STEERING COMMITTEE CHARTER

GALAXY: Generating Advancements through Longitudinal Analysis in X and Y Syndromes

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INTRODUCTION / OVERVIEW OF THE PROJECT

Please refer to the full study protocol for specific details

The GALAXY Registry is a prospective observational study of clinical and patient-provided outcomes for individuals with sex chromosome aneuploidy (SCA) conditions throughout the lifespan. SCAs, also known as X&Y variations, include Klinefelter (XXY), Trisomy X (XXX), and XYY, as well as tetrasomy and pentasomy conditions. The overarching goal of the GALAXY Registry is to establish a multicenter data and biospecimen repository that will ultimately lead to improved outcomes in individuals with SCAs. Historically, SCAs have been underdiagnosed and understudied. Most research to date is conducted in single centers, is focused on a limited age and/or specialty and has minimal longitudinal follow up. To address these limitations, advance care, and improve outcomes for SCAs, this project will establish a large, diverse cohort of individuals with SCA utilizing the infrastructure of a collaborative network of centers (AXYS Clinical and Research Consortium) and a unified, sustainable and centralized data and biospecimen repository. In the first five years of the project the aims will be to:

> **Aim 1 (a)** Establish a multicenter clinical research registry database utilizing common data elements and a centralized, HIPAA-compliant platform for >500 unique individuals with SCAs and **(b)** Establish a specimen biorepository (biobank) with plasma, serum, DNA, RNA and tissue samples for individuals with SCAs with corresponding clinical phenotyping.
>
> **Aim 2 (a)** Quantify global morbidity outcomes (number of chronic illnesses, number of medications) and healthcare utilization (number of outpatient visits/year, emergency room visits, hospitalizations, surgeries) in a large cohort of individuals with SCAs across the lifespan and in specific SCA conditions **(b)** Quantify the prevalence of medical and psychological comorbidities in this cohort and identify explanatory variables.

In addition to these aims, the GALAXY Registry will support quality improvement initiatives and future research proposals by establishing baseline outcome statistics, generating preliminary data, maintaining a coordinated biobank, and serving as a diverse resource pool of potential participants. Beyond the five-year timeframe, aims will focus on practices and interventions that will improve the baseline findings identified in Aims 1 and 2 above. New aims will be developed as the project advances and additional funding is obtained.

Study Design: Longitudinal clinical research study with both retrospective and prospective data collection

Outcomes: clinical data (diagnoses, medications/interventions, vital signs, labs, imaging), patient data (symptoms, quality of life, lived experience, access to care, social determinants of health), healthcare utilization data, biological data

Population: all individuals with a confirmed SCA

Database: REDCap is a widely used, HIPAA/research compliant, web-based application for managing databases. All data collection tools will be built within REDCap and either be completed as a survey by the patient or as a form for study staff to complete. Efforts will be made to export discrete elements directly from the Electronic Health Record (Epic, Cerner, etc.) into REDCap to minimize burden of data entry, with validation by trained study staff.

Analysis: Real-time descriptive summary statistics for many demographic variables will be made available on a publicly available dashboard. Descriptive statistics for key outcomes will be conducted at least annually (for annual reports). Cross-sectional and longitudinal analyses will be conducted to achieve the stated aims. Additional analyses will be conducted for abstracts, manuscripts, presentations, and Steering Committee requests.

Impact: The GALAXY registry will provide knowledge on measurable clinical and patient-centered outcomes in a diverse sample, standardize clinical practice, and provide an infrastructure for future quality improvement and research initiatives.

GALAXY STRUCTURE AND STAKEHOLDER ROLES

To accomplish these Aims, GALAXY will have a **Steering Committee** to guide study priorities, policies and procedures informed by multiple stakeholders; a **Lead Site/Data Coordinating Center** (DCC) that will manage all aspects of the study including ethical and regulatory approvals, protocol design and implementation, trainings, data collection instruments, data validation and homogenization, basic analyses, etc., **Participating Clinic Sites** that will recruit and enroll patients, input clinic-validated data, and update data longitudinally, and **Participants** who are individuals with SCA conditions who agree to participate in the registry at their preferred level of engagement.

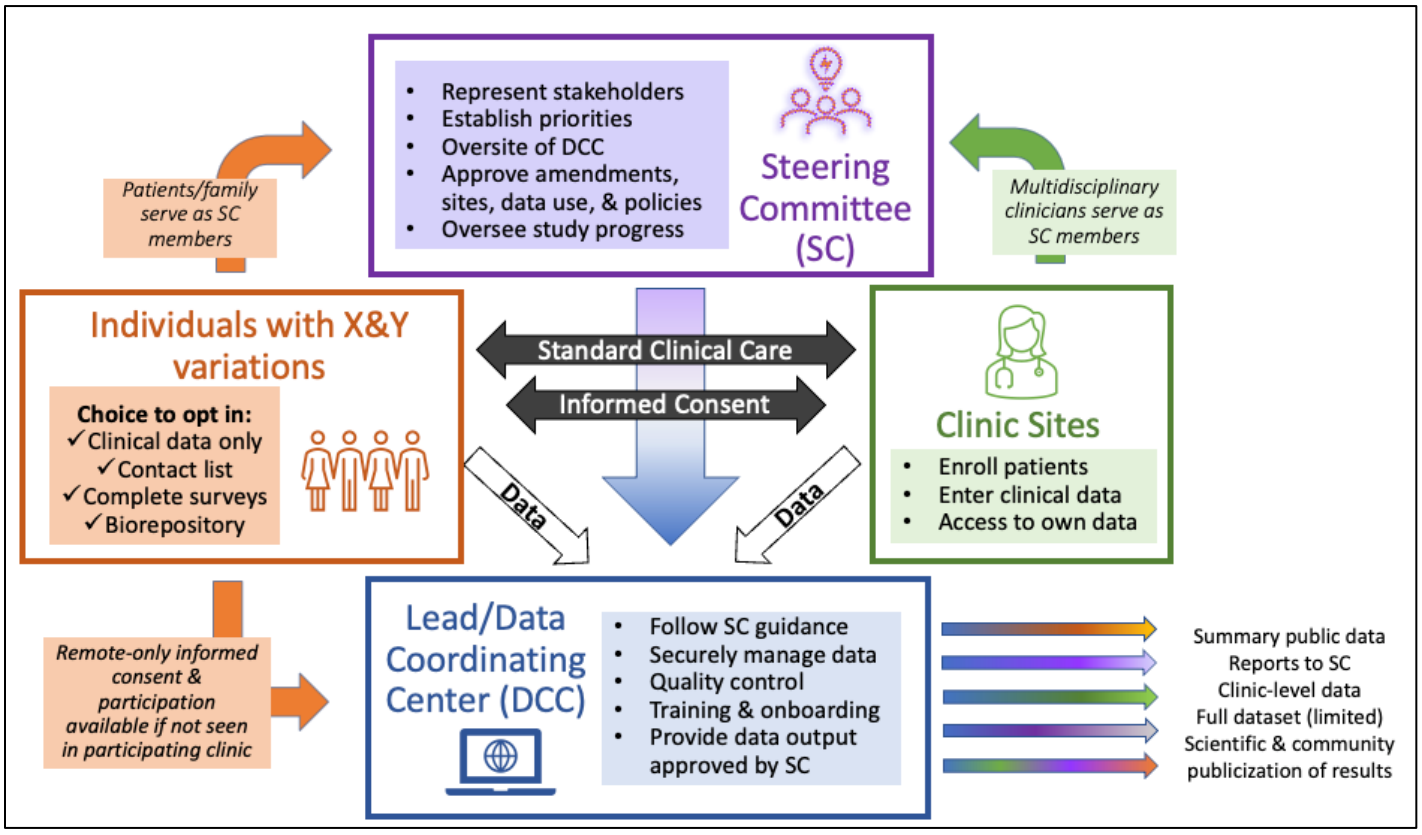

Figure 1. Overview of GALAXY stakeholders and roles

Participants: Any individual meeting the inclusion criteria listed below will be eligible to enroll in the GALAXY Registry. Individuals can enroll through a participating clinic site or independently online. If a participant enrolls through a participating site, that site will be responsible for confirming eligibility and inputting their data into the registry. If a participant enrolls remotely, they will be required to upload documentation to confirm eligibility.

Eligibility Criteria: A genetically confirmed SCA including but not limited to: 47,XXY (Klinefelter syndrome), 47,XXX (Trisomy X syndrome), 47,XYY (Jacob syndrome), 48,XXYY, 48,XXXY, 48,XXXX, 49,XXXXY, and 49,XXXXX. Mosaicism with any combination of cell lines will be allowed in any tissue type. Lack of ability to provide confirmatory genetic testing of an SCA (i.e. non-invasive prenatal screen only and/or no documentation available) will be excluded. An unborn individual (fetus) with a prenatal diagnosis is not yet eligible to enroll until they are born.

Non-discrimination: Individuals of any age, sex, gender, race, ethnicity, religion, nationality, disability status, insurance status, employment status, education level, income level, and native language are encouraged to participate. Some study materials may only be available in English and Spanish unless there is a demand for additional languages.

Participant involvement: Providing permission to use basic demographic and medical/clinical data for research purposes is required for study participation. Optional procedures include completing surveys, being on a list to be contacted about future study opportunities, and providing a blood sample to be stored in the biorepository.

Informed Consent: Participation is voluntary. Eligible individuals (and/or their parent/guardian/legally appointed representative) will be presented with a description of the study, potential risks and benefits, processes put in place to protect confidentiality, and study contacts. This informed consent process can either be completed independently or with direct interaction with a study team member depending on the individual's preference. Those agreeing to participate will sign a consent form using an electronic consent platform or on paper and will be provided a copy. In addition, individuals 7-17 years of age will provide assent. Consent for participation can be revoked at any time.

Participating Sites: Sites participating in the GALAXY registry will require approval by the Steering Committee and must meet all legal and ethical requirements for study engagement.

Minimum requirements for participating sites:

- Institution that provides clinical care for patients with X & Y variations
- Interest and capacity to conduct human subjects research (include appropriately trained personnel)
- Ability to enroll and contribute data to the registry for a minimum of 15 participants annually

While most participating sites will be ACRC clinics, this is not a requirement.

Responsibilities of participating sites:

- Sign a Registry Agreement with the lead center
- Submit all required documentation to the local IRB to either cede to COMIRB (preferred) or obtain local regulatory/ethics approval
- Complete protocol and REDCap training (at least 1 individual)
- Maintain a recruitment list with all potentially eligible participants and provide at least annual summaries that includes number of individuals eligible, recruitment status (not approached, approached/not enrolled, and enrolled), X&Y variation, race, ethnicity, payor status, and year of birth. (Personal Health Information will not leave the local site unless consent is granted.) This will help to recognize and rectify any disparities contributing to selection bias in the registry.
- Attempt recruitment of >80% of eligible patients; goal of enrolling >50% of eligible patients
- Obtain informed consent for local eligible patients
- Enter Core Elements data into REDCap for participants within one month of enrollment
- Validate local data and respond to data queries within one month
- Maintain local study documentation including personnel involved

Benefits for participating sites:

- Recognition as a participating site on AXYS website
- Contribution to advancing X&Y research and clinical care
- Full access to local data at all times
- Priority for access to all registry data (upon approval from Steering Committee)
- Opportunities for involvement/authorship on abstracts, manuscripts, and grant proposals

Lead Site / Data Coordinating Center: The University of Colorado at Anschutz Medical Campus will serve as the lead site and data coordinating center under the direction of Dr. Shanlee Davis (PI). The Colorado Multiple Institutional Review

Board (COMIRB) will serve as the IRB of record in accordance with the Single IRB policy. Responsibilities of the lead site include but are not limited to:

- Regulatory oversite for the entire study
- Develop the protocol, data collection instruments, and other study related documents
- Create and maintain the registry database
- Data management and validation
- Receive, process, catalog and store biospecimens
- Onboard new sites approved by the Steering Committee
- Train and support all study personnel
- Prepare progress reports
- Provide publicly available summary data and data as requested/approved by the Steering Committee
- All applicable responsibilities listed for participating sites

ORGANIZATION OF THE STEERING COMMITTEE

Composition of the Committee: The GALAXY Steering Committee will be made up of a minimum of 6 and no more than 14 stakeholders with the goal of representation from multiple disciplines, institutions, and perspectives.

Selection of Committee Members: The initial GALAXY Steering Committee Members will be appointed by the PI and AXYS leadership. If additional members are needed due to attrition or recognition of a gap in expertise, they can be recommended by any committee member and voted in by a majority vote of the committee members.

Committee Membership: Members will serve a two-year term at which point the roles and need for the committee will be reevaluated. Members will follow conflict of interest guidelines and be cleared of any real or potential conflicts of interest prior to agreeing to serve on the committee. If new conflicts of interest arise, the member is required to promptly inform the chair. Members serve at will and can elect to leave the steering committee at any time. There is no renumeration for this service.

RESPONSIBILITIES AND FUNCTIONS OF THE STEERING COMMITTEE

The role of the Steering Committee is to provide stakeholder input, consensus and oversite for the project that will then be carried out by the study team. The responsibilities of the Steering Committee will include reviewal, modification, and ultimately approval of the following documents:

1. Steering Committee Charter
2. Study protocol
3. Data collection instrument(s)
4. Patient-facing materials including consent/assent forms, marketing materials, etc.
5. Policy and Procedures for approving new sites interested in participating in the registry
6. Policy and Procedures for requesting and approving requests for use of GALAXY data or resources
7. Policy and Procedures for abstracts, presentations, and publications involving GALAXY data
8. Policy and Procedures for amendments to any committee-approved documents

In addition, the Steering Committee will prepare annual progress reports intended for AXYS, site investigators, and other stakeholders.

CONDUCT OF THE STEERING COMMITTEE MEETINGS

Scheduled Meetings: Meetings will be held via teleconference every 4-6 weeks in the first year of the project. Timing and duration of subsequent meetings will be determined by the committee dependent on needs. If feasible, an in-person meeting will be held annually.

Quorum: A minimum of 4 committee members constitutes a quorum for scheduled meetings.

Agenda: The agenda will be provided prior to the meeting by the Chair or Study Coordinator.

Voting: Any proposals, motions, or recommendations that require a committee vote will be announced prior to the meeting. Material that requires discussion and voting should be sent via email to all members at least one week ahead of time to allow sufficient time for review, unless urgent/unexpected. All members present in person or on the conference call are eligible to vote. A simple majority of members present is required to pass a proposal, motion, or recommendation.

Minutes: Meeting minutes will be kept for each meeting by the chair, or an individual appointed by the chair. Minutes will be available to all committee members within one week following the meetings.

No-Tolerance Policy: All meetings will be conducted in a professional manor with respect for all committee members and stakeholders. All committee members should strive to contribute to a welcoming, positive, and constructive environment. Discrimination, harassment, offensive or other inappropriate language will not be tolerated and may be grounds for immediate dismissal from the committee. If any committee member is uncomfortable, observes that another member is uncomfortable, or otherwise feels that the environment is incongruent with this stated mission they should discuss with the Chair and/or all committee members so this can be promptly rectified.

APPENDICIES:

APPENDIX B: TEMPLATE FOR MEETING MINUTES

Date:

Attendance:

Old Business:

Approval of last meeting's minutes

New Business:

Protocol Updates –

Regulatory Updates –

Enrollment Updates –

Data Management Updates –

Other Subcommittee Updates -

Next Meeting Date/Time:

APPENDIX C: TERMINOLOGY & ABBREVIATIONS USED

Term or Abbreviation	Definition/Explanation
SCA	Sex chromosome aneuploidies
X&Y variations	Alternative term for SCA, sometimes favored by stakeholders
AXYS	Association for X&Y variations: advocacy organization for SCAs
ACRC	AXYS Clinic & Research Consortium: group of clinics that provide care for SCAs
NIH	National Institutes of Health: among other things, funds biomedical research
REDCap	Research Electronic Data Capture: secure web platform for building and managing online databases and surveys
IRB	Institutional Review Board: group that reviews, monitors, and approves human subject research in accordance with local and federal regulations
COMIRB	Colorado Multiple Institutional Review Board: the IRB for the University of Colorado Denver | Anschutz Medical Campus and affiliates, acting as the single IRB of record