GCA-GLOBE Full Study Protocol

International Treatment and Outcome Study of Appendiceal Goblet Cell Adenocarcinoma

FULL PROTOCOL VERSION 1.0 · JUNE 2026

Protocol version: v1.0 **Date:** 12 June 2026 **Status:** COLLEAGUE REVIEW DRAFT. The study has not yet opened for data collection. Study initiation remains subject to colleague and steering-group review, feasibility assessment and ethics approval.

Study Title

GCA-GLOBE: International Treatment and Outcome Study of Appendiceal Goblet Cell Adenocarcinoma

Short Title

GCA-GLOBE

Study Type

International multicentre retrospective cohort study with planned prospective follow-up extension. Initial active recruitment will primarily use European surgical, pathology and oncology networks, while eligible centres outside Europe may also participate.

Coordinating Investigators

- Kim Boterbergh, General, Abdominal and Oncological Surgery, Sint-Elisabeth Hospital Zottegem, Belgium, kim.boterbergh@sezz.be
- Tommaso Violante, Surgery of the Alimentary Tract, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, Tommaso.violante@unibo.it
- Jan Colpaert, Colorectal Surgery, AZORG Hospital, Aalst, Belgium, jan.colpaert@azorg.be
- Stijn De Sutter, General, Abdominal and Oncological Surgery, Sint-Elisabeth Hospital Zottegem, Belgium, stijn.desutter@sezz.be

Substudy Lead Investigators

- Radiology and CT texture-analysis lead: Isabelle De Kock, UZ Gent, Ghent, Belgium

General centre-interest contact: interested@gca-europe.org Study website: https://gca-europe.org

Background and Rationale

Goblet cell adenocarcinoma (GCA) of the appendix is a rare appendiceal malignancy with mixed glandular and neuroendocrine features, but with clinical behaviour closer to adenocarcinoma than to classical appendiceal neuroendocrine tumours. Historically, this entity has been reported under heterogeneous terminology, including goblet cell carcinoid,

adenocarcinoid, mucinous carcinoid, goblet cell carcinoma, mixed carcinoid-adenocarcinoma and adenocarcinoma ex-goblet cell carcinoid.

The 2019 WHO Classification of Digestive System Tumours introduced goblet cell adenocarcinoma as the preferred terminology, replacing the older carcinoid-based nomenclature. This change has important implications for staging, grading, treatment decisions and interpretation of historical cohorts.

Due to its rarity, available evidence is largely derived from small institutional series or national registry studies. These studies are limited by historical diagnostic heterogeneity, incomplete pathology variables, limited treatment granularity and variable follow-up. There remains uncertainty regarding the optimal extent of surgery, the value of completion right hemicolectomy, the role of adjuvant chemotherapy, the management of peritoneal disease, and the prognostic impact of specific pathological factors such as perforation, pT stage, nodal disease, lymphatic invasion, venous invasion, perineural invasion and margin status.

The GCA-GLOBE study aims to establish an international collaborative cohort focused on the complete real-world care pathway, treatment decisions and survival outcomes in appendiceal GCA. The study will initially recruit mainly through European networks while remaining open to eligible centres outside Europe.

Study Concept

The study will be structured in two core phases and a limited number of predefined subanalyses. Guideline concordance, oncological yield of additional surgery and long-term outcomes are central to the core cohort. Patient experience and survivorship, colonoscopy yield, pragmatic CT interpretation and healthcare utilisation in localised low-grade disease will be evaluated as feasibility-dependent subanalyses.

The overarching concept is to first define real-world practice before attempting to propose guidance. The study will therefore map the complete pathway from preoperative imaging and index appendectomy to pathology reporting, patient communication, staging, multidisciplinary decision-making, definitive treatment and long-term outcome: who treated which patient, based on which findings, at what time point, using which treatment strategy, and with what oncological outcome.

The initial appendectomy pathology report will be treated as a key decision point, particularly in incidentally diagnosed cases where the patient may initially have been informed that the appendix has been removed completely, but staging and additional surgery may still be recommended. The study will evaluate how reported baseline features such as perforation, pT stage, margin status, lymphatic invasion, venous invasion, perineural invasion, grade and suspected peritoneal involvement influence subsequent patient counselling, staging, treatment decisions and outcomes.

Preoperative imaging will be evaluated as an additional pathway decision point. In patients initially diagnosed as acute appendicitis, the study will assess whether retrospective CT review can identify features suggestive of an appendiceal neoplasm, appendiceal base or caecal pole involvement, or a measurable enhancing lesion that correlates with pathological tumour size. This may help identify whether selected patients could benefit from a different index operation, such as appendectomy with caecal pole resection, and whether such an approach could reduce the need for later completion surgery in carefully selected cases.

Phase 1: Practice Patterns and Pathology Reporting

The first phase will evaluate how appendiceal GCA has been diagnosed, reported and treated across participating centres and countries.

Main focus:

- The clinical pathway from index appendectomy to definitive management.
- Preoperative imaging findings and whether appendiceal malignancy was suspected before surgery.
- Retrospective radiological features that may suggest an underlying appendiceal neoplasm in patients initially diagnosed with appendicitis.
- Historical and contemporary diagnostic terminology.
- Completeness of pathology reporting.

- Patient communication after incidental diagnosis, where documented.
- Surgical management strategies.
- Concordance between relevant guideline recommendations, MDT/MOC recommendations and treatment actually received.
- Oncological yield and morbidity of additional surgery, particularly completion right hemicolectomy and ovarian surgery.
- Timing and interval between index appendectomy, pathology diagnosis, multidisciplinary discussion and completion surgery.
- Use of systemic therapy.
- Use of cytoreductive surgery and HIPEC in peritoneal disease.
- Early oncological outcomes where available.

Planned manuscript 1:

From incidental appendectomy to definitive surgery: international practice patterns and pathology reporting in appendiceal goblet cell adenocarcinoma

Phase 2: Mature Five- and Ten-Year Oncological Outcomes

The second phase will evaluate mature oncological outcomes in patients with sufficient follow-up, with a planned update of recently diagnosed patients once five- and ten-year follow-up becomes available.

Main focus:

- Five-year overall survival.
- Five-year disease-free survival.
- Ten-year overall survival, where available.
- Ten-year disease-free survival, where available.
- Recurrence patterns.
- Prognostic value of pathological risk factors.
- Impact of completion right hemicolectomy.
- Impact of adjuvant systemic therapy.
- Pathology, immunohistochemical and molecular correlates of systemic therapy choice and response.
- Outcomes after CRS/HIPEC in patients with peritoneal involvement.

Planned manuscript 2:

Five- and ten-year oncological outcomes after treatment of appendiceal goblet cell adenocarcinoma: an international multicentre study

Patient-Reported Experience Subanalysis

A patient-reported experience subanalysis will be developed in participating centres where ethics approval and patient contact are feasible.

This subanalysis will evaluate how patients experienced the pathway from presumed benign appendicitis and appendectomy to unexpected pathology, staging, treatment decision-making and possible completion surgery. It will specifically address the communication challenge in incidental cases: patients may be told that an unexpected rare appendiceal tumour was found and apparently removed, while additional staging and possibly a completion right hemicolectomy are still recommended.

Unlike patients undergoing diagnostic colonoscopy for alarm symptoms, many patients with appendiceal GCA enter the pathway through presumed benign appendicitis and may experience the diagnosis as a sudden transition from a resolved acute surgical condition to a rare cancer diagnosis requiring staging and possible further treatment.

The patient-reported experience subanalysis should be designed as a separate prospective or cross-sectional module requiring patient consent. It should not be required for participation in the main retrospective cohort.

Potential focus:

- Patient understanding of the diagnosis.
- Experience of being informed about an unexpected rare cancer diagnosis after appendectomy.
- Perceived clarity of explanations regarding staging and additional surgery.
- Experience of uncertainty between pathology diagnosis and definitive treatment decision.
- Involvement in shared decision-making.
- Psychological burden of the incidental diagnosis and waiting interval.
- Satisfaction with information, coordination and follow-up.
- Patient preferences regarding written information, decision aids or structured counselling.
- Unmet informational and supportive care needs.
- Patient suggestions for improving the pathway.

Intended practical output:

- Development of patient-centred information material for individuals unexpectedly diagnosed with appendiceal GCA after appendectomy.
- Identification of key communication points for clinicians discussing unexpected appendiceal GCA pathology, staging and completion surgery.

Potential manuscript 3:

From appendicitis to rare cancer survivorship: patient experience after incidental appendiceal goblet cell adenocarcinoma

CT Interpretation and Exploratory Texture-Analysis Subanalysis

A feasibility-driven imaging subanalysis will evaluate whether acute-phase CT can identify an underlying appendiceal neoplasm in patients initially presenting with presumed appendicitis. It will combine a pragmatic radiologist reader study with an exploratory quantitative texture-analysis or radiomics study, led by the radiology substudy team.

Eligible preoperative contrast-enhanced CT examinations will be cross-read by radiologists from other participating centres who routinely and independently report acute abdominal CT examinations. Formal abdominal subspecialisation will not be required, but reader experience and practice profile will be recorded.

The initial pilot should remain deliberately pragmatic:

- Participating centres identify eligible preoperative CT abdomen examinations with intravenous contrast.
- De-identified examinations are assigned to radiologists from other participating centres, subject to governance and image-transfer feasibility.
- Readers are blinded to the original radiology report, pathology findings, treatment and outcome.
- A short standardised review form records whether an underlying appendiceal or caecal neoplasm is suspected, the level of confidence, the features supporting suspicion and whether the findings would have altered the proposed initial management.
- Each examination is preferably reviewed independently by two readers. A single cross-centre read may be accepted during the initial feasibility pilot.
- Where feasible, a limited sample of CT examinations from patients with appendicitis without appendiceal neoplasm will be included as matched controls. This is necessary to estimate false-positive suspicion, but should not be required to start the pilot.

For the exploratory texture-analysis component:

- GCA cases with suitable acute-phase contrast-enhanced CT imaging will be compared with non-neoplastic acute appendicitis controls, preferably matched by centre, age, sex and CT protocol.
- The appendix and any visible lesion will be segmented using dedicated software under radiology oversight.
- Quantitative morphology, attenuation, enhancement, heterogeneity and texture features may be extracted using a prespecified and preferably IBSI-conformant workflow.
- Scanner, contrast phase, slice thickness and reconstruction parameters will be recorded because these may materially influence radiomic features.
- Associations with WHO pathological grade will be explored while retaining Grade 1, Grade 2 and Grade 3 as recorded categories. Where sample size is limited, a prespecified Grade 1 versus Grade 2–3 comparison may be used.
- Associations with adverse pathological characteristics, including pT3–4 disease, lymphovascular or perineural invasion, nodal disease and peritoneal disease, will be exploratory.

The clinically relevant questions are whether imaging would have prompted a different initial pathway and whether quantitative CT features could support future risk stratification. The subanalysis will not assume that radiological suspicion or a radiomics result alone should automatically lead to immediate right hemicolectomy, particularly in an acute inflammatory setting.

Initial outputs will be descriptive and feasibility-focused:

- Proportion of eligible patients with transferable preoperative contrast-enhanced CT imaging.
- Proportion of examinations considered suspicious for underlying neoplasm on blinded cross-centre review.
- Agreement between the original report and retrospective review.
- Inter-reader agreement where two reviews are available.
- Imaging features most frequently associated with suspicion.
- Proportion of reviews in which the radiologist indicates that the findings would have changed the initial management pathway.
- Specificity and diagnostic discrimination only where an appropriate non-neoplastic appendicitis control group is available.
- Feasibility and reproducibility of appendix segmentation and quantitative feature extraction.
- Exploratory diagnostic discrimination of texture-analysis features between GCA and non-neoplastic appendicitis.
- Exploratory associations between quantitative CT features, WHO pathological grade and other adverse pathological characteristics.

Reader characteristics will be recorded descriptively, including years of independent practice, routine participation in acute CT reporting, approximate abdominal imaging workload, formal abdominal fellowship or subspecialisation, and GI or colorectal MDT participation. Given the expected sample size, comparisons by reader expertise will be exploratory.

Potential manuscript 4:

Can appendiceal goblet cell adenocarcinoma be suspected on preoperative CT? A pragmatic cross-centre interpretation study

Colonoscopy Yield Subanalysis

A pragmatic colonoscopy subanalysis will evaluate how often colonoscopy is performed after a diagnosis of appendiceal GCA, what lesions are identified and whether findings change staging, surgery, surveillance or other management. The analysis will distinguish polyps, advanced adenomas and synchronous colorectal carcinoma, and will report colonoscopy completeness and timing where available.

Guideline Concordance Analysis

For each patient, centres will record the relevant guideline or local policy context where identifiable, the MDT/MOC recommendation, treatment actually received and the documented reason for any difference. This analysis will not assume that guideline deviation represents inappropriate care. Differences may reflect patient preference, frailty, comorbidity, disease extent, evolving terminology, incomplete evidence or local resource availability.

Healthcare Utilisation in Localised Low-Grade GCA

An exploratory healthcare-utilisation analysis will focus primarily on patients with localised WHO grade 1 or otherwise documented low-grade GCA. It will describe the additional investigations, consultations, operations, admissions, complications, readmissions and surveillance associated with different care pathways.

The initial analysis will quantify resource use and clinical consequences rather than claim formal cost-effectiveness. A later health-economic evaluation may be considered if sufficiently comparable cost data and prospective quality-of-life measurements become available.

Potential manuscript 5:

Healthcare utilisation and consequences of additional treatment in localised low-grade appendiceal goblet cell adenocarcinoma

Primary Objectives

Phase 1 Primary Objective

To describe international variation in the care pathway after incidental or suspected appendiceal goblet cell adenocarcinoma, including preoperative imaging, initial appendectomy findings, pathology reporting, patient communication, staging, timing of decision-making, completion surgery and definitive treatment strategy.

Phase 2 Primary Objective

To evaluate five-year overall survival and disease-free survival in patients treated for appendiceal goblet cell adenocarcinoma.

Patient-Reported Experience and Survivorship Subanalysis Objective

To evaluate patient-reported experience of the diagnostic, treatment and survivorship pathway after incidental or suspected appendiceal goblet cell adenocarcinoma, with particular attention to communication, uncertainty, shared decision-making, long-term symptoms, follow-up coordination and the interval between unexpected pathology and definitive treatment.

Secondary Objectives

- To define real-world surgical practice patterns before developing future consensus recommendations.
- To evaluate whether preoperative imaging suspected appendiceal malignancy and whether this changed index surgery, staging or definitive treatment.
- To evaluate whether retrospective review of preoperative imaging can identify features suggestive of appendiceal GCA or caecal pole/base involvement.
- To assess whether radiological lesion size, wall thickening or enhancement correlate with pathological tumour size and tumour location.
- To assess, in a feasibility-driven imaging subanalysis, whether routine radiologist review or exploratory quantitative CT texture analysis can distinguish GCA from non-neoplastic acute appendicitis.
- To explore associations between acute-phase CT morphology or texture features, WHO pathological grade and other adverse pathological characteristics.
- To explore whether index caecal pole resection or limited ileocaecal resection is associated with lower rates of completion surgery, residual disease or reoperation in selected patients.
- To explore whether inclusion of the mesoappendix and regional lymph node tissue in an index appendectomy with caecal pole/cuff resection is associated with a different subsequent MDT/MOC recommendation, particularly completion right hemicolectomy versus surveillance or no further surgery.

- To quantify the oncological yield of completion right hemicolectomy after initial appendectomy, particularly the proportion of clinically non-metastatic and not previously node-positive patients in whom at least one positive regional lymph node is identified.
- To describe concordance between relevant guideline or local-policy recommendations, MDT/MOC recommendations and treatment actually received, including documented reasons for differences.
- To quantify the yield of postdiagnosis colonoscopy, including polyps, advanced adenomas, synchronous colorectal carcinoma and management-changing findings.
- To describe healthcare utilisation and treatment consequences in patients with localised low-grade GCA according to management pathway.
- To evaluate whether patient age, frailty/comorbidity, WHO grade and the pre-WHO versus post-WHO 2019 terminology era are associated with the MDT/MOC recommendation for surveillance versus completion right hemicolectomy, and with subsequent treatment received.
- To describe, among patients with incidentally detected GCA, whether the histopathological diagnosis led to additional staging, altered surveillance, completion surgery, systemic therapy or other clinically relevant management changes.
- To assess the frequency of historical diagnostic labels and their mapping to contemporary WHO GCA terminology.
- To evaluate completeness of pathology reporting before and after adoption of the WHO GCA terminology.
- To describe how the incidental diagnosis was communicated to the patient, where documented, and whether structured counselling or MDT discussion occurred before further staging or surgery.
- To perform, where feasible, a patient-reported experience subanalysis evaluating how patients perceived the transition from presumed appendicitis to rare cancer diagnosis, staging and possible further treatment.
- To describe the proportion of patients treated with appendectomy alone, completion right hemicolectomy, segmental colectomy, cytoreductive surgery, HIPEC and systemic therapy.
- To describe the interval between index appendectomy, pathology diagnosis, MDT discussion and completion surgery.
- To describe whether acute appendicitis was initially managed non-operatively before appendectomy and whether this influenced operative strategy, pathology findings or outcomes.
- To evaluate whether interval to completion surgery is associated with residual disease, nodal upstaging, recurrence or survival.
- To evaluate the association between pathological features and treatment decisions.
- To evaluate the association between pathological features and oncological outcomes.
- To describe recurrence patterns, including peritoneal, nodal, ovarian, hepatic, pulmonary and other distant recurrence.
- To describe ovarian assessment and management in female patients, including ovarian involvement at diagnosis or recurrence, recommendations regarding bilateral salpingo-oophorectomy, operative indications and pathological yield.
- To assess outcomes in patients with peritoneal metastases at diagnosis or recurrence.
- To describe systemic therapy regimens used in adjuvant, neoadjuvant and palliative settings.
- To evaluate whether pathology report features, immunohistochemistry or molecular findings were associated with systemic therapy choice.
- To evaluate radiological, biochemical, pathological and clinical response to systemic therapy where available.
- To describe which tumour markers are measured before and after definitive treatment and whether marker trajectories correlate with recurrence, progressive peritoneal carcinomatosis or systemic therapy response.
- To generate an international dataset that can support future prospective registration and consensus development.

Study Design

Multicentre retrospective observational cohort study with prospective follow-up extension. Separate patient-reported experience and survivorship, pragmatic CT interpretation, colonoscopy-yield and healthcare-utilisation subanalyses may be performed where the required data, approvals and operational arrangements are feasible.

Participating centres will identify eligible patients from pathology databases, surgical databases, oncology databases, multidisciplinary team records and institutional cancer registries.

Data will be collected retrospectively from medical records and pathology reports. Recently diagnosed patients who do not yet have mature five-year follow-up will remain eligible for the baseline cohort and may be included in planned follow-up updates.

No study-specific intervention will be performed.

The patient-reported experience subanalysis will require separate local approval and informed consent, because it involves direct patient contact or patient questionnaires.

International Recruitment Strategy

GCA-GLOBE will be positioned as an international multicentre study. During the initial feasibility and start-up phase, active recruitment will focus mainly on European surgical, pathology, oncology and rare-cancer networks. This focused first phase is intended to maintain manageable governance, communication and data harmonisation.

Eligible centres outside Europe may participate from the outset or join as part of an international extension cohort, provided that local ethics requirements, data-transfer arrangements and the common study dataset can be met. No protocol amendment should be required solely because a participating centre is located outside Europe.

Country, geographic region, healthcare setting and relevant guideline context will be recorded. Analyses will describe geographic variation and, where numbers permit, compare European and non-European centres while avoiding overinterpretation of small regional subgroups.

Feasibility and Sample Size

Because appendiceal GCA is rare, the study is primarily designed as a feasibility-driven multicentre retrospective cohort rather than a formally powered interventional study.

Before opening full data collection, participating centres will complete a feasibility survey reporting the estimated number of eligible patients, available study period, availability of pathology reports, availability of preoperative imaging, and availability of follow-up data.

The expected sample size will be refined after an international centre feasibility assessment. A cohort of at least 150 patients is considered the minimum analyzable feasibility threshold. The principal international recruitment target is approximately 300 patients, with a stretch target of 500 or more patients if broad participation across European and non-European networks is achieved. These targets are feasibility-based rather than formal power calculations and may be revised before final CRF lock. Mature five- and ten-year outcome analyses will be restricted to patients with adequate follow-up.

Multivariable survival modelling will only be performed if the number of outcome events is sufficient. If event numbers are limited, analyses will remain descriptive or limited to prespecified univariable and parsimonious multivariable models.

Study Population

Participating Centre Requirements

Each participating centre should appoint a minimum local study team consisting of:

- One local surgical investigator.
- One local pathology investigator.
- One local radiology investigator where preoperative imaging review is performed.

The core study requires surgical and pathology input at each participating centre. Radiology input is strongly recommended and required for centres participating in the imaging subanalysis. If local radiology participation is not feasible, preoperative imaging review may be coordinated centrally or through designated radiology review centres, subject to local governance and data transfer rules.

Additional local collaborators may be included where relevant, including medical oncologists, HIPEC/peritoneal surface malignancy specialists, geneticists, specialist nurses, psychologists, data managers or research coordinators. Gastroenterologists and primary care physicians may be involved if locally relevant, but are not required for centre participation.

Inclusion Criteria

- Adult patients, aged 18 years or older.
- Histologically confirmed primary goblet cell adenocarcinoma of the appendix, or historical diagnosis compatible with appendiceal GCA.
- Diagnosis made within the predefined study period.
- Patient treated, discussed or followed at a participating centre.
- Availability of at least basic clinical, pathological and treatment data.

Historical Diagnostic Terms Eligible for Screening

The following terms should be included in local search strategies:

- Goblet cell adenocarcinoma.
- Goblet cell carcinoma.
- Goblet cell carcinoid.
- Adenocarcinoid.
- Mucinous carcinoid.
- Mixed carcinoid-adenocarcinoma.
- Adenocarcinoma ex-goblet cell carcinoid.
- Crypt cell carcinoma.
- Mixed adenoneuroendocrine carcinoma of the appendix.
- MiNEN or MANEC of the appendix, if morphology is compatible with GCA.
- Signet-ring cell carcinoma of the appendix with possible goblet cell component.

Diagnostic Eligibility Triage

Cases identified under historical or ambiguous terminology will undergo diagnostic eligibility triage before inclusion in the final analysis dataset.

Suggested triage process:

- Local screening based on pathology database terms and medical records.
- Local pathology investigator confirms whether the original report is compatible with appendiceal GCA.
- Cases with uncertain compatibility are flagged for central pathology advisory review based on the original report, available slides or digital images where feasible.
- Cases are classified as confirmed GCA, probable GCA, uncertain, or excluded.
- Primary analyses will include confirmed and probable GCA. Sensitivity analyses may exclude probable cases if diagnostic uncertainty is substantial.

Exclusion Criteria

- Non-appendiceal primary goblet cell adenocarcinoma.
- Classical well-differentiated appendiceal neuroendocrine tumour without goblet cell adenocarcinoma component.

- Conventional appendiceal adenocarcinoma without goblet cell adenocarcinoma component.
- Low-grade appendiceal mucinous neoplasm or high-grade appendiceal mucinous neoplasm without invasive GCA.
- Insufficient data to confirm diagnosis or treatment.
- Paediatric patients, unless a participating centre specifically requests a separate paediatric subanalysis and appropriate approvals are obtained.

Study Period

Suggested baseline study period:

1 January 2010 to 31 December 2025

Rationale:

- Captures patients diagnosed before and after the 2019 WHO terminology change.
- Allows evaluation of changes in pathology reporting over time.
- Provides a subgroup with mature five-year follow-up for outcome analysis.
- Allows inclusion of recently diagnosed patients for a planned longitudinal follow-up extension.

The final study period may be adapted after feasibility assessment.

Dataset Structure

To preserve feasibility, variables will be divided into core variables and extended variables.

Core variables are required for the main retrospective cohort where available and should be prioritised by all centres. Extended variables are optional or subanalysis-specific and should be collected when reliably available without creating an excessive data burden.

The feasibility survey will test whether the proposed dataset is realistic before final CRF lock.

Core Dataset

Centre-Level Feasibility Data

- Centre name.
- Country.
- Principal local investigator.
- Local surgical investigator.
- Local pathology investigator.
- Local radiology investigator, if participating in imaging review.
- Additional local collaborators, if applicable.
- Estimated number of eligible patients.
- Available period of case capture.
- Availability of pathology reports.
- Availability of preoperative CT imaging.
- Availability of follow-up data.

- Availability of oncology treatment data.
- Willingness to participate in radiology review, if feasible.
- Willingness to participate in central data collection.
- Willingness to participate in pathology review, if feasible.

Patient Demographics

- Study ID.
- Centre ID.
- Year of birth or age at diagnosis.
- Sex.
- Date of diagnosis.
- Frailty status, performance status and ASA classification, if available.
- Presentation: incidental, acute appendicitis, perforated appendicitis, abdominal mass, bowel obstruction, peritoneal disease, ovarian mass, other.
- Initial management of suspected appendicitis: immediate surgery, initial non-operative treatment with delayed/interval appendectomy, other, unknown.
- Relevant comorbidity score, if available.
- Personal history of colorectal adenocarcinoma.

Diagnostic Work-Up

- Preoperative imaging performed.
- Imaging impression: appendicitis, appendiceal mass, caecal mass, peritoneal disease, ovarian disease, other.
- Complicated appendicitis on initial imaging: abscess, phlegmon/plastron, contained perforation, free perforation, not reported.
- Suspicion of appendiceal neoplasm on preoperative imaging: yes, no, unclear.
- Imaging finding that changed initial operative strategy: yes, no, unclear.
- Imaging finding that triggered additional staging before completion surgery: yes, no, unclear.
- Preoperative CT available for retrospective review: yes, no, unknown.
- Post-pathology staging CT performed.
- MRI performed.
- PET-CT performed.
- Colonoscopy performed.
- Preoperative tumour markers measured before index appendectomy: CEA, CA 19-9, CA 125, other, not measured, unknown.
- Post-pathology tumour markers measured before completion surgery or definitive treatment: CEA, CA 19-9, CA 125, other, not measured, unknown.
- Tumour marker values and dates: CEA, CA 19-9, CA 125, if available.
- MDT/MOC discussion: yes/no/date, if available.
- MDT/MOC recommendation: staging, appendectomy follow-up, completion right hemicolectomy, systemic therapy, CRS/HIPEC referral, surveillance, other.
- Documented reason for surveillance versus completion right hemicolectomy: age, frailty/comorbidity, patient preference, pathology risk profile, extent of index resection, absence/presence of nodal tissue, metastatic disease, guideline or terminology era, other, unclear.
- Whether the treatment received differed from the MDT/MOC recommendation and documented reason, if available.

Initial Non-Operative Appendicitis Management Module

This module applies to patients whose presumed appendicitis was initially managed non-operatively before delayed or interval appendectomy.

- Initial non-operative management: yes, no, unknown.
- Reason for non-operative management: appendiceal plastron/phlegmon, abscess, contained perforation, extensive local inflammation, anticoagulation/bleeding risk, frailty/comorbidity, patient preference, other, unknown.
- Percutaneous drainage performed: yes, no, unknown.
- Antibiotic treatment only: yes, no, unknown.
- Date of initial presentation.
- Date of delayed or interval appendectomy.
- Interval from initial presentation to appendectomy.
- Repeat imaging before delayed appendectomy: yes, no, unknown.
- Suspicion of tumour on repeat imaging: yes, no, unclear.
- Interval appendectomy planned from start versus triggered by persistent symptoms, recurrent appendicitis or imaging concern.
- Impact of initial non-operative management on operative strategy, if documented.
- Association with pathological perforation, tumour perforation, pT stage, margin status, completion surgery and outcome: exploratory analysis.

Patient Communication Module

This module will be limited to what is documented in the medical record, acknowledging that communication quality is often incompletely captured in retrospective studies.

- Incidental diagnosis after appendectomy: yes, no, unclear.
- Date patient was informed of unexpected pathology, if documented.
- Setting of communication: surgical outpatient clinic, telephone, oncology clinic, MDT clinic, other, not documented.
- Documented explanation that the appendix lesion was fully removed at index surgery: yes, no, unclear.
- Documented explanation that staging was required despite apparent complete removal: yes, no, unclear.
- Documented explanation that completion right hemicolectomy was recommended or considered: yes, no, unclear.
- Documented referral to colorectal surgeon, medical oncologist, HIPEC/peritoneal surface malignancy team or genetic counselling, if applicable.
- Documented shared decision-making or patient preference influencing further surgery: yes, no, unclear.

Patient-Reported Experience Module

This module should be collected only in centres with appropriate ethics approval and patient consent. It should not be required for the main retrospective cohort.

Suggested domains:

- Patient-reported preoperative understanding of the condition leading to appendectomy.
- Patient-reported perception of appendicitis as a resolved condition after appendectomy.
- Patient-reported mode of first communication of the unexpected diagnosis.
- Patient-reported understanding of the diagnosis at first disclosure.
- Patient-reported understanding of why staging was recommended.
- Patient-reported understanding of why completion right hemicolectomy was recommended, considered or not recommended.
- Patient-reported experience of the transition from appendicitis to rare cancer diagnosis.

- Perceived clarity of information.
- Perceived consistency of information between clinicians.
- Perceived involvement in treatment decisions.
- Emotional impact of the unexpected diagnosis.
- Anxiety during the interval between pathology report, staging and definitive treatment decision.
- Satisfaction with timing of appointments and investigations.
- Satisfaction with written information or information resources.
- Unmet information needs.
- Preference for future patient information material or decision aids.
- Suggestions for clinicians communicating unexpected GCA pathology after appendectomy.
- Current bowel-function or gastrointestinal symptoms and their impact on daily life.
- Ongoing consequences attributed to appendectomy, completion colectomy, systemic therapy, CRS/HIPEC or ovarian surgery.
- Anxiety regarding recurrence and experience of surveillance.
- Decision regret regarding additional surgery or surveillance.
- Patient-reported quality of life using a short validated instrument where feasible.
- Patient understanding of who is responsible for long-term follow-up.
- Perceived coordination between specialist care and primary care.
- Whether the general practitioner or primary-care physician was informed and meaningfully involved.
- Unmet survivorship, psychological, fertility, menopausal or supportive-care needs.

Potential methods:

- Short structured patient-reported experience questionnaire.
- Optional free-text questions.
- Optional semi-structured interviews in selected centres.
- Patient advisory input during questionnaire development.

Pathology Reporting Module

This module is central to the study.

- Original pathology diagnosis exactly as reported.
- Year of pathology report.
- Specimen type: appendectomy, ileocaecal resection, right hemicolectomy, segmental colectomy, CRS specimen, biopsy, other.
- Tumour location: tip, body, base, diffuse, not reported.
- Tumour size.
- WHO grade, if reported.
- Tang group, if reported.
- Tang classification is an older histopathological classification separating appendiceal goblet cell tumours into groups A, B and C based on morphology and increasing aggressiveness. It will be captured where historically reported, but contemporary WHO terminology and grade will be prioritised.
- Estimated low-grade and high-grade pattern percentage, if reported.
- pT stage.
- pN stage.

- pM stage, if applicable.
- Number of lymph nodes examined.
- Number of positive lymph nodes.
- Resection margin status: R0, R1, R2, unclear.
- Appendiceal base margin status.
- Circumferential/radial margin status, if applicable.
- Perforation status: yes, no, unclear.
- Tumour-related perforation versus perforation through a non-tumour-bearing appendix segment, including inflammatory/appendicitis-related perforation, if distinguishable.
- Appendix perforation reported: yes, no, unclear, not reported.
- Tumour perforation reported: yes, no, unclear, not reported.
- Distinction between tumour perforation and perforation through a non-tumour-bearing appendix segment explicitly made in pathology report: yes, no, unclear.
- Free perforation versus contained perforation/abscess, if reported.
- Serosal involvement.
- Mesoappendiceal invasion.
- Caecal involvement.
- Lymphatic invasion: L0, L1, not reported.
- Venous invasion: V0, V1, V2, not reported.
- Perineural invasion: Pn0, Pn1, not reported.
- Tumour deposits.
- Peritoneal metastases at diagnosis.
- Acellular mucin.
- Cellular mucin.
- Ovarian involvement.
- Laterality of ovarian involvement: unilateral, bilateral, not applicable, unknown.
- Immunohistochemistry performed.
- Synaptophysin.
- Chromogranin.
- CDX2.
- CK20.
- CK7.
- Ki-67, reported but not used as the primary grading parameter.
- Molecular testing, if available.

Treatment Module

- Index operation date.
- Index operation type.
- Index operation performed after initial non-operative management/interval appendectomy: yes, no, unknown.
- Reason for delayed/interval operation if applicable.
- Emergency versus elective surgery.
- Laparoscopic, open or converted approach.

- Caecal pole resection performed at index operation.
- Wedge caecal resection performed at index operation.
- Limited ileocaecal resection performed at index operation.
- Stapled appendiceal base/caecal cuff resection performed at index operation.
- Reason for caecal pole/base resection at index operation: inflamed base, suspected tumour, perforation, technical reason, other, unknown.
- Mesoappendix intentionally included in the index resection according to the operative report: yes, no, unclear.
- Mesoappendix or regional lymph node tissue present in the index pathology specimen: yes, no, unclear.
- Number of lymph nodes retrieved and number positive in the index specimen.
- Index appendix submitted for histopathology as routine practice versus because of macroscopic or clinical suspicion, if documented.
- Additional staging, treatment or surveillance initiated because of the incidental histopathological GCA diagnosis.
- Intraoperative suspicion of tumour at index operation.
- Macroscopic perforation or abscess at index operation.
- Visible mucin or peritoneal disease at index operation.
- Appendix extraction bag used, if reported.
- Surgical drain placed, if reported.
- Postoperative complication after index appendectomy, if available.
- Date of final index pathology report.
- Date of patient notification or referral, if available.
- Date of MDT/MOC discussion.
- MDT/MOC recommendation.
- Appendectomy alone.
- Appendectomy with caecal pole or caecal cuff resection.
- Index limited ileocaecal resection.
- Completion right hemicolectomy.
- Time from appendectomy to completion surgery.
- Time from pathology report to completion surgery.
- Time from MDT/MOC discussion to completion surgery.
- Completion surgery performed within predefined intervals: <=6 weeks, 6-12 weeks, >12 weeks.
- Reason for completion surgery.
- No completion surgery: reason if available.
- Completion surgery avoided because index caecal pole/ileocaecal resection considered adequate: yes, no, unclear.
- Residual tumour in completion specimen.
- Nodal upstaging after completion surgery.
- Number of lymph nodes retrieved at completion surgery.
- Number of positive lymph nodes at completion surgery.
- First pathological confirmation of regional node-positive disease occurred at completion surgery: yes, no, unclear.
- Completion-surgery findings changed the planned postoperative management or indication for adjuvant therapy: yes, no, unclear.
- Complications after completion surgery, if available.
- Length of stay after completion surgery, if available.
- CRS performed.

- HIPEC performed.
- PCI score, if available.
- Completeness of cytoreduction score.
- Bilateral salpingo-oophorectomy discussed or recommended at MDT/MOC: yes, no, unclear, not applicable.
- Oophorectomy performed: none, unilateral, bilateral, previously performed, unknown, not applicable.
- Timing of oophorectomy: index operation, completion surgery, CRS/HIPEC, surgery for recurrence, other, unknown.
- Indication for oophorectomy: macroscopically suspicious ovarian disease, radiologically suspicious ovarian disease, confirmed ovarian metastasis, prophylactic/risk-reducing, other, unknown.
- Menopausal status at oophorectomy: premenopausal, postmenopausal, unknown, not applicable.
- Ovarian pathology result: no malignancy, unilateral GCA involvement, bilateral GCA involvement, other malignancy, unknown, not applicable.
- Oophorectomy findings changed staging or postoperative management: yes, no, unclear, not applicable.
- Adjuvant chemotherapy: yes/no.
- Chemotherapy regimen.
- Number of cycles.
- Indication for systemic therapy: adjuvant, neoadjuvant, conversion, palliative, recurrence, other.
- Line of systemic therapy: first-line, second-line, later-line.
- Regimen category: colorectal adenocarcinoma-type, neuroendocrine carcinoma-type, other.
- Specific regimen: FOLFOX, CAPOX, FOLFIRI, FOLFOXIRI, fluoropyrimidine monotherapy, platinum/etoposide, temozolomide-based, other.
- Biological or targeted agent: bevacizumab, EGFR inhibitor, immunotherapy, other.
- Rationale for regimen choice, if documented.
- Pathology or immunohistochemistry explicitly cited in systemic therapy decision: yes, no, unclear.
- Molecular finding influencing systemic therapy decision: yes, no, unclear.
- Neoadjuvant or palliative chemotherapy.
- Targeted therapy or immunotherapy, if applicable.
- Radiotherapy, if applicable.
- Dose reduction or early discontinuation.
- Reason for discontinuation: completed planned treatment, toxicity, progression, patient preference, postoperative complication, other.

Tumour Marker Follow-Up Module

Tumour markers will be collected where available, with emphasis on CEA, CA 19-9 and CA 125. These markers are clinically plausible in appendiceal GCA, particularly for adenocarcinoma-like biology and peritoneal or ovarian disease, but their role in surveillance and progression detection remains insufficiently defined.

- CEA measured: yes, no, unknown.
- CA 19-9 measured: yes, no, unknown.
- CA 125 measured: yes, no, unknown.
- Timing of marker assessment: pre-index operation, post-pathology/pre-completion surgery, post-completion surgery, during surveillance, at recurrence, during systemic therapy, at progressive carcinomatosis.
- Marker values and dates.
- Marker normalisation after completion surgery or definitive treatment.
- Marker rise before radiological recurrence: yes, no, unclear.
- Marker rise at time of progressive peritoneal carcinomatosis: CEA, CA 19-9, CA 125, other, none, unknown.

- Dominant rising marker in patients with peritoneal carcinomatosis.
- Marker trend during systemic therapy: decreasing, stable, increasing, mixed, not available.
- Correlation between marker trajectory and radiological, clinical or surgical findings: exploratory analysis.

Systemic Therapy Response Module

This module applies to patients receiving systemic therapy in the neoadjuvant, conversion, palliative or recurrence setting, and to adjuvant therapy where recurrence outcomes are available.

- Baseline measurable disease before systemic therapy: yes, no, unclear.
- Site of measurable disease: peritoneal, nodal, liver, lung, ovarian, local, other.
- Response assessment method: CT, MRI, PET-CT, tumour markers, clinical assessment, surgical/pathological assessment, other.
- RECIST response reported: complete response, partial response, stable disease, progressive disease, not reported.
- Best radiological response.
- Tumour marker response: CEA, CA 19-9, CA 125, if elevated at baseline.
- Symptomatic or clinical response, if documented.
- Pathological response after neoadjuvant or conversion therapy, if surgery performed.
- Conversion to resectability or CRS/HIPEC after systemic therapy.
- Progression-free survival after start of systemic therapy.
- Time to treatment failure.
- Treatment-related grade 3 or higher toxicity, if available.
- Response according to pathology features, immunohistochemistry and molecular findings: exploratory analysis.

Extended Dataset and Subanalysis Variables

Extended variables include risk factors, detailed radiology review, patient-reported experience, molecular profiling and detailed systemic therapy response. These variables will be collected where available and analysed in predefined subanalyses.

Extended Patient Risk Variables

- Body mass index or obesity status, if available.
- Smoking status: current, former, never, unknown.
- Personal history of appendiceal neoplasm.
- Personal history of other malignancy.
- Personal history of inflammatory bowel disease.
- Family history of colorectal cancer.
- Family history of appendiceal cancer, if available.
- Family history of Lynch-associated malignancy, if available.
- Known Lynch syndrome or mismatch repair gene pathogenic variant.
- Known familial adenomatous polyposis or other hereditary colorectal cancer syndrome.
- Genetic counselling performed: yes, no, unknown.
- Germline testing performed: yes, no, unknown.
- Tumour mismatch repair or microsatellite instability testing performed: yes, no, unknown.

Extended Radiology Review Variables

- Retrospective imaging review performed: yes, no.
- Review type: local radiology review, central radiology review, cross-centre blinded review, not applicable.
- Reviewer blinded to final pathology and outcome: yes, no, partially, not applicable.
- Reader routinely independently reports acute abdominal CT: yes, no.
- Reader years of independent radiology practice.
- Reader approximate percentage of clinical practice involving abdominal imaging.
- Reader formal abdominal fellowship or subspecialisation: yes, no.
- Reader regular participation in GI or colorectal MDT: yes, no.
- Reader suspicion of underlying appendiceal or caecal neoplasm: yes, no, indeterminate.
- Reader confidence in suspicion: low, moderate, high.
- Reader recommendation if interpreting in routine practice: standard appendicitis pathway, senior surgical review, additional imaging or staging, oncological or MDT discussion, modified index resection, planned early reassessment, other.
- Reader-reported likelihood that imaging would change the initial management pathway: yes, no, uncertain.
- Appendiceal diameter on CT.
- Focal appendiceal wall thickening.
- Focal enhancing lesion or mass.
- Lesion location on imaging: tip, body, base, caecal pole, diffuse, not visible.
- Radiological lesion size, if measurable.
- Correlation between radiological lesion size and pathological tumour size: to be analysed where both are available.
- Suspicion of appendiceal base involvement on imaging.
- Suspicion of caecal pole involvement on imaging.
- Periappendiceal abscess or phlegmon.
- Free fluid.
- Local lymphadenopathy.
- Peritoneal nodules or mucinous/peritoneal disease suspected.
- Ovarian abnormality suspected.
- Quantitative texture analysis performed: yes, no, not feasible.
- Availability and suitability of acute-phase contrast-enhanced CT for texture analysis.
- Scanner manufacturer/model, contrast phase, slice thickness and reconstruction parameters.
- Segmentation method, software and reader.
- Appendix or lesion volume and segmentation reproducibility, where assessed.
- Prespecified quantitative morphology, attenuation, enhancement, heterogeneity and texture features.
- Matched non-neoplastic appendicitis control identifier, where applicable.
- Exploratory association of quantitative CT features with WHO pathological grade and adverse pathological characteristics.

Extended Molecular Variables

- Mismatch repair immunohistochemistry: MLH1, PMS2, MSH2, MSH6 status, if available.
- MSI testing result, if available.
- Somatic mutations, if available.

Guideline Concordance Variables

- Relevant guideline or local policy used at the time of MDT/MOC decision, if identifiable.
- Guideline recommendation applicable to the patient: completion right hemicolectomy, surveillance/no additional surgery, systemic therapy, CRS/HIPEC referral, bilateral salpingo-oophorectomy, other, unclear.
- MDT/MOC recommendation concordant with the identified guideline or local policy: yes, no, partly, unclear, not assessable.
- Treatment received concordant with MDT/MOC recommendation: yes, no, partly, unclear.
- Documented reason for non-concordance: patient preference, frailty/comorbidity, operative risk, pathology risk profile, metastatic disease, prior adequate resection, fertility/menopausal considerations, local resources, evolving evidence or terminology, other, unclear.

Healthcare Utilisation Variables

These variables are exploratory and should be prioritised for patients with localised WHO grade 1 or otherwise documented low-grade GCA.

- Number of additional specialist consultations after incidental diagnosis.
- Number and type of additional staging investigations.
- Number of surveillance CT or MRI examinations and colonoscopies during available follow-up.
- Additional operation performed because of GCA diagnosis.
- Length of stay, postoperative complication, readmission and reintervention after additional surgery.
- Days from diagnosis to definitive management and total number of hospital encounters, where reliably available.
- Documented time away from work or time to usual activities, where available.
- Local or national unit-cost data available: yes, no.

Follow-Up and Outcomes

- Date of last follow-up.
- Follow-up duration.
- Five-year follow-up available: yes, no.
- Ten-year follow-up available: yes, no.
- Disease status at last follow-up: no evidence of disease, alive with disease, dead of disease, dead of other cause, unknown.
- Recurrence: yes/no/date.
- Site of first recurrence: local, nodal, peritoneal, ovarian, liver, lung, other.
- Treatment of recurrence.
- Date of death.
- Cause of death, if available.

Endpoints

Phase 1 Endpoints

Primary endpoint:

- Description of the surgical pathway from index appendectomy to definitive management, including pathology-driven decision-making, timing and treatment variation across centres and time periods.

Secondary endpoints:

- Frequency of historical diagnostic labels.

- Proportion of reports including pT, pN, margin status, perforation, L status, V status and Pn status.
- Proportion of patients undergoing completion right hemicolectomy.
- Interval between index appendectomy and completion surgery.
- Rate of initial non-operative management for presumed appendicitis and reasons for delayed/interval appendectomy.
- Association between initial non-operative management and pT stage, perforation status, margin status, completion surgery and recurrence.
- Interval between pathology report and completion surgery.
- Interval between MDT/MOC discussion and completion surgery.
- Rate of preoperative or retrospective radiological suspicion of appendiceal neoplasm.
- Agreement between original radiology report and retrospective radiology review regarding suspicion of neoplasm.
- Agreement between cross-centre readers regarding suspicion of neoplasm and proposed management change, where multiple reviews are available.
- Correlation between radiological lesion size and pathological tumour size.
- Feasibility of de-identification, transfer and cross-centre review of preoperative CT imaging.
- Specificity and diagnostic discrimination only where non-neoplastic appendicitis controls are available.
- Feasibility and reproducibility of appendix segmentation and quantitative feature extraction.
- Exploratory diagnostic discrimination of quantitative CT features between GCA and non-neoplastic appendicitis.
- Exploratory associations between quantitative CT features, WHO pathological grade and other adverse pathological characteristics.
- Rate of index caecal pole/cuff resection or limited ileocaecal resection.
- Rate of subsequent completion surgery after appendectomy alone versus appendectomy with caecal pole/cuff resection or index limited ileocaecal resection.
- MDT/MOC recommendation after index caecal pole/cuff resection, stratified by whether the mesoappendix or regional lymph node tissue was included and whether lymph nodes were retrieved.
- MDT/MOC recommendation for surveillance versus completion right hemicolectomy, stratified by age, frailty/comorbidity, WHO grade and pre-WHO versus post-WHO 2019 terminology era.
- Proportion of incidentally detected GCA diagnoses resulting in additional staging, altered surveillance, completion surgery, systemic therapy or another clinically relevant management change.
- Rate of residual tumour and nodal upstaging at completion surgery.
- Oncological yield of completion right hemicolectomy: proportion with at least one positive regional lymph node, residual primary-site tumour or another finding that changes postoperative management.
- Proportion with at least one positive regional lymph node at completion surgery among patients who were clinically M0 and had no previously confirmed regional node-positive disease.
- Number needed to perform completion right hemicolectomy to identify one previously unrecognised node-positive patient, reported descriptively with confidence intervals where appropriate.
- Balance between oncological yield and postoperative morbidity of completion right hemicolectomy.
- Concordance between guideline or local-policy recommendation, MDT/MOC recommendation and treatment received.
- Yield of postdiagnosis colonoscopy, including advanced adenoma, synchronous colorectal carcinoma and management-changing findings.
- Healthcare utilisation associated with surveillance versus additional treatment in localised low-grade GCA.
- Proportion of patients receiving adjuvant chemotherapy.
- Proportion of patients treated with CRS/HIPEC.
- Proportion of female patients undergoing unilateral or bilateral oophorectomy, indication, pathological yield and frequency of occult ovarian involvement.
- Early recurrence and mortality, where available.

Phase 2 Endpoints

Primary endpoints:

- Five-year overall survival.
- Five-year disease-free survival.
- Ten-year overall survival, where available.
- Ten-year disease-free survival, where available.

Secondary endpoints:

- Cancer-specific survival, if cause of death is reliable.
- Recurrence-free survival.
- Site-specific recurrence patterns.
- Survival according to pT stage, pN stage, grade, perforation, margin status, L status, V status and Pn status.
- Survival according to surgical strategy.
- Survival according to adjuvant chemotherapy use.
- Response and survival according to systemic therapy regimen in patients treated with neoadjuvant, palliative or recurrence-directed systemic therapy.
- Tumour marker trajectories during surveillance, recurrence, progressive peritoneal carcinomatosis and systemic therapy.
- Outcomes after CRS/HIPEC.

Endpoint Definitions

- **Date of diagnosis:** date of the first pathology report establishing GCA or a historical diagnosis subsequently classified as compatible with GCA.
- **Overall survival:** time from date of diagnosis to death from any cause. Patients alive at last known follow-up will be censored on that date.
- **Disease-free survival:** among patients without distant or peritoneal metastatic disease who are rendered free of macroscopic disease, time from definitive treatment to first recurrence or death from any cause. Definitive treatment is the final operation or treatment completing the initial curative-intent pathway.
- **Recurrence-free survival:** time from definitive treatment to first documented recurrence, with death without documented recurrence censored in the primary recurrence-free analysis and evaluated as a competing event in sensitivity analysis where data permit.
- **Cancer-specific survival:** time from date of diagnosis to death attributed to GCA. This endpoint will only be reported where cause-of-death data are considered sufficiently reliable.
- **Treatment recommendation outcome:** the documented MDT/MOC recommendation following staging and review of the index pathology.
- **Treatment received outcome:** the definitive management actually delivered, analysed separately from the MDT/MOC recommendation.
- **Clinically relevant management change after incidental diagnosis:** additional staging, altered surveillance, completion surgery, systemic therapy, CRS/HIPEC referral or another documented management change attributable to the histopathological GCA diagnosis.

Statistical Analysis Plan

Descriptive statistics will be used to summarize baseline characteristics, pathology variables, treatment patterns and follow-up.

Categorical variables will be reported as counts and percentages. Continuous variables will be reported as means with standard deviations or medians with interquartile ranges, depending on distribution.

Comparisons between groups may be performed using chi-square or Fisher's exact tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables, as appropriate.

Determinants of the MDT/MOC recommendation for surveillance versus completion right hemicolectomy will be explored separately from determinants of treatment actually received. If sample size permits, multivariable logistic regression will include age, frailty/comorbidity, WHO grade, WHO terminology era and prespecified pathological risk factors. This distinction is intended to reduce conflation of multidisciplinary advice with patient preference, operative fitness or non-adherence to the recommendation.

Survival outcomes will be estimated using Kaplan-Meier methods. Differences between groups will be assessed using log-rank testing.

Univariable and multivariable Cox proportional hazards regression may be used to identify factors associated with overall survival and disease-free survival, depending on the number of events.

Comparisons involving completion surgery or adjuvant treatment are vulnerable to immortal-time bias and confounding by indication. Treatment groups will therefore be described cautiously. Where data and event numbers permit, sensitivity analyses will use a prespecified landmark after diagnosis or time-dependent treatment variables. Causal treatment effects will not be claimed from unadjusted retrospective comparisons.

The oncological yield of completion right hemicolectomy will be analysed descriptively using a prespecified denominator of patients undergoing completion surgery who were clinically non-metastatic and had no confirmed regional node-positive disease before that operation. The primary yield measure will be the proportion in whom at least one positive regional lymph node is identified in the completion specimen. Results will be stratified by pT stage, WHO grade, margin status, lymphatic invasion, venous invasion, perineural invasion, perforation type and index specimen nodal tissue where numbers permit. A zero or very low event rate will be reported with exact confidence intervals rather than interpreted as proof that nodal staging is unnecessary.

Centre-level clustering and geographic variation will be considered in regression analyses where the number and size of participating centres permit, using cluster-robust standard errors, random effects or stratified analyses as appropriate.

Multivariable modelling will follow an events-per-variable principle. As a default, at least 10 outcome events per candidate variable will be required for standard Cox regression. If fewer events are available, models will be restricted, penalised methods may be considered, or analyses will remain descriptive and univariable.

Potential prognostic variables include:

- Age.
- Frailty, performance status or relevant comorbidity score.
- Sex.
- Body mass index or obesity status.
- Smoking status.
- Personal history of colorectal adenocarcinoma.
- Family history of colorectal cancer or Lynch-associated malignancy.
- Known hereditary colorectal cancer syndrome.
- Year of diagnosis.
- Pre-WHO versus post-WHO 2019 terminology era.
- Incidental versus suspected diagnosis.
- Immediate surgery versus initial non-operative appendicitis management.
- Reason for initial non-operative management, including plastron/abscess versus anticoagulation/comorbidity.
- Original versus retrospective radiological suspicion of appendiceal neoplasm.
- Radiological appendiceal base or caecal pole involvement.

- Index operation type, including appendectomy alone versus appendectomy with caecal pole/cuff resection or limited ileocaecal resection.
- Inclusion of mesoappendix or regional lymph node tissue in the index specimen and number of lymph nodes retrieved.
- Interval from index appendectomy to completion surgery.
- pT stage.
- pN stage.
- WHO grade.
- Perforation.
- Tumour perforation versus perforation through a non-tumour-bearing appendix segment, including inflammatory/appendicitis-related perforation, if distinguishable.
- Margin status.
- Lymphatic invasion.
- Venous invasion.
- Perineural invasion.
- Peritoneal disease.
- Surgical strategy.
- Adjuvant chemotherapy.
- Systemic therapy regimen.
- Systemic therapy response.
- Baseline tumour marker elevation.
- Tumour marker trajectory during follow-up.

Given the rarity of the disease, modelling will be conservative and limited by event numbers. Missing data will be reported transparently. Multiple imputation may be considered for selected variables if appropriate, but complete-case and missingness-aware descriptive analyses will remain central.

The detailed statistical analysis plan, including landmark timing, covariate selection and handling of missing data, will be approved before database lock and before outcome analyses are performed.

Planned Subgroups

- European versus non-European centres and geographic region, where numbers permit.
- Pre-WHO 2019 versus post-WHO 2019 diagnosis.
- Appendectomy alone versus completion right hemicolectomy.
- Appendectomy alone versus appendectomy with caecal pole/cuff resection.
- Appendectomy with caecal pole/cuff resection with versus without mesoappendix or regional lymph node tissue in the index specimen.
- Appendectomy alone versus index limited ileocaecal resection.
- Original imaging suspicion versus no original imaging suspicion of appendiceal neoplasm.
- Retrospective imaging suspicion versus no retrospective imaging suspicion of appendiceal neoplasm.
- Radiological base/caecal pole involvement versus no base/caecal pole involvement.
- Immediate appendectomy versus delayed/interval appendectomy after initial non-operative management.
- Node-negative versus node-positive disease.
- Perforated versus non-perforated cases.
- Low-grade versus high-grade GCA, where available.

- Localized disease versus peritoneal metastatic disease.
- Patients with at least five years of follow-up versus recently diagnosed patients awaiting mature follow-up.
- Patients receiving systemic therapy versus no systemic therapy.
- Adjuvant systemic therapy versus no adjuvant systemic therapy.
- Colorectal adenocarcinoma-type regimen versus neuroendocrine carcinoma-type regimen.
- Responders versus non-responders to systemic therapy, where measurable disease is available.

Routine Histopathology Companion Study Concept

The main GCA-GLOBE cohort includes patients with a histopathological diagnosis of GCA and can describe the clinical consequences of that diagnosis. It can estimate how often incidental GCA detection leads to additional staging, surveillance, completion surgery or systemic therapy, and whether these interventions appear to provide clinically meaningful benefit.

However, the main cohort cannot determine whether routine histopathological examination of all appendectomy specimens is safe or cost-effective, because it does not include the denominator of all appendectomies or patients in whom histopathology was not performed. It also cannot estimate how many clinically consequential tumours would be missed by a selective strategy.

A separate prospective or retrospective companion study, conceptually modelled on selective histopathology studies such as the FANCY cholecystectomy study, may therefore be developed. This study would require inclusion of all appendectomies during a defined period and would evaluate macroscopic or clinical suspicion, final histopathological findings, clinically consequential unexpected diagnoses, changes in management, patient outcomes, pathology workload and costs. Any proposal to replace routine with selective appendix histopathology would require this separate denominator-based safety and health-economic analysis.

Pathology Confirmation Strategy

The study will prioritise feasibility and will not require a formal international pathology reproducibility substudy. At minimum, centres should collect the original pathology report wording and structured pathology variables, and a local pathology investigator should confirm compatibility with appendiceal GCA where possible. Selected diagnostically uncertain or historically labelled cases may be discussed with a pathology advisory group when feasible, but routine transfer of slides or digital images is not required for participation.

Study Governance and Publication Policy

The coordinating investigators will constitute the initial steering group. The steering group will approve the protocol, core dataset, study amendments, analysis proposals, writing groups and external data-access requests. Regional or methodological representatives may be added as participation grows.

Each participating centre will retain responsibility for the accuracy of its submitted data, local approvals and the local re-identification key. Contributing investigators may propose substudies or analyses using a standard analysis-proposal process. Proposals must be scientifically distinct, feasible, compatible with participant approvals and approved by the steering group before analysis begins.

Authorship and collaborator recognition will follow transparent contribution-based principles and applicable journal guidance. Centre participation, eligible case identification and timely delivery of sufficiently complete data will qualify contributors for collaborator recognition. Writing-group authorship will additionally require substantial contribution to study design, analysis, interpretation or manuscript preparation.

The coordinating study database will not be used for unrelated analyses or shared with external parties without steering group approval and the required legal, ethical and institutional permissions. Protocol amendments and material deviations will be documented with dates and reasons.

Data Governance

Data will be collected in coded or pseudonymised form. Each participating centre will retain the local re-identification key. No directly identifiable patient data should be transferred to the coordinating centre.

Data collection may be performed using REDCap or an equivalent secure research database.

International data transfer agreements should be established where required. The legal basis and consent waiver strategy should be confirmed by the lead ethics committee and local participating centres according to national rules.

For centres outside the European Economic Area, transfer mechanisms and safeguards must be confirmed before data transfer. Participation may use local analysis or federated approaches where direct transfer of coded individual-level data is not permitted.

Funding and Conflicts of Interest

Funding sources will be declared in all protocol amendments and resulting publications. At protocol version 1.0, no dedicated external funding has yet been secured.

Potential funding may be sought from institutional research funds, surgical or oncology societies, cancer foundations, rare cancer initiatives or national and international research funding mechanisms.

All steering group members, national delegates, site investigators and writing group members will be asked to disclose relevant conflicts of interest according to journal and institutional requirements.

Ethics and Registration

This is a non-interventional retrospective observational study. It is not expected to fall under the EU Clinical Trials Regulation or require CTIS submission, because there is no investigational medicinal product and no study-specific intervention.

Ethics approval should be obtained from the lead institutional ethics committee. Participating centres should obtain local approval or confirmation of coverage according to national and institutional requirements.

A waiver of informed consent may be requested where permitted, given the retrospective design, rarity of the condition, minimal risk and use of coded data.

The patient-reported experience subanalysis will require separate ethics approval and informed consent for direct patient contact, questionnaire completion or interview participation. Patient-reported data should be stored separately or linked only through coded study identifiers.

Voluntary public registration is recommended for transparency. Potential options include:

- ClinicalTrials.gov, as an observational study.
- HMA-EMA Catalogue of Real-World Data Studies.
- OSF Registries.

Existing Registry Landscape

A preliminary search did not identify an obvious disease-specific international prospective or retrospective registry dedicated to appendiceal goblet cell adenocarcinoma with detailed pathology reporting and treatment/outcome data.

Existing evidence appears to come mainly from:

- National cancer registry analyses, including English cancer registry data.
- SEER and National Cancer Database analyses.
- Single-centre or small multicentre retrospective series.
- Older neuroendocrine tumour databases in which goblet cell tumours were captured under historical terminology.

This supports the rationale for an international disease-specific multicentre cohort with explicit attention to pathology reporting.

Study Initiation Plan

1. Obtain steering group approval of protocol version 1.0.
2. Circulate a feasibility invitation and survey through national, European and selected international networks.
3. Confirm participating centres, expected case numbers and local data availability.
4. Finalise the core case report form, data dictionary and statistical analysis plan.
5. Submit to the lead ethics committee and complete required local approvals and data-transfer agreements.
6. Build and validate the secure study database.
7. Open retrospective data collection after approvals are in place.
8. Perform the prespecified phase 1 analysis on pathology reporting and treatment patterns.
9. Maintain the prospective follow-up extension for mature five- and ten-year outcomes.

Candidate Collaborating Networks

- National colorectal surgery societies.
- European and international colorectal surgery networks.
- Peritoneal surface malignancy networks.
- Gastrointestinal pathology networks.
- Rare cancer networks.
- National appendiceal tumour or peritoneal malignancy groups, where available.

Key References and Sources for Rationale

The protocol rationale is informed by the following key classifications, reviews and registry-based studies. A complete referenced bibliography will accompany ethics and publication submissions.

- WHO 2019 Classification of Digestive System Tumours: reclassification of goblet cell adenocarcinoma.
- Goblet Cell Adenocarcinoma of the Appendix: systematic review and English cancer registry analysis.
- Japanese multicentre retrospective study on appendiceal goblet cell adenocarcinoma.
- Registry-based analyses using SEER, NCRAS and NCDB datasets.
- Bastiaenen et al. Safety and economic analysis of selective histopathology following cholecystectomy: multicentre, prospective, cross-sectional FANCY study. British Journal of Surgery. 2022;109:355-362. DOI: 10.1093/bjs/znab469.
- Swank et al. Is routine histopathological examination of appendectomy specimens useful? A systematic review of the literature. Colorectal Disease. 2011. DOI: 10.1111/j.1463-1318.2010.02457.x.
- EMA/CTIS guidance indicating that CTIS applies to interventional clinical trials with investigational medicinal products.
- HMA-EMA Real-World Data Catalogue as a voluntary transparency option for non-interventional real-world data studies.