ART in PSA).

Physician First Name:

Physician Last Name:

Institution:

Country:

Primary Castleman Treating Physician: Yes/No

Currently Treated by: Yes/No

32.4 *Pulse Inframe documentation*

INTERSYSTEMS WHITE PAPER

Accelerating Clinical Trials Through Shared Access to Patient Records



**Improved Access to Clinical Data Across Hospitals and Systems
Helps Pharmaceutical Companies Reduce Delays and the Costs
Associated With Bringing New Treatments to Market**

INTERSYSTEMS®

Improved Access to Clinical Data Across Hospitals and Systems Helps Pharmaceutical Companies Reduce Delays and the Costs Associated With Bringing New Treatments to Market

Executive Summary

The pharmaceutical and life sciences industry has a strategic imperative to accelerate clinical research in order to reduce overall R&D costs while delivering innovative treatments.¹ Yet virtually all pharmaceutical manufacturers and contract research organizations (CROs) recognize that the limited quantity and quality of available patient data are fundamental problems that have led to escalating costs and delays in clinical trials for new drugs and treatments.

The underlying problem is accessing and sharing connected, comprehensive, and credible patient records across hospitals, healthcare organizations, communities, and countries.

The answer is to provide the clinical trials ecosystem with a foundational health informatics platform and complementary solutions that enable researchers to access and use clinical data from hospitals and other healthcare providers. With such a solution in place, clinical researchers can more quickly evaluate protocol feasibility, identify and recruit viable patient candidates for trials, track patients enrolled in clinical trials, and conduct efficient, accurate health surveillance and observational studies once a drug or treatment is on the market.

Delays Due to Poor Access to Patient Information

One of the biggest challenges for pharma and life sciences to overcome is reducing the time it takes to bring a drug or treatment to market. Every day of delay can cost the sponsors of a clinical trial up to \$8 million (U.S.) in lost revenue opportunity.²

Almost half of all clinical trial delays are caused by patient recruitment problems³, and 50% of today's clinical trials fail to reach the target recruitment rate⁴. Researchers' poor access to comprehensive information on the patient population of interest is a major source of these challenges. The lack of patient information is dragging down the entire clinical research process, across all phases of clinical trials:

- **Protocol feasibility**—Is there clinical data available to support the study design? Simply determining whether the appropriate data exists requires the ability to query, normalize, and aggregate clinical records in different formats and from disparate sources.
- **Trial site selection**—Which hospitals and health systems can assemble the critical mass of patients needed for the study?
- **Patient identification and recruitment**—Can the right patients for the study be identified and contacted?
- **Observational studies**—After a drug is released, how can populations of patients and widely dispersed clinical data be accessed and studied?

The questions may be simple, but arriving at the answers is complex, and significant obstacles stand in the way.

The Challenges in Clinical Trials Today

- Patient records are currently stored in disparate systems (care, pharmacy, lab) in different clinical settings (hospital, primary care, community services), and in different formats (data models, structured vs. unstructured data). The data may also be in multiple languages, use a variety of clinical terminologies, and be governed by different regulatory and privacy policies.
- The current lack of comprehensive and searchable patient data to support clinical research is perhaps the biggest cause of patient recruitment delays in clinical trials. A given hospital may have a searchable health records system, but no such system exists for entire populations across different health systems, markets, and/or countries—which is often necessary, especially in Europe, in order to identify and recruit the required number of patients who fit the defined profile.
- Once a drug or treatment is on the market, researchers are no longer working with a defined, enrolled group of patients. Still, they must be able to find instances of drug/therapy utilization and associated outcomes, adverse reactions, and allergies in order to conduct accurate observational studies. In addition, researchers must now contend with a greater number of caregivers, data sources, and patients. In these instances, a project such as the European Medical Information Framework (EMIF), which convenes organizations as part of an information network, plays an important role in mining clinical data from many sources.

Any solution addressing the use of clinical patient data for research requires a connected, interoperable information ecosystem that links pharmaceutical companies, CROs, and healthcare organizations.

Some pilot initiatives are already under way to enable the use of clinical data for clinical research. These projects have helped clarify the need for a commercial solution. For example, in the U.K., a new National Health Service (NHS) system will allow anonymized patient information to be stored centrally and shared to help improve care and research. In Europe, the Innovative Medicines Initiative (IMI) is facilitating collaboration between the key players involved in healthcare research, including universities, the pharmaceutical industry, small and medium-size enterprises, patient organizations, and medicines regulators. The consortium project Electronic Health Records for Clinical Research (EHR4CR) is implementing a proof-of-concept project integrating 11 hospitals and 10 pharmaceutical companies across seven European countries, to demonstrate interoperability and achieve the goal of using patient data for clinical research.

These initiatives have helped stakeholders identify the four requirements that a commercial solution must satisfy in order to make patient records readily available for research, create the required comprehensive patient data set, and accelerate the process of clinical trials.

The Four Solution Requirements

While no vendor or technology can single-handedly address all aspects of the use and sharing of patient data for clinical research, a health informatics platform is the essential foundational element of the four solution requirements. A health informatics platform provides the advanced technology needed for interoperability among systems and for creating connected, comprehensive, credible, and current patient records that aggregate all of a patient's clinical data from disparate systems and locations while integrating with data security, privacy, and access controls.



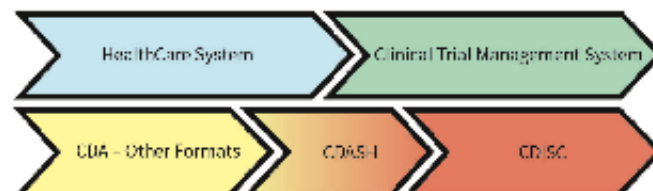
1. Interoperability

Imperative: Overcome semantic interoperability challenges arising from the use of different languages, data models, and systems.

Patient records are generated by single institutions—that is, a doctor has a set of information for each patient; if the patient goes to a different doctor, another set of information is created. How can the records be combined? Through interoperability. Interoperable health information systems “make the right information available to the right people at the right time across applications and organizations in a way that can be relied upon and meaningfully used by recipients.”²

Interoperability among clinical, administrative, and other third-party systems is the core functionality required to aggregate and use comprehensive patient records from disparate sources. Interoperability eliminates the bottlenecks presented by separate systems, different data models, different coding and content standards, different usage of structured (e.g. laboratory result) and unstructured (e.g. clinical narrative) data, and different languages.

In its source system, the clinical data may adhere to a specific data standard, such as HL7 Clinical Document Architecture (CDA). As it moves from its source healthcare system into the clinical trials management system, the data may need to be translated into other standards that can address the full life cycle of a clinical trial, such as Clinical Data Acquisition Standards Harmonization (CDASH) or the Clinical Data Interchange Standards Consortium (CDISC).



In addition to the technology needed to support structural and semantic interoperability, mapping, and terminology services for data that use different languages and coding models, a human element is also required to develop and maintain the mapping tables for new codes and sources of data.

2. Data security, privacy, and regulatory compliance

Imperative: Protect the security of the data, and comply with privacy and reporting regulations, which vary worldwide.

Ethical, legal, and privacy requirements differ from country to country. Patient consent must be gathered, and patient data must be anonymized and/or de-identified at various phases in order to protect patient privacy. These functions are typically performed by trusted third parties that partner with platform providers and that specialize in ensuring data security, enforcing access policy, protecting patient privacy, and meeting compliance regulations as patient data is shared among systems. Again, these capabilities must cross systems, regions, and countries.

3. Comprehensive data

Imperative: Ensure the quality and completeness of data, and be able to evaluate both structured and unstructured data.

All clinical data must be connected, comprehensive, and credible to ensure fitness for its intended purpose and engender confidence in the results. Additionally, for patient recruitment and observation studies, the data must be current.

Interoperability addresses the issue of connected, standardized data. The issue of comprehensive data is addressed by an interoperability platform that can aggregate heterogeneous health information. Clinical records comprise images, structured diagnoses, adverse reactions, medication administrations, orders, results, nursing and physician notes, survey responses—in short, anything and everything. It is therefore essential that the platform be able to find meaning in comprehensive records that include both structured and unstructured data. For example, a patient with a condition of interest may have a relevant structured diagnosis code, a descriptive pathology result, or a comment in a clinical note.

For the connected, comprehensive data to be credible, it must also be free from errors that may be introduced during transmission and aggregation. Ideally, healthcare information is captured as close to the time and place of care delivery as possible, since a single error in capturing data presents risks that can be magnified as the data is transmitted downstream through the clinical trials process.

4. Sustainable and scalable

Imperative: Leverage the platform to support a spectrum of business cases that deliver benefits across the entire clinical trials ecosystem—to pharma/life sciences companies, CROs, payers, providers, and patients.

The informatics platform and other solution components used across the phases of clinical trials must be adaptable, reusable, standards-based, and governed within a sustainable ecosystem. The selected solution must be built for the long term and support other pharma business cases beyond the use of clinical data to support research. Additional business cases include:

- Pre-clinical trial analytics to identify patient groups most suited for a drug or treatment.
- Electronic data entry that eliminates error-prone and time-consuming manual re-entry of data from the hospital system to the system used to conduct the clinical trials.
- Safety monitoring, such as accessing updated patient records to detect adverse events.

Where InterSystems Provides Value

For registries, researchers, hospitals, and health-care organizations in many countries, InterSystems' HealthShare informatics platform successfully integrates, delivers, and enhances data. These capabilities provide comprehensive patient information that helps improve care coordination, manage population health, support observational research, and control healthcare costs. The pharmaceutical industry has a similar, urgent need for comprehensive patient information—and HealthShare is a natural and strategic fit in the clinical trials ecosystem. The querying systems used by clinical researchers connect to hospital systems containing patient information, with InterSystems HealthShare providing data integration and interoperability among systems.

One of HealthShare's unique strategic advantages is its ability to evaluate and integrate unstructured data, such as clinical notes, as well as structured data. Unstructured data constitutes 80% of clinical data, and its availability for querying and analysis is integral to the success of the clinical trials process.

InterSystems has the presence, expertise, and relationships with trusted third parties in the global healthcare community to provide all the capabilities required for the sharing of clinical data for research purposes, including system and semantic interoperability services, terminology services, language translations, unstructured data management, consent management, auditing services, patient privacy protections, security services, anonymization and de-identification of patient records, and user authentication.

InterSystems has been widely recognized as a healthcare industry leader by experts and analysts. Gartner positioned InterSystems as a Leader in the "Magic Quadrant for Operational Database Management Systems."⁶ In addition, in its study "*HIE 2014: Revisiting Great Expectations*," research firm KLAS reported that InterSystems HealthShare was the only product that 100% of customers surveyed described as a "part of their long-term plans" and said that they "would buy this again."⁷

Bottom line: HealthShare reduces costs and accelerates the pace of clinical trials because it can more quickly deliver the clinical data to researchers in a format that helps them validate protocols, identify a panel of patient candidates, and track patients throughout the clinical trials process.

InterSystems' Success in Supporting Clinical Research

- **University Hospital Brussels**—Conducted analysis of predominantly unstructured data (notes) along with structured data to identify patients for clinical trials.
- **Belgium**—Teamed with a pharmaceutical company to identify patients at risk of developing Hepatitis C by analyzing unstructured clinical notes for the prevalence of tattoos, acupuncture, piercings, prison stays, and other high-risk factors rarely reported in structured data.
- **Hixny**—Provided platform and services for the leading health information exchange in the state of New York that connects disparate data sources and types, and accommodates different governance organizations and varying policies to create comprehensive patient records for use at the point of care or for research purposes.

InterSystems technology sets the gold standard for healthcare:

- Nearly all U.S. academic medical centers are InterSystems customers.
- All 17 of the U.S. News & World Report 2014-2015 Honor Roll of Best Hospitals are InterSystems customers.⁸
- InterSystems is the leading supplier of state- and country-wide solutions in Scotland, Sweden, Denmark, Brazil, Chile, the U.S., and elsewhere.
- Two-thirds of Americans receive care where InterSystems technology plays a key role.
- Two of the three major EHR solutions that Gartner calls "Global Solutions" run on InterSystems technology.⁹

¹ "Integrating New Approaches for Clinical Development: Translational Research and Relative Effectiveness," by Jean-Pierre Lehner, Robert S. Epstein, and Teseen Salimi. *Journal of Comparative Effectiveness Research*, Vol. 1, Issue 1s, 2012.

² "Recruiting Special Patient Populations," by Donna Beasley, *Applied Clinical Trials*, June 1, 2006.

³ "Study Participant Recruitment and Retention in Clinical Trials," by Business Insights, May 31, 2007.

⁴ "Fixing the Protocol Feasibility Process," by Beth Harper and Nikki Christison. *Journal of Clinical Research Best Practices*, Vol. 8, No. 1, 2012.

⁵ "Connecting Health and Care for the Nation: A 10-Year Vision to Achieve Interoperable Health IT Infrastructure," from The Office of the National Coordinator for Health Information Technology, June 5, 2014.

⁶ "InterSystems Recognized as a Leader in Gartner Magic Quadrant for Operational Database Management Systems," Oct. 21, 2014.

⁷ "Healthcare Providers Weigh In on InterSystems HealthShare in KLAS 2014 HIE Report," April, 2, 2014.

⁸ Best Hospitals 2014-15: Overview and Honor Roll, by Kimberly Leonard, U.S. News & World Report, July 15, 2014.

⁹ "Magic Quadrant for Global Enterprise EHR Systems," by Thomas J. Handler, Gartner, Sept. 9, 2013.

An *InterSystems* Technical White Paper



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INTERSYSTEMS ENSEMBLE® AND INTERSYSTEMS HEALTHSHARE®
HL7v2 MESSAGE THROUGHPUT

Ensemble (v 2015.1, build xxx) HL7v2 Performance & Scalability; March 2015

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By: Mark Bolinsky, Technology Architect Manager, and
David Loveluck, Director of Product Management

InterSystems Confidential

EXECUTIVE SUMMARY

InterSystems HealthShare® and InterSystems Ensemble® both provide a rapid integration and development platform with built-in capabilities for the high-speed processing of HL7 messages. For the purposes of HL7 v2 message routing the two products are equivalent in performance. For brevity, this document will just say Ensemble in many places but it should be taken to apply equally to both products.

We have recently completed a performance and scalability benchmark of Ensemble version 2015.1, focusing on HL7 version 2 messaging. This document describes the observed characteristics, and also provides general configuration and sizing guidelines for systems where Ensemble is used as an interface engine for HL7v2 messaging.

The benchmark simulates workloads that have been designed to closely match live environments. The details of the simulation are described in the Workload Description and Methodology section. The tested workloads comprised HL7v2 Patient Administration (ADT) and Observation Result (ORU) payloads and included transformations and re-routing.

Ensemble was demonstrated to sustain a throughput of over 200 million (total inbound plus outbound) messages per 10-hour day on the tested 28-core system with adequate headroom for further scaling.

Throughout these tests, Ensemble was configured to preserve first-in/first-out order, and to fully persist messages and queues for each inbound and outbound message. By persisting the queues and messages, Ensemble provides data protection in the event of a system crash, and full search and resend capabilities for historic messages.

Further, configuration guidelines are discussed in the sections below, which will assist you in choosing an appropriate configuration and deployment to adequately meet your workload's performance and scalability requirements.

The results demonstrate that Ensemble is capable of satisfying extreme messaging needs on commodity hardware, potentially allowing a single small server to provide HL7 messaging support for an entire organization.

InterSystems Confidential

OVERVIEW OF RESULTS

Three workloads were used to represent different aspects of Ensemble activity:

- The T1 workload used simple pass-through of HL7 messages, with one outbound message for each inbound message. The messages were passed directly from the Ensemble Business Service to the Ensemble Business Operation, without a routing engine. No routing rules were used and no transformations were executed. One HL7 message instance was created in the database per inbound message.
- The T2 workload used a routing engine to modify an average of 4 segments of the inbound message and route it to a single outbound interface (1-to-1 with a transform). For each inbound message, one data transformation was executed and two HL7 message objects were created in the database.
- The T4 workload used a routing engine to route separately modified messages to each of four outbound interfaces. On average, 4 segments of the inbound message were modified in each transformation (1-to-4 with 4 transforms). For each inbound message four data transformations were executed, four messages were sent outbound, and five HL7 message objects were created in the database.

The three workloads were run on a 28-core Intel E5-2697 v3 based system running Red Hat Linux. The data is presented as the number of messages per second (and per hour) inbound, the number per second (and per hour) outbound, as well as the total messages (inbound plus outbound) in a 10-hour day. Additionally, CPU utilization is presented as a measure of available system resources at a given level of throughput. In all cases, 32 inbound and 32 outbound interfaces were used.

SCALABILITY

Table 1 summarizes the best scenarios for each of the three workloads at a 28-core configuration:

Test	Inbound		Outbound		Total (in + out) messages/day (10 hours)	CPU Utilization
	Per Second	Per Hour	Per Second	Per Hour		
T1	5,151	18,543,600	5,151	18,543,600	370,872,000	32%
T2	2,953	10,630,800	2,953	10,630,800	212,616,000	43%
T4	1,280	4,608,000	5,120	18,432,000	230,400,000	43%

Table 1: 28-core Ensemble 2015.1 HL7v2 scalability

WORKLOAD DESCRIPTION AND METHODOLOGY

The tested workloads included HL7v2 Patient Administration (ADT) and Observation Result (ORU) messages, which had an average size of 1.2KB and an average of 14 segments. Roughly 4 segments were modified by the transformations (for T2 and T4 workloads). The tests represent 32 inbound and 32 outbound interfaces receiving and sending messages over TCP/IP. The scalability was measured by gradually increasing traffic on each interface to find the highest throughput with acceptable performance criteria. For the performance to be acceptable the messages must be processed at a sustained rate, with no significant queuing, no measurable delays in delivery of messages and the average CPU usage must remain below 75%. The reported numbers have been reduced by a 20% benchmark discount in line with common practice to allow for statistical variations and other factors that might arise in a synthetic test environment.

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Earlier tests with much larger numbers of interfaces made little difference to the overall throughput or performance, which is why 32 inbound and outbound interfaces were used for these tests.

Previous testing has demonstrated that the type of HL7 message used is not significant to the performance or scalability of Ensemble; the significant factors are the number of inbound messages, the size of inbound and outbound messages, the number of new messages created in the routing engine, and the number of segments modified.

Additionally, previous testing has shown that processing individual fields of an HL7 message in a data transformation is not usually significant to performance. The transformations in these tests used fairly straightforward assignments to create new messages. Note that complex processing (such as use of expensive SQL queries in a data transformation) may cause results to vary.

Previous testing has also verified that rules processing is not usually significant. The routing rule sets used in these tests averaged 32 rules, with all rules being simple. Each rules in the rule sets were equally often. Note that extremely large or complex rule sets may cause results to vary.

HARDWARE USED

The tests utilized a server with dual 14-core Intel Xeon E5-2697 v3 “Haswell” processors providing 28 cores @ 2.6GHz on a 2-socket system, 14 cores per chip, with 64 GB RAM, and 800GB internal SSD disk. Red Hat Enterprise Linux Server 7 operating system was used for this test.

In addition to standard InterSystems platform-specific configuration and tuning guidelines for Caché and Ensemble, the following guidelines apply:

CPU CONFIGURATION

The Standard Performance Evaluation Corporation (SPEC) provides standardized benchmarks that can be run across various platforms and configurations in order to provide a baseline for configuration across platforms. One of the components that SPEC benchmarks test is the CINT2006, which is the integer component of the SPEC benchmarks. SPEC defines a base runtime for the benchmark programs, which is known as the reference time. Timed tests are then run on various test systems, and those numbers are compared to the reference time, and a ratio is computed. That ratio is then referred to as the SPECint2006 score (also known as CINT2006 score) for that test. The SPECint score can typically be used to compare cross-platform configurations.

The system under test was configured with two 14-core Intel Xeon E5-2697 v3 processors (2.6 GHz). This processor has a [CINT2006 base](#) of 63.4, which is the standardized performance score for one single processing core. The 28-core configuration has a [CINT2006 rate](#) baseline score of 1190, which is the standardized scalability score for all 28-cores. These numbers can be used as a guideline to compare other platforms, so as to determine the amount of computing power required on those platforms to sustain the levels achieved on the Intel Xeon E5-2697 v3 platform.

For example, the Intel Xeon E5-2650 v3 (2.30 GHz) processor has a [CINT2006 baseline](#) of 54.1, which indicates that its throughput is approximately 15% lower (54.1/63.4) than the tested Intel Xeon E5-2697 v3 system. Therefore, if you configure a system with the Intel Xeon E5-2650 v3 processor @2.30 Ghz instead of the Intel Xeon E5-2697 v3 processor @ 2.60 Ghz, one would expect that Ensemble would process approximately 15% fewer messages for comparable configurations and a higher reported percentage CPU utilization due to fewer processors cores per chip.

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DISK CONFIGURATION

Messages passing through Ensemble are fully persisted to disk. In the case of this test a 800GB SSD disk internal to the system was used for both database and journal files. In addition to ensure real-world comparison synchronous commit is enabled on the journals to force data durability. For the T4 workload as described previously in this document, each inbound HL7 message generates roughly 50KB of data, which can be broken down as described in Table 4. Transaction journals are typically kept on line for less time than message data or logs and this should be taken into account when calculating the total disk space required.

Contributor	Data Requirement
Segment Data	4.5 KB
HL7 Message Object	2 KB
Message Header	1.0 KB
Routing Rule Log	0.5 KB
Transaction Journals	42 KB
Total	50 KB

Table 4: Disk Requirement per inbound HL7 T4 Message

Recall that the T4 workload used a routing engine to route separate modified messages to each of four outbound interfaces. On average, 4 segments of the inbound message were modified in each transformation (1-to-4 with 4 transforms). For each inbound message four data transformations were executed, four messages were sent outbound, and five HL7 message objects were created in the database.

When configuring systems for production utilization, net requirements should be calculated by considering the daily inbound volumes as well as the purging schedule for HL7 messages and the retention policy for journal files. Additionally, appropriate journal file space should be configured on the system so as to prevent the journals from filling up. The journal files should reside on physically separate disk from the database files, for both performance as well as reliability considerations.

ABOUT HEALTHSHARE



Used worldwide, InterSystems HealthShare® is the premier informatics platform and solutions set for connected healthcare, enabling organizations to capture and share all patient data, with the interoperability and real-time analytics to drive informed action across a hospital network, community, region, or an entire nation.

HealthShare Health Connect provides the integration functionality of Ensemble plus support for additional healthcare protocols and document formats.

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ABOUT ENSEMBLE



InterSystems Ensemble® is a seamless platform for integration and the development of new connected applications. It is used by enterprises that want a rapid integration platform, and by application providers who want to create breakthrough “*connectable*” applications that can share data with other applications. Ensemble also leverages previous software investments through composite applications, and establishes an enterprise service bus (ESB) or SOA infrastructure.

For enterprises with challenging integration tasks, Ensemble is the easiest integration platform to use because it’s not a stitched-together suite of separate parts. We created it as a single, architecturally consistent technology stack (integration server, data server, application server, and portal development software). So Ensemble projects are typically completed in half the time required with previous generations of integration products.

For application providers, the Ensemble platform enables the rapid development of new connectable applications that have embedded integration capability. In addition, Ensemble makes it easy for developers to enhance existing products with valuable features such as adaptable workflow, browser-based user interfaces, dashboards and rules-based business processes – without rewriting code.

For more information, visit InterSystems.com/Ensemble.

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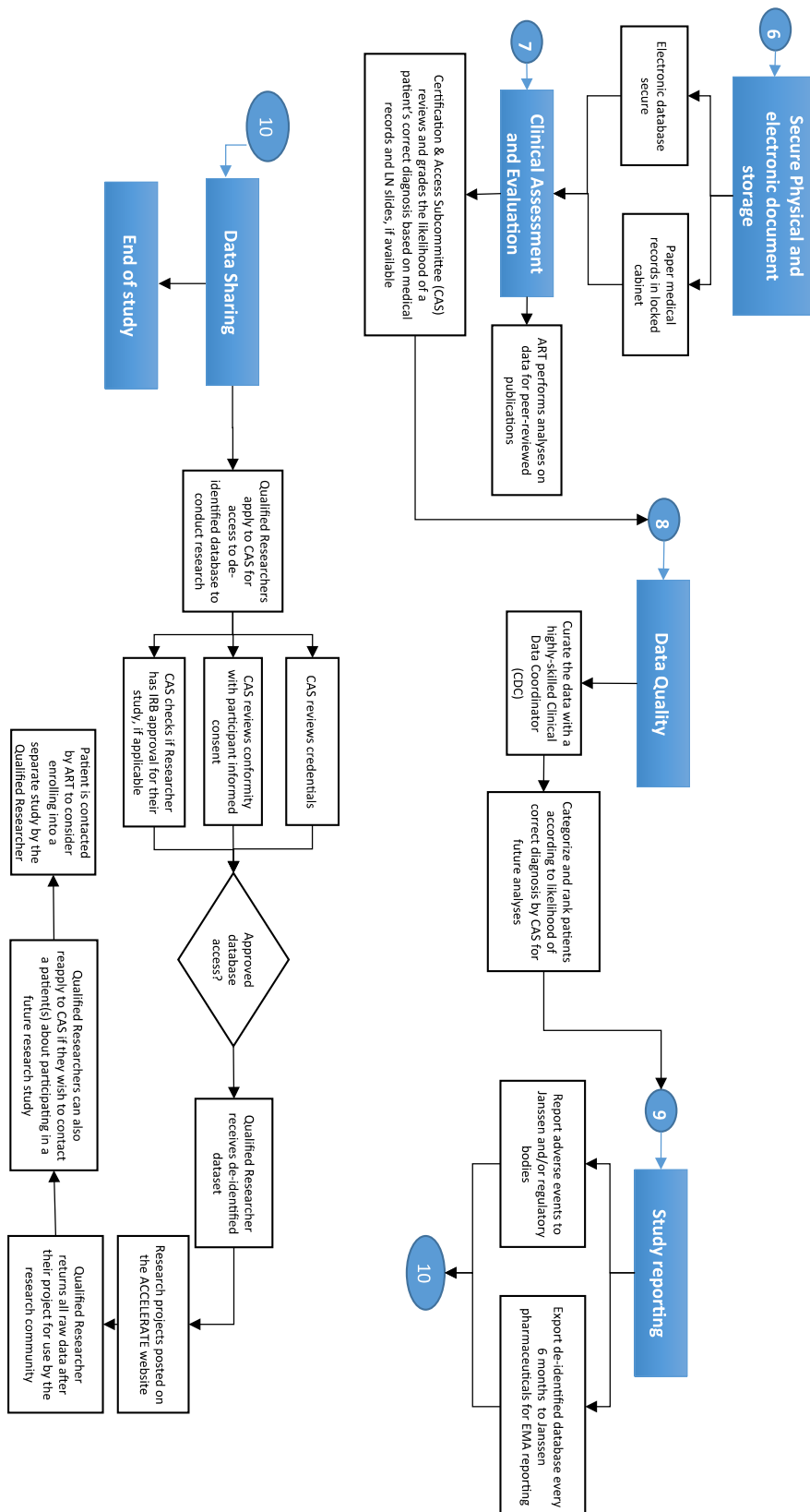


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32.5 Data management for the PPA and PDA



32.6 Abbreviations and definitions of terms

ADR	Adverse Drug Reaction
AE	Adverse Event
ALPS	Autoimmune lymphoproliferative syndrome
ANA	Antinuclear antibody
AP	Asia-Pacific
ART	ACCELERATE Registry Team, based at the University of Pennsylvania
ASC	ACCELERATE Steering Committee
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
BUN	Blood Urea Nitrogen
CARE	Castleman's Awareness & Research Effort
CAS	Certification & Access Subcommittee
CDCN	Castleman Disease Collaborative Network
CRF	Case Report Form
CRP	C-reactive Protein
DRB	Designated Regulatory Body
eCRF	Electronic Case Report Form
EHA	European Hematology Association
ESR	Erythrocyte sedimentation rate
EU	European Union
FAERS	US FDA Adverse Events Reporting System
FDA	Food & Drug Administration (US)
FDC	Follicular dendritic cells
HGG	Hypergammaglobulinemia
HIV	Human immunodeficiency virus
HHV-8	Human herpes virus-8
HV	Hyaline vascular
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
Janssen	Janssen Pharmaceutica NV
LA	Latin America
mAb	monoclonal antibody
iMCD	idiopathic multicentric Castleman disease
MCD	multicentric Castleman disease
MCD-SS	Multicentric Castleman Disease Symptom Scale
MGUS	Monoclonal Gammopathy of Undetermined Significance
NIH	National Institutes of Health (US)
OS	Overall Survival
PC	Plasma cell
PDA	Physician Directed Arm
PFS	Progression-Free Survival
PPA	Patient Powered Arm
PQC	Product Quality Complaint
PRO	Patient-Reported Outcome(s)
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SCEPTRE	Strategic Clinical and Epidemiological Pharmacovigilance Technology for Risk Evaluation
SmPC	Summary of Product Characteristics
SPEP	Serum protein electrophoresis
TAFRO	Thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly

TFI	Treatment-Free Interval
TNT	Time to Next Therapy
UCD	Unicentric Castleman disease UPEP Urine protein electrophoresis
UPenn	University of Pennsylvania
US	United States of America
VEGF	Vascular endothelial growth factor

Definition of Terms

Case Report Form (CRF):	The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”.
E-Repository	A virtual database that tracks the type and location of tissue samples that exist for a patient to facilitate transfer of tissue to researchers
Participating Physician:	A physician in the PDA who is selected to enroll patients and receives IEC/IRB approval (if applicable per local regulations) at one of the registry sites and contributes data into the registry.
Patient-Reported Outcomes (PRO):	Reports directly from the patient on personal health status and quality of life.
Prospective:	Outcome of interest occurs after the research begins.
Qualified Researcher:	A researcher interested in conducting research on the ACCELERATE data set who applies to the CAS and is qualified to conduct their proposed project.
Registry:	A patient registry is an organized system that uses observational methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
Source Documents:	Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, patients’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.