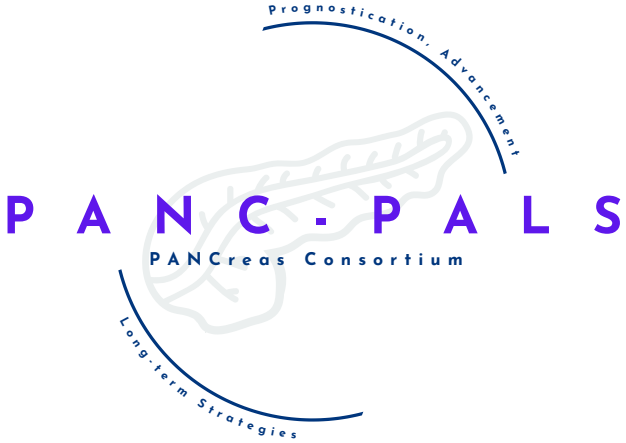
Study Protocol

PANC-PALS Registry

PANcreas **C**onsortium for **P**rognostication, **A**dvancement, and **L**ong-term **S**trategies in Pancreatic Neoplasms



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Background

Pancreatic surgery research, and in turn daily practice, has seen remarkable progress as leading centers started collaborating with the aim of improving standards of care through research.(1) Although recent advances in technology have allowed collaborations of increasingly wide geographical capture, there is a long-standing history of exchange of ideas among pancreatic surgeons. Direct communication among the then thought leaders in the field paved the way for pancreatic surgery as we know it today. Anecdotally, they would often detail their experience of performing a resection on a single patient and their postoperative recovery over post mail, as was the case at the time. In a sense, these exchanges between surgeons made them pen-pals.

While a paradigm shift in the approach to research favoring collaborative efforts has been invaluable to the field, the current approaches to collaboration have limitations. These limitations are mostly two-fold, in size and in scope. First, only a small number of centers are often involved in a single common project. These multicenter efforts commonly involve centers within limited geographical regions, thus diminishing the broader applicability of their findings.(2) Second, collaborations to date tend to focus on specific research questions, which means that both the data and conclusions drawn may lack granularity for continued research potential. As a result, multiple independent collaborations are required over time thus duplicating data abstraction efforts and study set up every time. The use of non-standardized data elements in different collaborations also impedes data transformation and unification of databases across centers. Ultimately, these limitations lead to collaborative efforts fading over time.

A global partnership is required to build a robust international registry and to lead the important work that needs to be accomplished in the field of pancreatic surgery if we are to improve the

quality of care delivered to patients and their outcomes. In the case of premalignant pancreatic lesions, such as intraductal papillary mucinous neoplasms (IPMN), the fine line between curative surgical treatment versus overtreatment is a widely recognized dilemma. Individualized management and surveillance strategies for IPMN, beyond the current treatment algorithms, are needed. For malignant pancreatic lesions, surgical resection remains the mainstay curative treatment, with the potential addition of systemic therapy for those with pancreatic ductal adenocarcinoma (PDAC).(3) Although the incidence of PDAC is relatively low, it is one of the most lethal cancers, with the lowest 5-year cancer-related survival of approximately 13%.(4) The introduction of multiagent chemotherapy regimens and therapeutic strategies have improved both median survival and cure rates as compared to surgery alone.(5) Systemic therapy is now widely used with the intent of downsizing borderline resectable and locally advanced disease preoperatively as well as to eradicate micrometastatic spread (6). Faced with a new level of complexity as the heterogeneity in disease course and oncological outcomes becomes increasingly evident, pancreatic surgery research must also progress.

The PANC-PALS consortium will establish a modern-day platform for experts in the field from very high-volume centers to become “panc(reatic) pals” and lead an international multicenter registry to provide the granularity in data required for new prognostic and decision support tools.(7, 8) Additionally, the use of deep learning models in this context promises a new approach to patient care. Prior experience in the field, through *The International Study Group of Pancreatic Fistula*, *The Dutch Pancreatic Cancer Group*, and *International Association of Pancreatology*, optimally equips the current team to lead this effort.

Goal of the registry

The PANC-PALS registry will generate real-world evidence on outcomes after pancreatic surgery to gain a broader understanding of the implications of treatment variations in outcomes and disease course. The initial output of PANC-PALS will subsequently guide future research by identifying the most pressing clinical issues in pancreatic surgery. Members of the consortium will propose research studies focusing on prognostication in pancreatic diseases and advancement of management strategies in the field using the registry data. Establishing an international partnership of leading pancreatic surgery centers may also accelerate and facilitate efforts in pragmatic registry randomized clinical trial (RRCT) and treatment guidelines development. The vision of PANC-PALS is to improve care with tailored patient management.

Methods

Recruitment

Registry recruitment will be at hospital level; otherwise referred to as pancreatic surgery centers. Eligible centers will be identified from previous collaborative research projects, international associations of pancreatic surgeons, and international colleague networks. Centers will be enrolled through pancreatic surgeons interested in the registry. Invitations will be sent to the chief of surgery/pancreatic surgery departments from pancreatic surgery centers worldwide and via the *www.pancpals.com* website. Centers will be vetted based on volume of pancreatic resections per year (minimum 100), ability to recruit patients, internal resources, and availability of local PI. Three individuals per participating center, including the local PI and two investigators chosen at the discretion of the local PI, will be registered members of the PANC-PALS registry.

Initiating centres

The PANC-PALS registry will be initiated at NYULH (primary site) and Amsterdam UMC (site 1), where approximately 250 to 300 pancreatic resections were performed in 2023 in each center. Multiple other pancreatic surgery centers have also shown interest in joining PANC-PALS.

Eligibility criteria

Center eligibility

Eligible centers will be very high-volume pancreatic surgery centers from any nation worldwide. We define a very high-volume pancreatic surgery center as a medical institution or hospital performing a minimum of 100 pancreatic resections per year including all types of pancreatic resections combined, for all diagnoses. We aim to enroll and register at least 40 very high-volume medical centers from at least 4 continents (i.e. Americas, Europe, Asia, Australia/Oceania, Africa). Commitment to consecutive case submission of patients undergoing pancreatic resections at their institution from their initiation of participation date will be required. Participating centers will also be expected to have the capacity to review and correct submitted data if requested to by the PANC-PALS data manager.

Patient eligibility

Adult patients (18-99 years of age) undergoing a surgical resection of the pancreas from 2014 to date and prospectively will be eligible for inclusion in PANC-PALS. Patients requiring a pancreatic resection for any pancreatic neoplasm, including premalignant and malignant lesions of the pancreas will be eligible. All surgical approaches, open, robotic or laparoscopic, will be included. As an observational registry, patients enrolled in experimental research studies such as randomized controlled trials, will also be eligible for inclusion in the PANC-PALS registry.

Data

Data collection and storage

The multi-institutional PANC-PALS registry database will be housed at a centralized encrypted electronic platform managed by the PANC-PALS project managers at NYULH. Clinical data will be collected directly via a central Research Electronic Data Capture (REDCap) electronic Case Report Form (eCRF)[1]. Image data will require transfer to the PANC-PALS NYULH UltraViolet High-Performance computing (HPC) system. To achieve this, the external collaborating center PI and two investigators from each center will be assigned unique user ID and password combinations (Kerberos computer-network authentication protocol) by NYULH to access the PANC-PALS platform. The two local investigators at each center will be tasked with data abstraction duties.

Data domains

Data domains will be outlined following the *framework for creating standardized outcome measures for patient registries (9)* into characteristics, treatment, and outcomes (Figure 1). Data elements within characteristics will further be subdivided into participant data, disease data, and provider data. Participant data will include demographics, functional baseline at presentation, past medical history, social history, family history, and germline mutation status. Disease data will include presenting symptoms, workup, diagnostic investigations, biopsy/cytology, imaging, laboratory tests, and somatic mutations. Imaging data will be collected in both the reported form for specific interpretations through the eCRF as well as in de-identified raw file format such as DICOM files for Computed Tomography (CT) scans. Provider data will include center geographic location, yearly volume of pancreatic resections, and mode of referral to tertiary center.

[1] https://redcap.nyumc.org/apps/redcap/redcap_v14.0.29/index.php?pid=114402

Data elements within the treatment domain will be further subdivided into type and intent. Type of treatment data will include surgery and systemic treatment such as chemotherapy, radiation therapy or immunotherapy. Intent will specify whether the treatment was of curative or palliative intent.

Data elements within the outcomes domain will include survival, disease response, postoperative complications, patient reported outcomes, and health system utilization. Loss to follow-up (LTF) will also be included in the outcomes domain to capture final follow-up and reasons for incomplete follow-up or survival data.

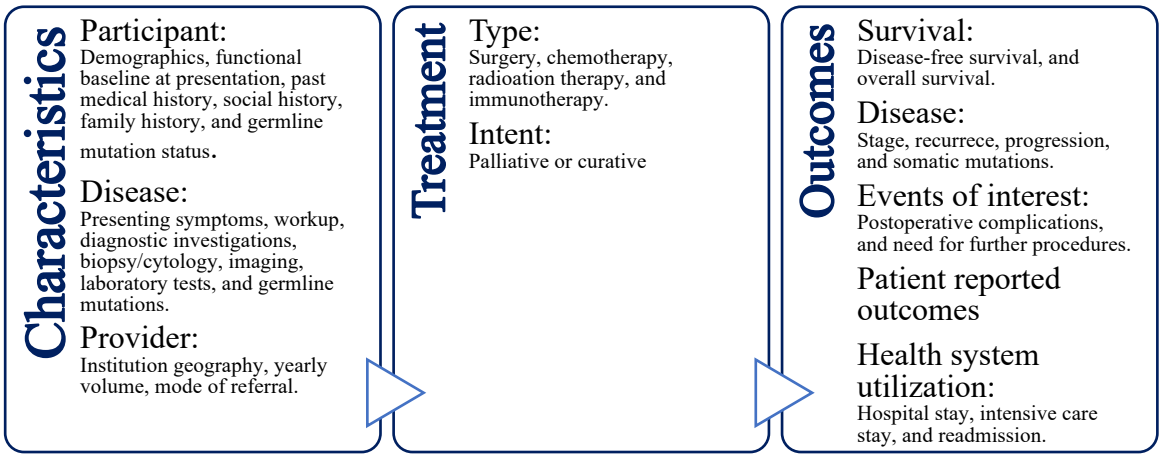

Figure 1. Summary of data elements.

Data standards

To maximize internal validity, established clinical data standards will be used whenever possible. For example, outcome data elements will include standardized outcomes measures established by the International Study Group for Pancreatic Surgery (ISGPS). Standard terminology will also be incorporated into the registry throughout all domains as extensively as possible to minimize data abstraction burden on sites. The eCRF will contain the relevant summary explanations for standardized clinical data measures and terminology to aid data abstractors. Where data standards do not exist then commonly used data elements and internationally accepted data elements will be used instead. The NIH common data elements (CDEs) repository was examined for participant characteristics data such as race, ethnicity, sex,

and baseline status. Definitions used will also be aligned with currently existing databases such as the E-MIPS to facilitate training and data abstraction process for sites. An "unknown" option will be provided for data elements that are commonly collected retrospectively from patient records to distinguish data that is not documented and missing data. Because of the international nature of the consortium, different units for laboratory tests will be allowed. The data collection tool will be pilot tested prior to launch of the consortium to ensure all data elements are satisfactory.

Data quality assurance

A risk-based approach to focus on the most important sources of error will be taken for data quality assurance. Errors in interpretation of data elements or coding from data abstraction will be minimized by pilot testing the eCRF for inter-rater reliability and by providing training for data collectors on definitions. Structured training will be offered to data collectors on an as-needed basis. Errors in data entry will be prevented by restricting entry fields to integers, defined number of decimal places, or letters as appropriate, by limiting ranges of values to clinically possible lower and upper limits, and by rigorous data cleaning. Errors of intention (cherry-picking cases) will be addressed by checking for data consistency between centers in similar geography and recorded center case volume as well as by performing onsite audits at random or if any concerns arise. Quality assurance concerns include missing data, incomplete cases and errors in data entry. Automated monitoring and alerts on data completeness as well as quality trending and alerting based on set thresholds (missing data >5% and >10% incomplete cases for longer than 3 months).

Data sources

Secondary data (data collected for routine medical care) will be the main data source. Primary data sourcing may be necessary for certain data elements, such as patient reported outcomes, in some centers. Centers participating in other registries such as the European Consortium on

Minimally Invasive Pancreatic Surgery (E-MIPS) or national pancreatic surgery databases, may request data transformation and import into the PANC-PALS registry, however missing data elements may then need to be sourced from patient records or primarily in follow-up.

Data de-identification

None of the 18 patient identifiers under the Safe Harbor de-identification method for protected health information (PHI) will be collected by the PANC-PALS registry. All raw file images transferred to the registry will be in de-identified format. This will make the PANC-PALS registry a *limited dataset* as defined by the Privacy Rule. Participating centers will allocate each patient entered in the database a random study ID number. Each center will be required to store an encrypted electronic identifying key to the patient's random study ID with password lock within their own institution's network or as paper copy under double physical lock be able to amend or complete their own records over time. The key to the direct identifiers will never be shared with the PANC-PALS central hub and will always remain inaccessible to the researchers analyzing the de-identified data. Health information that can be used in conjunction with other information to identify individuals such as treatment event dates or recurrence dates will be recorded as time intervals and will not be accessible to researchers performing data an analysis.

Data ownership

Participating centers will remain rightful owners of the data generated by their own center and will have full access to manage their own institutional data by accessing the PANC-PALS platform with their unique Kerberos ID. The unique access codes will be assigned individually to the participating center PI and two investigators following identity verification. Periodical password change will be required. Direct data access via unique Kerberos ID will be limited to their own center's data. Access to further data will require study proposal approval at the PANC-PALS triannual meeting and confirmation of consent of participation between the

investigating center and collaborating centers in the registry. Every center will therefore stay in **full** control of the use of their own data. Wider data access for research purposes will subsequently be provided via a dedicated data enclave restricted to prespecified data elements, length of time, and will not allow download or permanent storage outside the PANC-PALS platform.

Registry ethics

Institutional review board (IRB) approval for the PANC-PALS consortium will be sought and maintained at NYULH. Local IRB approval will be mandatory for every center wishing to partner with the PANC-PALS consortium and contribute to the registry. Data use agreements will be established by the partnering centers and the central data hub after local IRB approval. The project managers will assist individual centers in this process.

Informed consent

As an observational registry, research performed using registry data will involve no more than minimal risk to patients. Where regulations allow, a waiver of informed consent will be sought together with IRB approval. Each site PI will be responsible for obtaining appropriate approvals at their own center. A waiver of consent will not adversely affect the rights and welfare of the patients included. The PANC-PALS registry will solely contain de-identified patient data, through which patient's identity will not be readily ascertained, health information that can be used in conjunction with other information to identify individuals such as treatment event dates or recurrence dates will be encoded in random number sequences inaccessible to investigators. Every attempt possible will therefore be made by the registry to make indirect identifiers inaccessible to the investigators using PANC-PALS registry data for research purposes by recoding date data into time intervals and uncoupling center data from all clinical data. The investigators using PANC-PALS registry data for research purposes will thus not be

able to re-identify subjects nor contact patients in the registry. In line with US Department of Human Services (HHS) 45 CFR part 46.104 and part 46.117, a request for waiver of consent will be sought at NYULH. Patients may opt out of the registry at any time if they choose not to be involved in research or explicitly state they wish not to participate in PANC-PALS.

Retention of recruited centers

The PANC-PALS steering committee, consisting of one local site PI from each participating center and the PANC-PALS organizing scientists across NYUH and Amsterdam UMC will be tasked with center retention duties. The structure of the PANC-PALS consortium is outlined in detail in the manual of operation. Retention duties will include maintaining visibility at relevant international meetings, annual outcome reports, monthly newsletters, and regular website updates. Confidential live summary graphics of institutional outcome data for each center will be made available to participating centers' investigators accessing the platform with their unique access codes. The main incentive for continued participation will be the ability for participating centers to publish using the PANC-PALS platform and registry data.

Dissemination

Annual outcomes report

Detailed dissemination of overall outcomes will be through bi-annual PANC-PALS registry report publications. Annual reports and regular updates of data contributed to the registry will also be summarized on the PANC-PALS website. Annual reports will include descriptive analyses of all pancreatic resections reported, treatment variations, postoperative and long-term outcomes. These will serve as regular updates of global progress in pancreatic surgery to inform clinical practice, guide further research efforts and potentially highlight knowledge gaps.

Research study proposals

Active PANC-PALS consortium members will be eligible to access PANC-PALS registry data to perform research studies with an emphasis on prognostication and management strategies in

pancreatic surgery. Annually, at least four centers will be provided prespecified access via data enclaves to analyze data for proposed studies (Figure 3). Further details on data requests and limited access are outline in the manual of operations.

Timeline

Registry study cohort

The PANC-PALS registry will capture a retrospective cohort from 2014 to date together with a prospective cohort from the date of registry initiation for a minimum of 5 calendar years. Continuation of the prospective registry will be evaluated in the last quarter of 2028. The entire registry data will be held and maintained by the PANC-PALS central hub until then. If the decision is made to close the PANC-PALS registry after the 5 calendar years, then contributing centers will be allowed to retrieve their own data for institutional records before all the data held by the registry is safely deleted.

Registry creation and maintenance

The PANC-PALS registry will be established first at NYULH and Amsterdam UMC before it is officially launched to very-high volume pancreatic surgery centers worldwide. Data cleaning and reviewing will be performed quarterly, and the collaborating center PI will be contacted directly if concerns arise. There will be quarterly website updates with overview of data outcomes. Quarterly newsletters will include an overview of contributed patients. Each center will have (confidential) access to live summary statistics of center specific outcomes. Annual reports, as described above will provide further detailed registry data analysis (Figure 2).

PANC-PALS Registry timeline

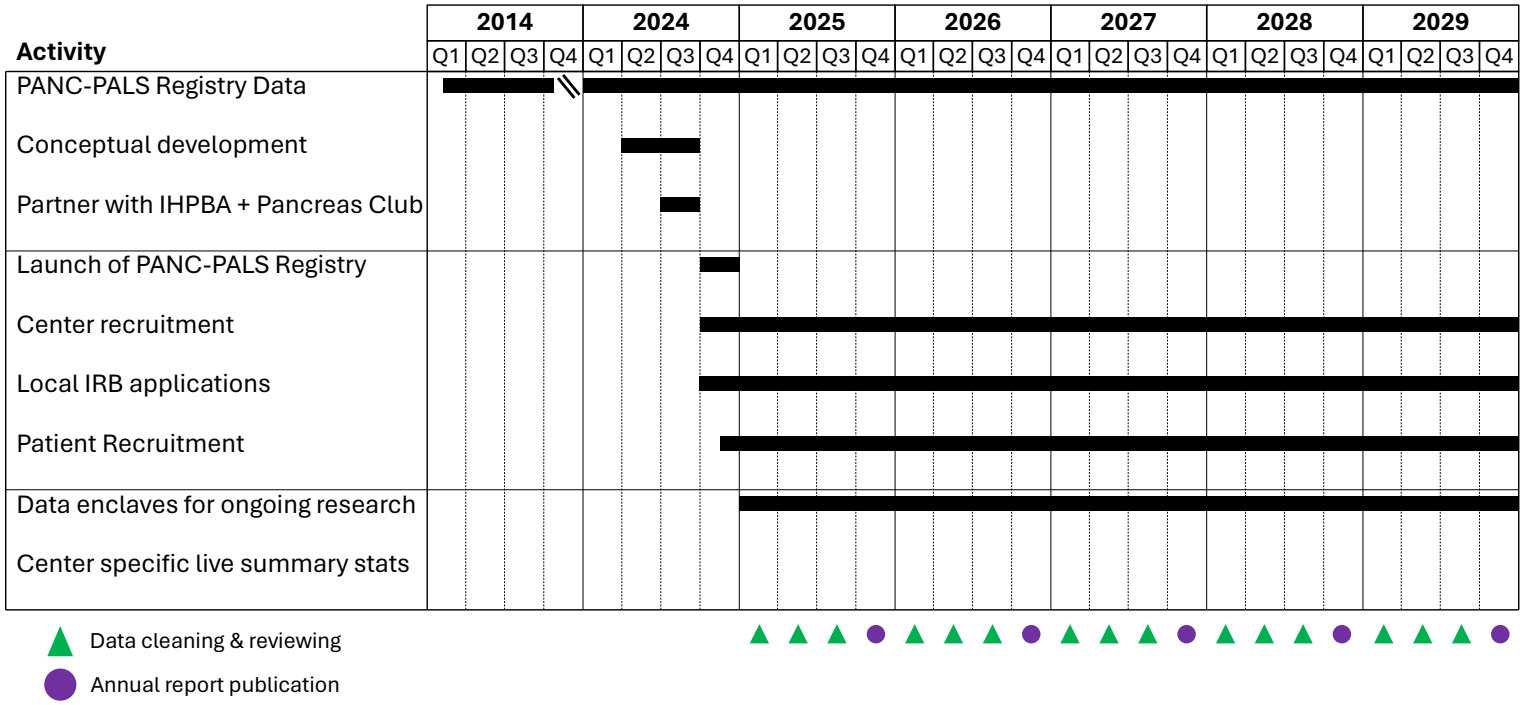

Figure 2. PANC-PALS Registry Timeline

PAN-PALS Registry data flow

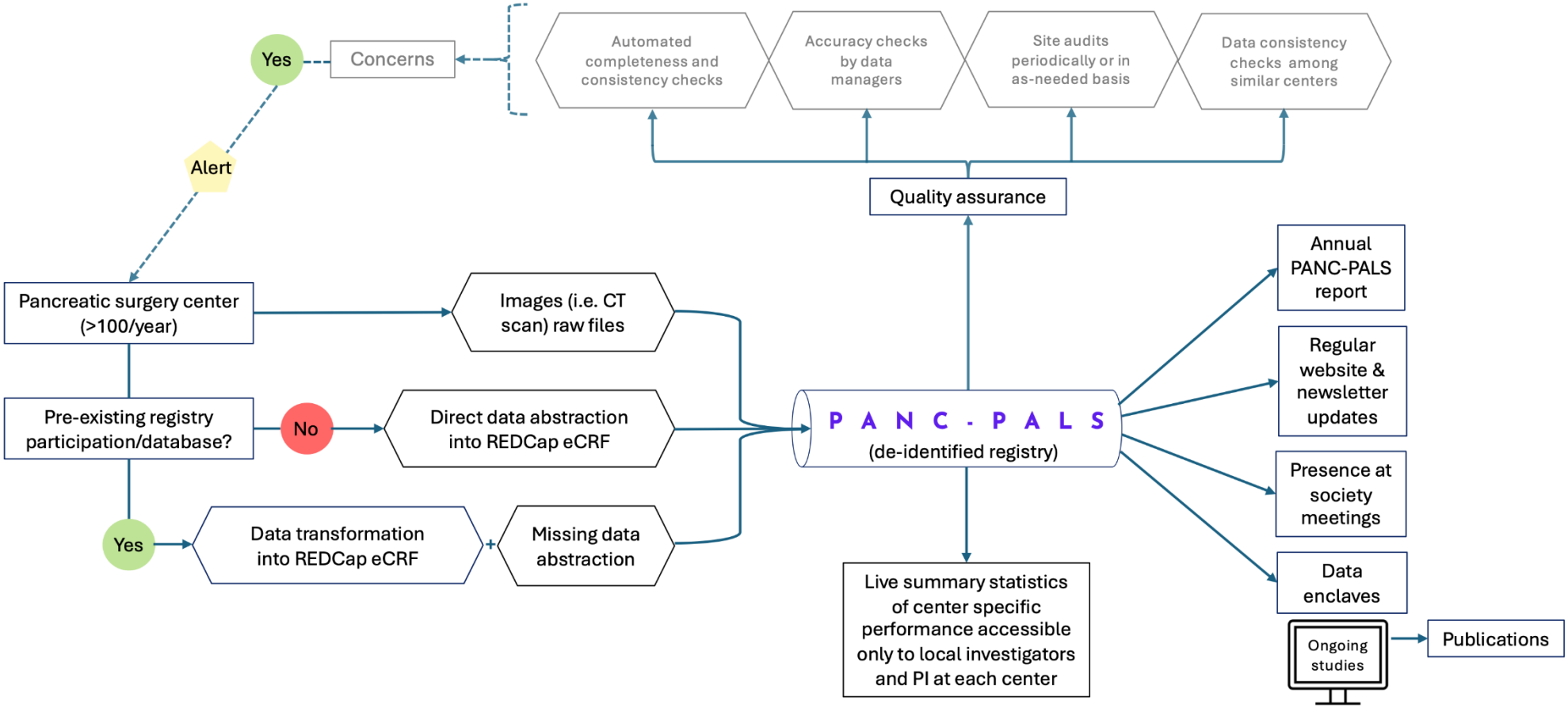

Figure 3. PANC-PALS Registry Data Flowchart

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