Study: Neuroendocrine Tumors - Patient Reported Outcomes (NET-PRO)

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Neuroendocrine Tumors – Patient Reported Outcomes

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Northern California CarciNET Community (NorCal CarciNET) https://norcalcarcinet.org/
The Neuroendocrine Cancer Awareness Network (NCAN) https://www.netcancerawareness.org/
The Neuroendocrine Tumor Research Foundation (NETRF) https://netrf.org/
The Healing NET Foundation https://www.thehealingnet.org/

Participating PCORI Networks & Sites
GPC (6): University of Iowa, Allina Health, University of Kansas Medical Center, Medical College of Wisconsin, University of Texas Southwestern Medical Center, University of Utah
OneFlorida (1): University of Florida
STAR (4): Medical University of South Carolina, University of North Carolina at Chapel Hill, Vanderbilt University Medical Center, Mayo Clinic
PATH (3): University of Pittsburgh Medical Center, Ohio State University, University of Michigan

Protocol Version and Amendment Tracking

Version Number/Amendment	Date	Summary of changes
Original Protocol, Version 1.0	10/22/2021	
Revision, Version 1.1	4/7/2022	Removed appendices; added EMR messaging as recruitment method (excluding UIHC); revisions to: background, study measures and outcomes, and computable phenotype for identifying patients; and changes to recruitment processes and subject payments.
Revision, Version 1.2	4/13/2022	Added NET Registry at UIOWA as recruitment source; clarified data sources to be used for identifying eligible patients.
Revision, Version 1.3	4/22/2022	Clarified recruitment and survey follow up contact procedures.

Abbreviations

Abbreviation	Meaning
BRE	Business Reply Envelope
CDM	Common Data Model
CER	Comparative Effectiveness Research
CgA	Chromogranin A
CRNs	Clinical Research Networks
EMR	Electronic Medical Record
EORTC	European Organization for Research and Treatment of Cancer
FDA	Federal Drug Administration
G1/G2/G3	Grade 1, 2, 3 tumors
GEP	Gastroenteropancreatic
GFR	Glomerular Filtration Rate
HRQoL	Health-related Quality of Life
IRB	Institutional Review Board
MCID	Minimal Clinical Important Difference
mTOR	Mammalian target of rapamycin
NAACCR	North American Association of Central Cancer Registries
NECs	Neuroendocrine carcinomas
NET-PRO	Neuroendocrine Tumors - Patient Reported Outcomes (Study Title)
NETs	Neuroendocrine tumors
OS	Overall survival
PAC	Patient Advocacy Committee
PCORI	Patient Centered Outcomes Research Institute
PCORnet	Patient Centered Outcomes Research Network
PFS	Progression Free Survival
PHI	Patient Health Information
PHR	Personal Health Record research portal (i.e.: Study Web Portal)
PI	Principal Investigator
PPV	Positive Predictive Value
PROs	Patient Reported Outcomes
PRRT	Peptide Receptor Radionuclide Therapy
SEER	Surveillance Epidemiology End Results
SSAs	Somatostatin analogues
TDPS	Time Dependent Propensity Score
UICC	University of Iowa Coordinating Center
WHO	World Health Organization

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PROTOCOL SYNOPSIS

Neuroendocrine tumors (NETs) are a group of rare and heterogeneous neoplasms which are typically slow-growing in nature. Thus, patients with NETs experience a prolonged clinical course with active disease, with the highest symptom burdens in patients with gastroenteropancreatic (GEP) and bronchopulmonary NETs. However, **assessment of health-related quality of life (HRQoL) and patient reported outcomes (PROs)** outside of therapy trials still remains **scarce and of poor quality**. What's more, **there are no clear consensus guidelines as to the optimum sequencing of therapeutic options** for NET patients. As clinicians attempt to tailor treatment selection on the characteristics of the patient and their tumor, NET patients must navigate a protracted sequence of treatment decisions as benefits wane and the next modality is tried. **The purpose of this study is to partner with patients to examine the impact of treatment choices on QoL and PROs to achieve the goal of alleviating undue toxicity and optimizing effectiveness and sequencing of therapy for NET patients.**

The Neuroendocrine Tumor – Patient Reported Outcomes (NET-PRO) project is a prospective cohort study of all newly occurring GEP and lung NET cases aged 18 years and older diagnosed between 01/01/2019 and 12/31/2023. Participants will be recruited across 14 participating Patient Centered Outcomes Research Network (PCORnet) sites (from across 4 PCORnet clinical research networks), enrolling an average of 215 patients per site over the 3-year study period (~3,000 patients total), allowing up to a maximum of 60 months of follow-up. Participants will complete four online (or paper) surveys over 18 months; these surveys will focus on patient-reported outcomes, including questions on quality of life, treatment decisions, and experiences with cancer care. These survey data will be linked to individual participant level tumor and clinical characteristics from medical record data.

Project specific aims:

AIM 1: To describe the frequency of treatment regimens and examine their association with symptom burden and PROs and HRQoL outcomes. Enroll a cohort of patients to collect HRQoL and PROs data every 6 months, for 18 months (i.e.: baseline, 6, 12 and 18 month follow-up surveys). We will determine what combinations of therapy are being used, and the changes in symptoms, PROs and HRQoL associated with these different therapeutic choices.

AIM 2: To examine the association of patient, clinical, and tumor characteristics on treatment choice. We will use EMR data to investigate the impact of pre-existing comorbidities (i.e.: cardiovascular, renal and liver disease and diabetes), prognostic tumor factors (derived from cancer registry data) i.e.: stage, grade and nodal status, on the selection of therapies received and outcomes of survival and disease progression (collected via targeted chart reviews).

AIM 3: To compare the effectiveness of peptide receptor radionuclide therapy (PRRT) regimens on outcomes of renal toxicity, disease progression, and patient symptoms and HRQoL. We will utilize the combined PROs gathered in aim 1 and EMR data mined in aim 2 (i.e.: predictors), to compare the effectiveness of various PRRT treatment combinations and sequences, on outcomes of reduced creatinine clearance (renal toxicity), HRQoL and symptom burden, and survival and disease progression. We will further study the heterogeneity of these treatment effects by grade of differentiation (G1/2 vs G3) and NET subsite (GEP vs lung).

AIM 4: To develop and leverage PCORnet infrastructure for the study of NETs and other rare diseases, and to disseminate lessons learned. Finally, we plan to share the infrastructure this study will generate (i.e.: electronic identification of NET patients, entry and completion of tumor table data in PCORnet, and a unique NET personal health record research portal), to foster future studies in NETs and other rare

diseases utilizing the PCORnet data resource, and expand our prospective enrollment through our four nationally representative partnering patient advocate organizations.

1. INTRODUCTION

1.1. Background

NETs are a group of rare and heterogeneous neoplasms that originate in specialized neuroendocrine cells, predominantly in the small bowel, pancreas and lung, collectively affecting fewer than 172,000 individuals in the United States [1]. Although NETs may arise in most organs, more than half originate from endocrine cells of the gastrointestinal tract and the pancreas [2], referred to as gastroenteropancreatic NETs (GEP-NETs). Both GEP-NETs and lung NETs, including typical and atypical carcinoid tumors and bronchial NETs, meet the criteria for orphan disease status. Despite this, the age-adjusted incidence rate of NETs increased 6.4-fold from 1973 (1.09 per 100 000) to 2012 (6.98 per 100 000) [3, 4], and serves only to highlight the growing impact and burden these cancers will continue to have on the health of our population.

1.1.1. Health related quality of life impact of NETs

NETs are typically slow-growing in nature with prolonged survival and significant symptom burdens, however few studies have examined quality of life impacts. Their vague antecedent signs and symptoms cause significant delay and difficulty in their diagnosis and detection [3]. Metastatic disease is observed in up to 40% of NETs at initial diagnosis [1], and many patients with liver or other distant metastases experience carcinoid syndrome, a direct result of the tumors capacity to synthesize and secrete an excess of bioactive amines, peptides, and polypeptides. Carcinoid syndrome manifests with clinical symptoms ranging from watery diarrhea and flushing to bronchospasm, to hypotension and right-sided cardiac deficits (carcinoid heart disease) due to serotonin hypersecretion [4]. In fact, a Surveillance Epidemiology and End Results (SEER) analysis has shown that 19% of all NET patients have symptoms of carcinoid syndrome at diagnosis, increasing to over 50% in patients with metastatic well-differentiated small bowel NETs [5]. Thus, NET patients typically experience prolonged survival with active disease, and many have significant symptom burdens. With a conscious shift in medical practice from disease-centered to patient-orientated care, quality of life represents an important measure for gauging patient perspectives on treatment effectiveness and outcomes. However, the assessment of health-related quality of life (HRQoL) in NET patients is relatively infrequent and transfer of HRQoL results into clinical practice is hindered by the often limited quality of HRQoL outcomes reporting [6]. Unsurprisingly, where these studies have been undertaken, some have identified worse HRQoL scores in NET patients as compared with the general population [7-10], specifically poorer patient-reported outcomes and unmet needs [11, 12]. In fact, a high prevalence of moderate to severe symptoms especially tiredness (44-50%), lack of well-being (37-49%) and anxiety (30-40%), have been observed up to five years after diagnosis, with the highest symptom burdens in patients with bronchopulmonary and GEP-NETs [13].

1.1.2. Nomenclature of NETs

The complex and confusing nomenclature of NETs contributes to a thin evidence base for optimal management. This is very unfortunate as tumor differentiation and tumor proliferation are important indications of underlying tumor biology, carrying predictive, prognostic, and therapeutic significance. In 2010 the World Health Organization (WHO) introduced a common framework for the classification of NETs [14], morphologically dichotomizing the tumors into well differentiated NETs, and poorly differentiated neuroendocrine carcinomas (NECs) on the basis of the tumor's mitotic rate and Ki67 index [15]. However, this dichotomous grading criteria is imperfect, and a new subset of well-differentiated grade 3 NETs (predominantly in the pancreas, stomach and colon) has since been recognized, with a

worse prognosis than G2 NETs, and non-standardized treatments straddling G1/2 tumors and poorer prognosis NECs [16] (Figure 1).

WHO 2017	Mitoses/10 HPF*	Ki-67 Index*
Well-differentiated NENs		
NET grade 1	< 2	< 3
NET grade 2	2–20	3–20
NET grade 3	> 20	> 20
Poorly differentiated NENs		
NEC grade 3	> 20	> 20
Small-cell type		
Large-cell type		
MiNEN*		

HPF = high power fields, MiNEN = mixed endocrine non-endocrine neoplasm, NEC = neuroendocrine carcinoma, NET = neuroendocrine tumor, WHO = World Health Organization
*Mitotic count counted in 10 HPF. 10 HPF=2mm^2. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th ed.
*Ki-67 index: percent positive after count of 2000 cells in area of highest nuclear labelling. Cut-offs per American Joint Commission on Cancer Staging Manual, 7th Ed.

Figure 1: *WHO 2017 GEP-NET nomenclature and classification*

1.1.3. Gaps in Optimal therapy selection and sequencing

Figure 2 presents an algorithmic overview of the investigation and treatment of GEP-NETs (the most common NET subtype) [17]. For low to intermediate grade NETs, surgery remains the mainstay of treatment and the requirement for adjuvant therapy is questionable [18-20]. However, as over half of GEP-NETs present with metastases at the time of diagnosis, they are not considered candidates for curative surgery, and so many are offered some form of long-term medical treatment for symptom relief and tumor growth suppression. Somatostatin analogues (SSAs) are established first-line agents for low-grade GEP-NETs, largely given their demonstrated improvements in overall survival in two placebo-controlled randomized trials (PROMID and CLARINET) [21, 22]. However, there are no clear consensus guidelines as to the optimum sequencing of other therapeutic options [17, 21, 23-27]. Systemic, non-liver directed therapies may include peptide receptor radionuclide therapy (PRRT), interferon alpha, everolimus (an mTOR inhibitor), sunitinib (a tyrosine kinase inhibitor), bevacizumab and cytotoxic agents [17]. Liver-directed therapies include ablative therapy, transarterial embolization and chemoembolization, and internal radiation therapy with yttrium-90 coated microspheres [28]. Interestingly, an assessment of the clinical benefit of systemic treatments in GEP-NETs found that currently used treatments had low health benefit scores according to the ASCO-NHB, and none could be graded as meaningfully clinically beneficial according to the ESMO-MCBS [29]. Therefore, one of the greatest challenges in the current NET oncology management landscape is how best to sequence these many therapeutic options (if warranted at all), and how to tailor treatment selection on the basis of the individual characteristics of the tumor and patient.

PRRT represents a true breakthrough in treatment of NETs but many questions remain about sequencing of PRRT with other therapies. PRRT is a form of molecularly targeted therapy, the main goal of which is to selectively deliver a high dose of radiation to the tumor cells, thus limiting irradiation of normal tissues. Unfortunately, due to tubular reabsorption and intracellular trapping of the radionuclide, PRRT therapies can accumulate in the renal cortex inducing toxicity [30]. Proper kidney protection, with the co-infusion of positively charged amino acids, is mandatory. Whilst the radiation dose to the kidneys can be reduced with this pre-treatment, the kidney remains a dose limiting organ

[31] with a creatinine clearance loss of about 3.8% per year for 177Lu-octreotate and 7.3% per year for 90Y-DOTATOC [32]. Moreover, studies have demonstrated a higher and more persistent decline in creatinine clearance if risk factors for delayed renal toxicity are present, particularly long-standing and poorly controlled diabetes and hypertension [33, 34]. On January 26, 2018, the US Food and Drug Administration (FDA) approved Lutathera (177Lu-DOTATATE), a radiolabeled somatostatin analog, for the treatment of adults with somatostatin receptor–positive GEP-NETs [35]. Lutathera, is the first radiopharmaceutical to be approved by the FDA for this patient population. We are likely to see an increase in the use of 177Lu-DOTATATE outside specialist NET centers. Therefore, real-world data on variables that may influence patient reported outcomes (i.e.: toxicities and adverse effects) and risk of progression after PRRT in combination with other biological therapies, is much needed.

Optimal sequencing of therapy is a key concern for most patients. As NETs are relatively slow-growing, even patients with metastatic disease can be expected to be treated for protracted periods of time, and must navigate a prolonged sequence of treatment decisions as benefits wane and the next modality is tried [26]. NET patients have been left wondering not only 'what therapy would be best to try next?', but 'if I were to take this option now, what treatment options will be closed off to me in the future?' (personal communication, Josh Mailman, lead patient advocate Co-I). As numerous toxicities may result from these therapies including hematologic [36-38], renal [27], and hepatoxicity [39], patients may run out of resilience to withstand toxicity before they run out of therapeutic options. This real concern was underscored in a recent network meta-analysis of 30 randomized trials finding severe and life-threatening adverse effects ranged from 3.0% to 83.9% depending on the treatment combinations utilized [40], underlining the importance of mitigating toxicity and optimizing sequencing of therapy for patients with prolonged survival.

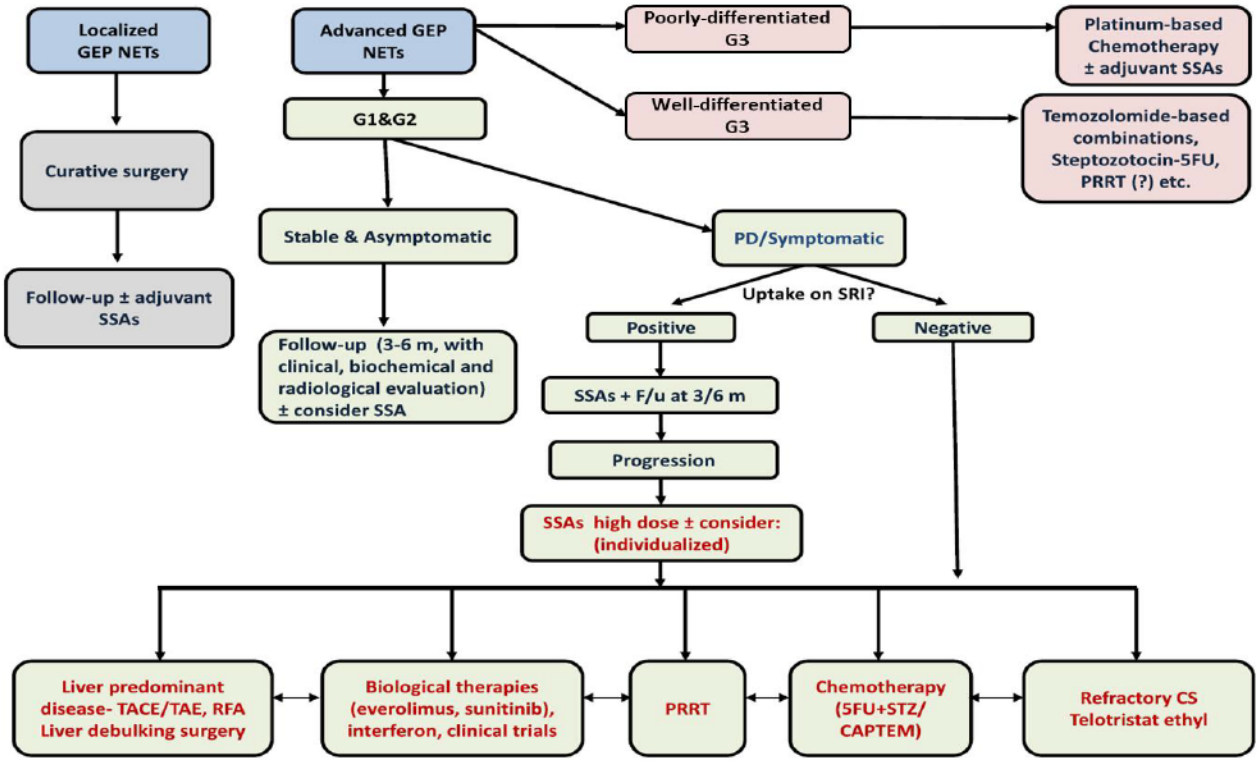


***Figure 2**: Overview of treatment for GEP-NETs*

SSA:Somatostatin Analogues, PRRT: Peptide receptor radionuclide therapy,5FU: 5-fluorouracil, STZ: Streptozocin-based chemotherapy, CAPTEM: capecitabine with temozolomide, SRI: somatostatin receptor imaging, TAE: Trans-arterial embolization, TACE: Trans-arterial chemoembolization, CS: refractory carcinoid syndrome, RFA: radiofrequency ablation.

1.1.4. Important NET subgroups

Metastatic well-differentiated grade 3 NETs are a challenging and heterogeneous subgroup. Predominantly localized to the pancreas, stomach and colon the prognosis of these tumors is poorer than grade 2 NETs. Current European and American guidelines recommend surgical resection for localized disease (irrespective of grade), but chemotherapy is indicated in grade 3 NETs, particularly if it would enable a surgical procedure [16]. Researchers from the University of Iowa [41] and Vanderbilt (Dr Satya Das, Co-I), two large dedicated multidisciplinary NET clinics, are showing that earlier utilization of PRRT (neo-adjuvantly) in these patients may improve patient outcomes (progression-free survival), indicating that there may be other treatment sequences and combinations in this subgroup of equal or greater effectiveness, and with potentially reduced long-term toxicities.

There are currently several ongoing NET phase III clinical trials. NETTER 2 examines Lutathera (177-Lu DOTATATE) in comparison to high dose SSA in higher G2 and low G3 GEP-NET patients. COMPETE compares Lu177-DOTATOC with everolimus treatment in G1/G2 GEP-NET patients. The CABINET trial is comparing use of a tyrosine kinase inhibitor vs placebo in a variety of NET patients previously treated with everolimus. Further, a more recent phase III trial COMPOSE (not yet recruiting), will evaluate the efficacy, safety & patient-reported outcomes of 177Lu-Edotreotide to best standard of care options (including chemotherapy and everolimus) in G2/G3 GEP-NETs. Importantly however, these trials will take several more years to report results and will enroll fewer than 400 patients each. Moreover, there is a marked disservice in these clinical trials to patients with lung NETs. In fact, typical and atypical carcinoids (low-grade NETs of the lung and bronchus) are neglected diseases in respect to both high-grade NETs of the lung (i.e.: small-cell lung cancer and large-cell neuroendocrine carcinoma) and GEP-NETs, with therapeutic options often extrapolated from studies undertaken in patients with GEP-NETs [42]. The conduct of a comparative effectiveness research (CER) study in the setting of typical and atypical carcinoids is particularly warranted.

1.1.5. Significance

The lack of consensus guidelines as to the optimum sequencing of treatments, means that NET patients and clinicians are confronted with very real and difficult treatment decisions. Due to the relatively small number of patients included in clinical trials related to the important NET subgroups previously highlighted, it is difficult to evaluate both the factors that may affect treatment receipt and their influence on patient-reported outcomes and prognosis. Our large study's rigorous collection of symptom, tumor and treatment burdens and their impacts on HRQoL indicators will improve patient outcomes through the application of more informed treatment sequencing and monitoring of disease burden. While patients with a localized, resectable tumor may go straight to surgery, those with locally advanced or synchronous metastatic disease may benefit from the delivery of a more complicated series of treatments which are somewhat personalized to the preference of the patient and the proliferative profile of their tumor.

The NET-PRO study will address at least three large challenges patients face in what they are offered for the current management of NETs.

a. Unknown optimal sequencing of systemic and non-systemic therapeutic options. Because clinicians currently do not understand what options (with the lowest toxicities) should be tried first given a patient's particular proliferative tumor burden, they are not able to provide evidence-based recommendations. Our communications with NET patients and our patient advocacy partners strongly attest that this is a research question that is important to them. This is what is driving our study aim 3, which will compare the effectiveness of various PPRT treatment combinations and sequences on outcomes of renal toxicity and radiographic evidence

of disease progression. This prospective CER study may ultimately help improve the standardization and optimization of PRRT procedures [43], increasing therapy effectiveness, driving adoption of protective interventions, and improving patient outcomes.

b. Treatment of grade 3 well differentiated NETs is an area of controversy. Data from two of our participating sites (Iowa and Vanderbilt) is supportive of earlier initiation of PRRT in these patients (neo-adjuvant setting), and a large CER study with targeted chart review and electronic medical record (EMR) data would be able to assesses progression-free survival outcomes.
c. Lung NETs are an underserved NET cohort currently prescribed the same treatment/management practices as GEP-NETs, even though they are recognized as a specific entity; the lower frequency of these tumors at single academic medical institutions precludes robust investigation and inclusion in randomized trials. CER studies in lung NETs are therefore particularly appealing in this often neglected population.

1.1.6. Potential to advance rare disease research using PCORnet

There is currently no large nationally recruiting prospective study of NET patients. The PCORnet resource is the ideal platform to evaluate in large patient numbers, real-world CER questions on the disease burden and treatment effects and toxicities that matter most to NET patients, their caregivers, and clinicians involved in their care. We expect that the lessons learned by partnering with patients to design the interactive NET patient health record (PHR) portal will yield generalizable knowledge about the information needs for other rare disease populations.

2. SPECIFIC AIMS

The aims of this project will be addressed through the conduct of a prospective cohort study. The general approach to the creation and workflow of this cohort (in reference to the study specific aims) are briefly outlined below.

2.1. Purpose

The purpose of this project is to partner with patients on CER to achieve the goal of mitigating toxicity and optimizing effectiveness and sequencing of therapy for patents with NETs.

In order to achieve this overall goal, we have four specific aims. Aim 1 addresses the patient question of 'what therapy would be best to try next?' in the context of symptom burden and quality of life. Aim 2 addresses patient concerns surrounding the question of 'If I were to take this option now, what treatment options will be closed off to me in the future', by examining patient and tumor factors associated with overall survival and disease progression. Aim 3 leverages the data obtained in aims 1 and 2 to inform a comparative effectiveness study of contemporary concern, with a focus on patient-centered quality of life and toxicity outcomes. Aim 4 will aid dissemination of our study results and contribute to PCORnet rare disease infrastructure.

AIM1: To describe the frequency of treatment regimens received by line of therapy, and examine their association with symptom burden and changes in 6, 12 and 18 month HRQoL outcomes. The influence of patient preferences, beliefs, attitudes, and experience of care on choice of these treatment regimens will also be examined.

Expected outcomes of aim 1: This aim will enable the ascertainment of patient-reported outcomes (PROs) related to the experience of symptom burden and toxicities for various therapies (and combination treatments) and explore the patient's attitudes and beliefs that impact the choice of treatment sequencing beyond the basis of clinical and tumor characteristics. Descriptive analyses of these important PROs (that do not exist in the patient's EMR will determine what combinations of therapy are being used, and the changes in symptoms and HRQoL associated with these therapeutic choices.

AIM 2: To examine the association of patient, clinical, and tumor characteristics on the selection of first-line and beyond treatment regimens and compare the effects of common treatment sequences on frequency of subsequent treatments received and outcomes of overall survival and disease progression.

Expected outcomes of aim 2: This aim will collect existing EMR data among the patients identified in aim 1. We will investigate the patients' pre-existing comorbidities (i.e.: cardiovascular, renal and liver disease and diabetes), prognostic tumor factors (derived from the population of PCORnet cancer registry tumor data tables i.e.: stage, grade nodal status, mitotic count and Ki-67 index) and the effect of these on the selection of multiple line therapies received. We will additionally examine the effect of these patient, clinical and tumor factors on outcomes pulled via targeted chart reviews i.e.: disease progression and overall survival.

AIM 3: To compare the effectiveness of PRRT regimens on outcomes of renal toxicity, disease progression, and patient-reported symptoms and HRQoL.

Expected outcomes of aim 3: We will complete a comparative effectiveness study of PPRT with or without administration of other systemic therapies (e.g.: everolimus). We will utilize the combined PRO's gathered in aim 1 and EMR data mined in aim 2 (i.e.: predictors), to compare the effectiveness of various PRRT treatment combinations and sequences, on outcomes of reduced creatinine clearance (renal toxicity) and HRQoL and symptom burden. We will additionally examine the effect on disease

progression of embolization therapy and chemotherapy prior to/following PRRT. Exploring the effectiveness of these outcomes in grade 3 well differentiated NETs and lung NETs (current areas of controversy and under study respectively) will be greatly beneficial.

AIM 4: To disseminate lessons learned and expand enrollment of the prospective cohort to other interested PCORnet sites, patient advocate organizations, and to use the infrastructure developed to aid in the study of other rare diseases.

Expected outcomes of aim 4: By collaborating with several key national NET patient advocacy organizations, and by fulfilling our stakeholder engagement plan, we will fashion a robust and early dissemination plan distributing findings to NET patients before the close of the study. Partnering with 14 participating sites from 4 PCORnet clinical research networks (CRNs) and their institutional media outlets, we will share results that are customized to local settings of care. The NET patient phenotype, tumor table data quality curation scripts, and NET patient health record (NET PHR) portal infrastructure this study will generate, will be loaded to open-source tool-sharing sites and to the PCORnet Commons. These tools will be useful for fostering other CER studies in NETs and could easily be re-purposed for applications in other rare diseases. Finally, we expect to submit grants to conduct new studies with this infrastructure, including following more patients for longer-term outcomes of this indolent disease. If our NET PHR portal is found to offer value to patients, we expect to maintain it as part of this ongoing research.

3. STUDY OVERVIEW

3.1. Overview and approach

We will conduct a prospective cohort study of approximately 3,000 patients with GEP-NETs and lung NETs leveraging datamarts from 14 partnering PCORnet sites to describe the experience of symptom burden, sequencing of therapies and their associated toxicities on outcomes relevant to patients, including HRQoL and overall survival.

Our first step will be to enroll a cohort of patients to collect patient reported outcomes data every 6 months. Step two will involve the extraction and assimilation of clinical data from EMR and targeted chart reviews of these same patients. The third step will leverage the full dataset to characterize treatment regimens and compare their effectiveness. We will further study the heterogeneity of these treatment effects by grade of differentiation (G1/2 vs G3) and NET subsite (GEP vs lung). Finally, we plan to share the infrastructure developed through our aims (i.e.: the NET PHR portal, NET phenotype, Common Data Model (CDM) tumor table quality curation package), disseminate our study findings and expand our prospective enrollment through our four nationally representative partnering patient advocate organizations.

The study setting, relevant time anchors for cohort derivation, the specific criteria for inclusion, and methods for cohort identification and selection are detailed below.

3.2. Setting

We have identified 14 PCORnet partners (Table 1), chosen as subcontracted sites for the NET-PRO study based on their potential to prospectively recruit on average 215 patients over the 60 months study period. Importantly, all 4 partnering CRNs have previously collaborated in the PCORnet Cancer Collaborative Research Group, and 3 of the networks participated in a PCORnet Rapid Cycle Project of molecular targeted therapies to efficiently share individual-level data [44, 45]. All 4 CRN partners are able to link North American Association of Central Cancer Registries (NAACCR) required variables to their CDMs.

As shown in Table 1, 12 of our 14 PCORnet partners are affiliated with an NCI-designated Comprehensive Cancer Center. These are institutions dedicated to research in the development of more effective approaches to prevention, diagnosis and treatment of cancer involving a multidisciplinary team approach with skilled clinicians and specialized tumor boards. Importantly, these 14 partners also reflect the diverse clinical environments accessible to NET patients, including a mixture of high volume multidisciplinary specialist NET centers vs. some less specialized units, enabling the examination of the real-world experiences and outcomes of care across a variety of practice settings.

Table 1: List of 14 PCORnet partners

Clinical Site (Clinical Research Network (CRN))	NCI Cancer Center Designation
University of Iowa (GPC)*	Yes
Allina Health (GPC)	No
University of Kansas Medical Center (GPC)	Yes
Medical College of Wisconsin (GPC)	Yes
University of Texas Southwestern Medical Center (GPC)	Yes
University of Utah (GPC)	Yes
University of Florida (OneFlorida)	No
Mayo Clinic (STAR)	Yes
Medical University of South Carolina (STAR)	Yes
University of North Carolina at Chapel Hill (STAR)	Yes

Clinical Site (Clinical Research Network (CRN))	NCI Cancer Center Designation
Vanderbilt University Medical Center (STAR)	Yes
Ohio State University (PaTH)	Yes
University of Michigan (PaTH)	Yes
University of Pittsburgh Medical Center (PaTH)	Yes
*Includes the University of Iowa Coordinating Center (UICC)	

4. STUDY DESIGN

4.1. Time anchors for study cohort

Study Period: 01/01/2019 to 12/31/2023 (5 years, max 60 months follow-up)
Index Date: Date of diagnosis of eligible NET tumor in the study period
Source Data Range: 01/01/2017-12/31/2023 (7 years, includes 2-year look-back period)

4.2. Inclusion/Exclusion Criteria

To be eligible for this prospective cohort study subjects must meet **all** of the following criteria:

i. Incident GEP-NET/Lung NET diagnosis*(see **Appendix A**)
ii. Diagnosed 01/01/2019-12/31/2023
iii. No known prior GEP-NET/Lung NET diagnosis
iv. Aged ≥18 years at diagnosis
v. At least one site encounter within the study period of January 1, 2019 to December 31, 2023

* See **Appendix A** for a full list of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes used to define a NET diagnosis. This appendix also lists the ICD-0-3 site codes and eligible histology codes for implementation in tumor registry data sources.

4.3. Cohort Identification and Selection

Some study sites may find it most effective to use a highly sensitive phenotype to identify participants from their clinics; clinic staff could then easily screen out the concomitant false positives that would also be flagged with such a sensitive phenotype. For other sites, however, recruiting through e-mail may be most appropriate. In which case, high positive predictive value would be essential to ensure the patients contacted actually have a NET diagnosis. In order to accommodate these varied approaches, we are developing a staged algorithm that balances sensitivity and positive predictive value (PPV) with each step.

4.3.1. Potential modes of subject identification

To identify potentially eligible patients for invitation into the NET-PRO study, enrolling sites will manually review - and/or, use a NET computable phenotype (provided by the UICC) that is run against - existing EMR, research warehouse, and / or oncology research database or cancer registry data.

4.4. Development of a NET Computable Phenotype

Specific codes for GEP-NETs will include 209.00-209.27, 157.4, 156.2 (ICD-9) and C7A.01-C7A.096, C24.1 and C25.4 (ICD-10), and for lung-NETs will include 209.21 (ICD-9) and C7A.090 (ICD-10). The current algorithms we have developed are similar to that used by ADAPTABLE for identifying patients with a history of atherosclerotic cardiovascular disease [46].

Query logic and codes will be provided with enough documentation that it will be easy to adopt by sites. An example of the technical specifications and SAS code for a high PPV and a high sensitivity computable phenotype is shown in **Appendix B**. We have also included a phenotype that uses data from institutional tumor registries. All but the high sensitivity phenotype are intended for a 'low-touch' method of recruitment. The lung-NET High PPV phenotype had a PPV of 92%, and the GEP-NET High PPV phenotype had a PPV of 90-98% when compared with chart review at The University of Iowa. The estimated sensitivity was 59.0% and 45.2%, respectively. The high sensitivity phenotype (for use when resources can confirm eligibility first i.e.: chart review or in-person clinic recruitment), resulted in a sensitivity of

84.6% for lung-NETs, and 89.2% for GEP-NETs **Appendix B**. We will disseminate the phenotype to all collaborating sites and via PCORnet webinars to encourage its amendment and use in other disease settings. The computable phenotype will be openly deposited on a public phenotype database (i.e.: PheKB) and posted on the PCORnet iMeet Central site.

5. RECRUITMENT, ENROLLMENT AND STUDY ACTIVITIES

5.1. Overview

The UICC will provide support for enrolling sites to identify and implement multiple modes of approaching and recruiting patients. Recruitment materials will direct patients to their assigned study website account. Additional accommodations will be made for patients without internet access or who do not feel comfortable using the study website (see Section 5.5.3 for details). Once logged in, the website will direct patients through the enrollment process, and information on local site contacts for questions will be available on the website. See Figure 3 for a schematic of study recruitment and enrollment activities.

All sites relying on the University of Iowa IRB as the IRB of Record will be provided with IRB approved templates as appropriate for recruitment and enrollment materials (e.g., Informed Consent Document, invitations, brochures). These materials will be tailored to site needs and requirements based on review of the local context documents supplied by relying sites.

5.2. Roles and responsibilities of enrolling sites and UICC

Enrolling sites will be responsible for patient contacts up through and including participant enrollment defined as completion of consent and contact information (Step 4 of enrollment [Section 5.7 below]). In some instances, such as those that involve non-electronic enrollment in which participant contact information is not available by the UICC, sites may be responsible for patient contacts up through and including completion of Survey #1. The UICC will be responsible for patient contacts related to follow-up data collection from patients directly (i.e.: baseline/6/12/18 month surveys). However, both enrolling sites and the UICC may be contacted by patients at any point in the study and should be positioned to address patient questions accordingly.

5.2.1. University of Iowa Coordinating Center (UICC) roles and responsibilities

1) Coordinate all aspects of the study conduct across clinical sites
2) Train site staff on implementation of the research protocol
3) Track enrollment status of patients who visit the PHR website or return paper study packets and communicate this patient-level information to sites
4) Communicate Institutional Review Board (IRB) approvals, continuing reviews, and modifications to sites
5) Provide templates for all study materials
6) Provide hard copy materials when needed and as appropriate (i.e.: to support paper-based enrollment by sites).
7) Answer patient questions pre- and post-enrollment
8) Administer the study website (PHR)
9) Maintain security and integrity of collected data

5.2.2. Enrolling site roles and responsibilities

1) Run queries to identify potentially eligible patients initially, and then every 2-4 weeks (i.e.: using local data sources/warehouse or CDM) as appropriate based on rate of potentially eligible patient accrual
2) Screen and recruit patients to the study
3) Provide missing contact information for enrolled subjects (I.e.: phone number, mailing address, email address)

4) Collect medical record data on enrolled subjects and return those data to the UICC (see 6.1 below)
5) Answer patient questions pre-and post-enrollment
6) Maintain a tracking database (REDCap) of eligible and approached patients, including maintenance of the link between UICC-assigned PARTICIPANTID and CDM PATID
7) Provide monthly enrollment reports to the UICC
8) Populate the PCORnet TRIAL table for enrolled patients

5.3. Identifying patients for recruitment at participating sites

Data groups at each site will run the computable phenotype against their EMR, research warehouse, and / or oncology research database or cancer registry data every two to four weeks to identify incident and recently diagnosed NET patients using the approaches outlined in 4.3 and 4.4 above.

5.3.1. Data elements used to identify potential subjects for recruitment

The following data elements will be useful fields for clinical sites to aid identification/initial contact with potential study participants. These variables will not be shared with the UICC prior to enrollment.

i. Name(s) (surname and forename)
ii. MRN (Medical Record Number)
iii. Date of birth
iv. Address
v. Contact number(s) (home/mobile/both), and contact preferences
vi. E-mail address
vii. EMR data (diagnosis codes (see Appendix A), tests and procedures, medications and encounters)
viii. Vital status

5.4. Assigning and maintaining unique IDs and PHR credential linkage to patients

The UICC will provide sites with a unique PARTICIPANTID and credentials for patients to access the study website and to establish linkages to patients in their CDM datamart. The PARTICIPANTID will incorporate site identifying information (e.g.: 15XXXX = University of Iowa). Patient website credentials will include (1) a temporary username and password, and (2) a unique URL.

Once eligible patients are identified (see 5.3), sites will link patient information with a PARTICIPANTID and credentials provided by UICC. The UICC will set up a REDCap tracking database for sites to use. For sites that do not wish to use the REDCap database set up by the UICC, a template will be provided for sites to use to set up a local version of a REDCap tracking database. Site staff will be asked to update patient activities in the UICC REDCap project. This information will help guide next steps for patient enrollment contacts.

5.5. Patient recruitment and recruitment materials - initial contacts

Once the linkage between patient contact information and UICC-provided information is established in REDCap, initial patient contacts by local site personnel can begin. Sites are encouraged to optimize recruitment strategies based on available resources, institutional factors and/or study team preferences.

Sites may initially contact potentially eligible patients by email, direct-to-patient messaging (e.g., MyChart, EMR messaging features, etc.), or ground mail; sites may also approach patients directly in-person in a private setting during a clinic visit/consultation (i.e.: an exam room). At that time, the research team member may provide the patient with information about the study per a letter

(described above), email, direct-to-patient messaging (like MyChart), or study packet, depending on patient preference. (Direct-to-patient messaging (like MyChart) will not take place at UIHC but may occur at other relying sites.)

UICC may also provide a study brochure or similar materials to be used during the recruitment process by sites as applicable or appropriate. For example, these materials may be presented to eligible patients during an initial in-clinic visit to provide introductory information about the NET-PRO study before a study invitation (or study packet) is extended.
Ideally, all recruitment materials will be personalized with the institution logos/letterheads of the recruiting site to foster site affiliation with the NET-PRO study and provide familiarity and local site contact details.

5.5.1. E-mail

An e-mail invitation is sent by the site coordinator directly to the patient. The e-mail body includes a brief study summary and unique NET-PRO website credentials and/ or a link that takes recipients directly to their study website account.

5.5.2. Direct-to-patient communication (e.g., MyChart, other EMR messaging, etc.)

An electronic invitation is sent by the site research team member directly to the patient, in accordance with local policies and procedures. The content of the communication will be identical to that of an email communication.

5.5.3. Letter

A research team member can mail an invitation letter to patients. The letter will contain the study website and unique credentials for accessing the study PHR.

5.5.4. Study packets

Sites can elect to provide or send patients a "study packet" as a non-internet-based option for patients who express difficulty or discomfort with using the study website. Study packets will contain:

- A cover letter
- A copy of the consent summary and two copies of the informed consent document (one to return to the UICC, one to keep)
- Survey #1
- A business reply envelope (BRE) addressed to the UICC research team (not the study site)

The UICC will provide copies of all packet materials except for the cover letter, as the cover letter will need to include the patients name and address. Site coordinators will write or mail merge the PARTICIPANTID on the front of the survey so the UICC can identify the patient if/when a survey is returned to the UICC using the provided BRE. After enrollment to the study and completion of Survey #1, the UICC will assume responsibility for data collection.

5.6. Patient recruitment contacts and recruitment materials – follow-up contacts

Following the initial contacts, site research team members can make up to an additional five (5) contact attempts to potentially eligible patients.After initial electronic, mail or in-person contacts are made, and if allowable per site policy, sites may contact patients by phone (included in the max of 6 contacts) to follow up with the initial invitation and address any questions patients may have about the study.

Similarly, sites may approach patients in-person who were previously invited to participate in the study. Sites are encouraged to vary approaches to maximize patient enrollment.

Patients who do not want to participate and do not want to be contacted further can notify the research team in a variety of ways:

1. By calling or emailing the local study team
2. By calling or emailing the UICC NET PRO team (contact information will be provided on the study website)
3. After reviewing the consent document online, by selecting the 'not interested' option.
4. By returning the study packet blank to the UICC (for patients who were sent a study packet)

The UICC will include dates of all notifications by patients that they are declining participation in the updates provided to sites to eliminate the possibility of subsequent contacts.

5.7. Enrollment via NET-PRO PHR research portal

Patients who receive invitations to visit the study website will proceed sequentially through five steps after logging into their study account:

Step 1 - Answer eligibility statement (see 5.7.1 below)
Step 2 - Review the consent summary and consent document, and electronically sign the consent document
Step 3 - Create new login credentials for their PHR study account
Step 4 - Enter contact information
Step 5 - Complete Survey #1

5.7.1. Patient-Reported Eligibility Criteria

Given the difficulty of specifying a computable phenotype in a rare disease like NET (i.e.: potential for false positives), and that the nomenclature for NETs can be uncertain, patient self-report will be used to verify the patient's belief that they have been diagnosed with a NET (and to ensure patients are not distressed by receiving the study invitation if they do not think they have a tumor). The language below has been drafted for review by the patient advisory committee and clinician group for use in the invitation to participate:

"You are receiving this study packet because your medical records indicate that you were evaluated in clinic for a possible neuroendocrine condition. If the neuroendocrine condition you were evaluated for was diagnosed as a neuroendocrine/carcinoid tumor, you may be eligible to participate in this study. To be eligible, you must have been diagnosed with a neuroendocrine tumor of the lung or bronchus and/or gastrointestinal tract (i.e.: stomach, duodenum, jejunum, ileum, colon, pancreas, rectum or appendix) on or after January 1, 2019. In addition, you must have been 18 years of age or older at the time of diagnosis. If the above criteria does not apply to you or you feel you've received this packet in error, please accept our apologies. In addition, please check the box and return the blank packet in the enclosed postage paid envelope."

5.7.2. Eligibility outcomes

Patients who remain eligible after attesting to the eligibility criteria above in the study website will be directed to Step 2 (review / sign consent) on the website. Patients who are ineligible will be taken to a screen that thanks them for their time and informs them they are ineligible.

5.7.3. Review and Signing Informed Consent Document

After reviewing the informed consent document, but before being asked to sign it, patients will have the ability to download and print it out and discuss their potential participation with others. Following review of the consent document, patients will be asked if they want to join the study. If they agree, they will be prompted to electronically sign the informed consent document online by entering their first and last name. The date of e-signature will be auto-generated by the study website and maintained by the UICC. An electronic copy of the signed and dated informed consent document will then be available for enrollees to access.

Patients will have an option both to decline participation and for more time to consider enrollment.

5.8. Enrollment via Study Packet

Site coordinators will have written or printed the PARTICIPANTID assigned by the UICC on the study packet before sending/providing it (i.e., in-person) to patients.

Patients who were provided a study packet will attest to the patient-reported eligibility statement outlined in 5.7.1 above. If they are ineligible, or decline to participate, they will be asked to return the study packet blank to the UICC using the provided BRE. If they are eligible, they will be instructed to review the consent summary and informed consent document, and if interested in joining the study, will be instructed to sign and date one of the included copies and to retain a copy for themselves. Inadvertently returned duplicate copies of consent documents will be mailed back to subjects using the address information provided. Receipt of a completed consent document to the UICC will denote consent to participate in the study. The UICC, or site research team in consultation with the UICC, will contact persons who did not complete the consent document (to ask them to complete and return it) if only a completed survey was returned.

5.9. Enrollment Monitoring and Reporting

Enrolling site staff will record all patient contacts and status updates (e.g., declined, deceased, etc.) in the UICC REDCap project. The UICC REDCap project will establish the linkage between patient identifying information at the clinical site and UICC-provided PARTICIPANTID and credentials and will provide real-time updates on patient PHR access and use to site staff. Sites have the option to stand up their own, additional copy if preferred, and UICC will not have access to these site local REDCap instances (aside from UIOWA's).

As the UICC is required to update the Patient Centered Outcomes Research Institute (PCORI) on enrollment activities by all sites, sites will be asked to maintain case tracking information in the UICC REDCap project including information related to:

- How eligibility was assessed
- Invitation contacts to eligible patients
- Patient declines/withdrawals
- For deceased patients, the date and (if known) cause of death

UICC will provide templates for / access to the above.

5.10. Post-consent study procedures

5.10.1. Baseline survey

5.10.1.1. Participation via the NET-PRO PHR

After the subject signs the informed consent document, they will be prompted to create their study account by changing their username and password. Thereafter, they will be invited to complete the first study survey, which will take approximately 40 minutes to complete. This survey asks about current and past health conditions and treatments, symptoms, health behaviors, feelings, concerns, and general preferences about health and health care, physical and mental health, and basic information (like marital status, and height and weight). There are also a few questions to assess comfort with and understanding of health information. Once completed, subjects will be invited to explore the study website which contains a way to view their survey responses, consent document, their study status, and other NET resources.

5.10.1.2. Participation via paper study packet

After the subject signs and dates the informed consent document, they will be invited to complete Survey #1 (which will be part of the provided packet). Once completed, they will return the study packet - which includes a copy of the signed/dated consent and the completed Survey #1 - to the UICC using a pre-paid BRE.

Once received, a UICC research team member will enter subject survey responses into the study website.

5.10.2. UICC Reminder Contacts

Subjects who provide consent and contact information but do not complete Survey #1, will be contacted by email, letter and/or phone after 7 days as a reminder that their survey is not complete. A maximum of 6 reminder contacts will be made. Enrolling sites will be asked to provide subject contact information to the UICC if the subject has not provided it (or it was not valid) in the study website (Steps 3 and 4) to enable these reminder contacts.

5.10.3. Follow-up surveys

Approximately six months after subjects complete the first survey, the UICC will send invitations for subjects to complete the 6-month survey via email (for study website enrollees) or mail (for mail enrollees). Content for this and the remaining follow-up surveys (at 12 and 18 months) are similar to the Survey #1 (baseline), except they do not include questions about chronic conditions, demographics, thoughts on cancer diagnoses and treatment decisions, or health literacy.

If the subject has not completed the 6-month survey within 7 days of the invitation, a reminder email, mail, or phone invitation will be sent/made. These reminders will be automated by the UICC or PHR, as applicable. This process will be repeated (every 7 days) for a maximum of six contacts until the subject completes the survey or declines to complete it. Identical invitation and nonresponse procedures will be implemented for the 12- and 18-month surveys. (See Appendix C for details on pre- and post-consent contacts.)

If the UICC is unsuccessful at contacting subjects using the information provided by the subject (e.g., data entered erroneously on the PHR), the UICC will communicate with the enrolling site to review the patient medical record to attempt to find and share updated contact information with the UICC.

Subjects will be able to access their study accounts (PHR website) at least through the end of 2025. A UICC research team member or the PHR will be used to send automated reminders to patients for

subsequent completion of the 6-, 12- and 18-month follow-up questionnaires (calculated from the date of their baseline questionnaire completion).

5.10.4. Subject Compensation

Regardless of the enrollment means, subjects will be compensated $40 for completing Survey #1, and $20 for completing each subsequent survey (i.e.: Surveys #2-4), for a total of $100.00. Checks will be sent by the UICC to the address provided by the subject on their PHR registration page or mailed questionnaire (using personal data collected post consent).

5.11. Post-enrollment monitoring

The UICC will record all subject contacts and status updates and will share this information as needed with enrolling sites.

In some cases, it may be necessary for an enrolling site or the UICC to confirm the identities of enrolled persons and/or to confirm that the linkage between person and assigned credentials is correct. Information collected from subjects post-enrollment may be shared between a site and the UICC to resolve any such discrepancies.

5.12. Population of CDM PCORnet_TRIAL table

UICC will provide guidance to sites on populating the PCORnet_TRIAL table. This is necessary as the outcomes query provided to sites will reference this table. Sites will need to populate the table prior to running the outcomes query. The UICC will share a list of all persons who enrolled in the study as a check against site records to confirm that the PCORnet_TRIAL table is populated correctly at all sites.

5.13. Data Crosswalks

As illustrated in Figure 3, it is necessary to establish and maintain the following data crosswalks to ensure the integrity of data linkages across sources:

Responsible party	Linkage of…	To…	Notes
UICC	PARTICIPANTID	Study Website Credentials	UICC will establish this linkage and maintain it in the study database (SQL)
Sites	PARTICIPANTID and Study Website Credentials	CDM PATID	Establish linkage in REDCap as eligible patients are identified from your source EMR data. UICC to provide PARTICIPANTID and Study Website Credentials
Sites	CDM PATID	MRN or similar ID	Sites should already have a way to link CDM PATID to MRN or similar ID that can be used to directly identify patients. This will be needed for chart review activities.

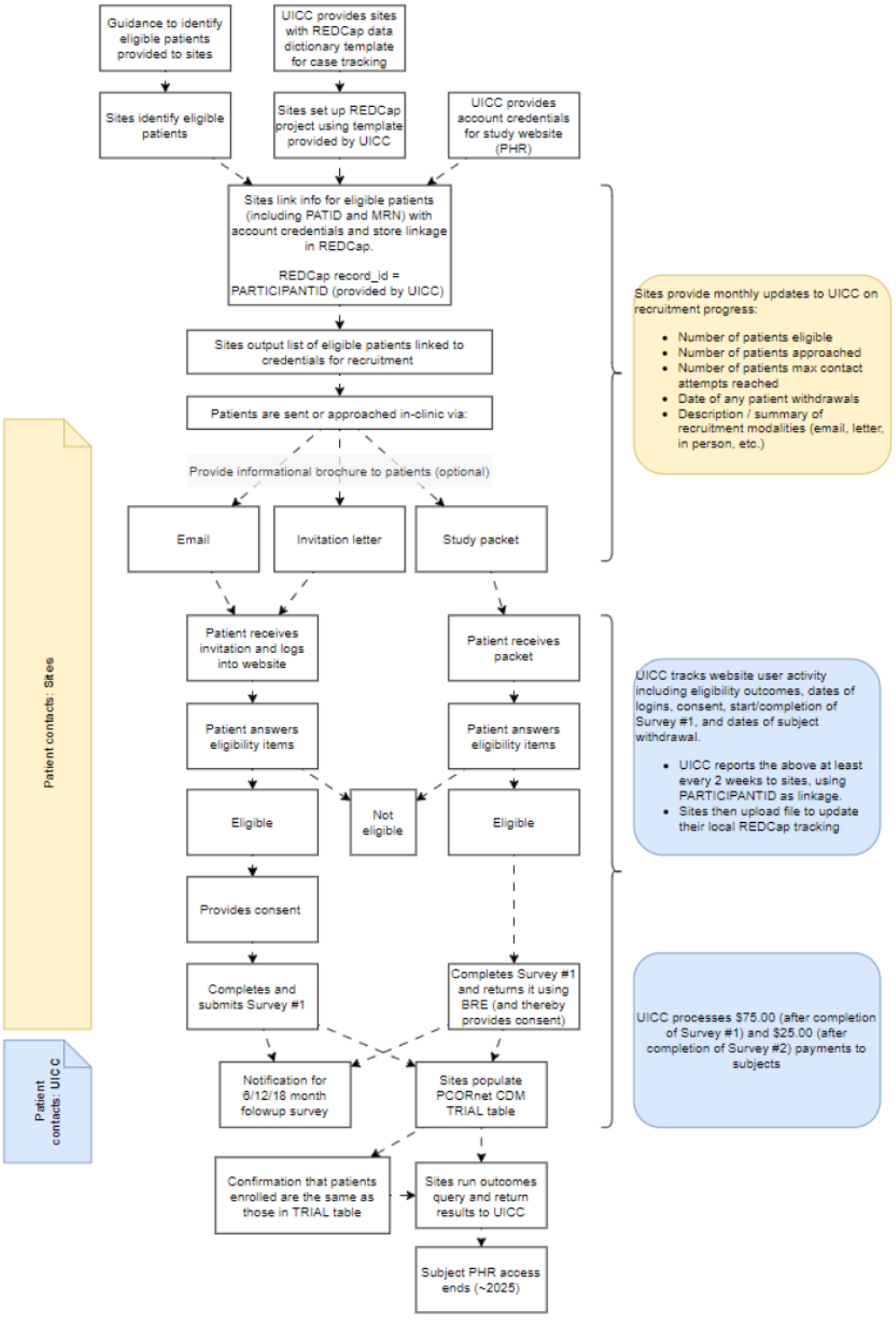


Figure 3: NET-PRO study enrollment workflow

6. DATA SOURCES

The data sources for NET-PRO will include:

1) EMR data
    - Clinical and billing data from the PCORnet CDM
    - Abstracted medical record data (per chart review)
2) Patient surveys (Baseline, 6, 12, and 18 month follow-up)
3) Patient study website navigation data

6.1. EMR data – Clinical and billing data from the PCORnet CDM

The PCORnet CDM is a key component of the PCORnet Distributed Research Network infrastructure, and will serve as the primary data source for the NET-PRO study. In late 2023, the UICC will request data from sites on all enrolled subjects. Data will include demographics, toxicity outcomes, vitals and vital status, treatments, laboratory tests and results, health conditions (comorbidities), tumor characteristics (from tumor registry variables/tumor tables in the CDM), disease status, and encrypted IDs used to link patient care across sites. The data will cover the period two years prior to the subject's NET diagnosis through approximately 36 months after the date they joined the study. Note, as per the inclusion criteria, we will not be excluding patients who do not have 2 years of look-back data prior to their diagnosis date. Table 2 summarizes the variables that will be obtained from the CDM. The specific code lists for derivation of these variables in the CDM will be later specified and distributed to sites.

Table 2: Patient, clinical and tumor variables that will be measured from the CDM

Concept/variable		*CDM Tables*
Demographics	Date of birth, sex, Hispanic, Race	Demographic Table
Toxicity outcomes	Acute renal failure, dialysis, liver failure	Diagnosis Table
Vitals	Height, weight, systolic and diastolic blood pressure, smoking	Vitals Table
Cancer Treatments	Somatostatin Analogues (SSAs) (octreotide, lanreotide, pasireotide) Bevacizumab, Cytotoxic chemotherapy, Everolimus, Interferon alpha, Hepatic Artery Bland-, Chemo- or radioembolization, PRRT -Lutetium Lu-177 dotatate, PRRT-Yttrium-90 Dotatoc, Small molecule TKIs, Telotristat ethyl)	Dispensing, prescribing, procedures, and medications administered Tables
Lab values	Alanine transaminase (ALT), Albumin and Microalbumin Albumin/Creatinine and Microalbumin/creatinine Ratio, Alkaline phosphatase (ALP), Aspartate transaminase (AST), AST/ALT ratio, Blood Urea Nitrogen, Chromogranin A, Cystatin C, Hemoglobin, Ki-67, Lymphocytes, Pancreastatin, Serum or Blood Creatinine, Somatostatin, Total Bilirubin	Lab results
Comorbid conditions	Chronic Pulmonary Disease, Congestive Heart Failure, Coronary Artery Disease, Diabetes with complications, Diabetes without complications, Hypertension, End Stage Renal Disease, Mild Liver Disease, Severe Liver Disease, Peripheral vascular disease, Renal Disease, Myocardial Infarction	Diagnosis Table, Conditions Table (for conditions in the 2 years prior to GEP-NET/lung NET diagnosis)
Vital status	Vital status (death date, cause of death)	Death Table. Death Cause Table – supplemented with local site linkages and patient survey data

Linkage	Patient ID, token	Hash token table (Datavant link module)
Tumor Characteristics	Tumor characteristics (NAACCR required variable list (i.e.: tumor grade, stage, nodal status and other relevant pathological characteristics))	Tumor Table or cancer registry data sources

6.2. EMR data – Abstracted medical record data (per chart review)

Targeted chart reviews will be conducted at one point in time (towards the end of study follow-up period i.e.: Dec 2023) for all subjects enrolled in NET-PRO. Chart reviews will be undertaken to evaluate the following items:

1) Disease status (four-category variable defined below)
2) Clinical variables found to be insufficiently populated in the CDM
3) Other Clinical/pathological characteristics not recorded elsewhere (examples below)

The UICC has budgeted $100 for chart abstraction for each case. In consultation with the clinician group, the consensus was that application of the RECIST criteria may be impracticable given current NET-PRO resources. Targeted chart abstraction will include a four-level categorization of disease status:

1) Disease control
2) Progression (no change in treatment)
3) Progression (with changes in treatment)
4) Indeterminate.

It was agreed that the clinical assessment and plan, would be the best source for identification of disease status for chart abstractors.

Other variables that may be selected for targeted chart review include clinical variables found to be insufficiently populated in the CDM. These may include interval lab values related to serum creatinine, BUN and eGFR (related to ascertainment of kidney toxicity for Aim 3) before and after PRRT cycles. It will also be important to collect tumor variables (i.e.: stage, grade, nodal status) for patients who were not identified from institutional tumor registries. An additional target for chart review may be other prognostic clinical/pathological characteristics not recorded elsewhere in the CDM or cancer registry data sources. For example information on mitotic count, chromogranin A (CgA) and Ki-67 proliferation index.

6.2.1. Chart review form

The UICC will develop, test and distribute to sites an agreed REDCap form, which will include the minimum data elements required for chart abstraction. This form will be designed with input from all NET-PRO stakeholder groups (i.e.: clinician, informatics and patient advocacy committees).

6.2.2. Chart review training

All research team members engaged in chart review and abstraction will receive training from the UICC in an effort to standardize the process. The UICC will develop a manual that will provide detailed instruction on the information and variables to be collected.

6.3. Patient surveys

Table 3 outlines the measures that will be collected from the baseline and follow-up surveys which will be administered through the PHR. The UICC has prepared a data dictionary for the baseline survey. Data dictionaries will also be made available for the follow-up surveys.

Whilst many of the current survey items are derived from validated instruments, or have been used in empirical research studies, we are receiving input from the clinician group and patient advocacy organization committees to adapt and tailor many of these items to a NET population. We anticipate that several physical and psychosocial themes may be missing from the HRQoL questionnaires that we are using which may be important to patients and/or help clinicians in their patient interactions. Therefore, in working with our patient partners and clinician groups we may identify further themes, concepts and items impacting on HRQoL and incorporate these additional measures into the baseline and study follow-up questionnaires.

Table 3: Overview of concepts and measures examined on the baseline and follow-up surveys

Concept/measure	*Baseline Survey*	*Follow-up Surveys*
Sociodemographic data (date of birth, sex and gender orientation, race, marital status, ethnicity, state of residence, household income, highest level of educational attainment, health literacy)	X	
Height and weight	X	X
Health Related Quality of Life, QLQ-C30, QLQ-GINET21,	X	X
Other impacts of cancer (worry, other life events)	X	X
Norfolk Carcinoid Symptom Score [47]	X	X
History of chronic conditions (20-item checklist)[48]	X	
Preferences and attitudes (quality vs quantity of life [49], preferred decision-making role [50, 51], family's role in decision-making)	X	
Attitudes (fatalistic thinking, spirituality) [52],	X	
Experiences of care (physician communication, coordination and responsiveness of care [53], actual decision-making role [50]	X	X
Self-reported treatments, including over-the-counter medications and supplements	X	X

6.4. Patient study website navigation

Logins and website navigation data (dates and times that features were accessed) from subject use of the study website will be collected; website data collected prior to consent will also be linked to other subject data. This information will be useful in exploring uptake of developed features (see 9.3) and in identifying any problems with use of the website.

7. STUDY OUTCOMES

Table 4 summarizes the primary and secondary outcomes of the NET-PRO study by project aims.

7.1. Primary Outcomes

1) **European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire (EORTC QLQ-C30).** The EORTC QLQ-C30 is one of the most widely used HRQoL questionnaires in cancer research. A validated tool, it consists of 30 questions with a 4-point Likert scale (from "not at all" to "very much") incorporating five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease. Responses to the QLQ-C30 will be linearly transformed to a 0-100 scale using EORTC guidelines, a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. A mean difference of 10 points (positive or negative) has been widely accepted as the minimal clinically important difference (MCID) for the EORTC QLQ-C30 [58]. A specific MCID for carcinoid syndrome and NET has not been identified. However a recent study in advanced colorectal cancer has indicated MCIDs for improvement (deterioration) ranged from 6 to 18 (-11 to -5) points for within-group change and 5 to 15 (-10 to -4) for between-group change for the EORTC QLQ-C30, with summarized MICDs (in absolute values) per scale mostly ranging from 5 to 10 points [59]. An MCID was not identified in the literature for the QLQ-GI.NET21 module.
   [Time Frame: Change in mean score across baseline, 6, 12, and 18 month time points.]
2) **European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire - Neuroendocrine Carcinoid Module** (EORTC QLQ-GI.NET21) The EORTC QLQ-C30 can be used in conjunction with the EORTC QLQ-GI.NET21 specific questionnaire, which comprises a total of 21 items: four single-item assessments relating to muscle and/or bone pain (MBP), body image (BI), information (INF) and sexual functioning (SX), together with 17 items organized into five proposed scales: endocrine symptoms (ED; three items), GI symptoms (GI; five items), treatment-related symptoms (TR; three items), social functioning (SF21; three items) and disease-related worries (DRW; three items). Responses to the QLQ-GINET21 will be linearly transformed to a 0-100 scale using EORTC guidelines, with higher scores reflecting more severe symptoms.
   [Time Frame: Change in mean score across baseline, 6, 12, and 18 month time points.]
3) **Sequencing of treatment regimens from electronic medical records.** This will involve identifying which treatments a patient used during their follow-up, and also in what order they received treatment. Dates and types of therapy initiated will be pulled from each patients EMR in reference to the patient's index date (date of diagnosis). We will also be asking patients about their treatments (self-reported) in the baseline survey to ascertain potential missed therapies in the EMR. We will be comparing the frequency (N) and proportion (%) of use of a variety of therapies (i.e.: SSAs, bevacizumab, cytotoxic chemotherapy, everolimus, Interferon alpha, embolization, PRRT, small molecule TKIs) and the effects of their ordering/sequencing on outcomes of symptom burden and HRQoL.
   [Time Frame: Up to 5 years, baseline to end of follow-up]
4) **Renal function.** Glomerular filtration rate (GFR) is the best overall index of kidney function. Normal GFR declines with age, and varies according to sex, race and body size. We will calculate creatinine clearance loss [54] by combining individual level CDM and enrollment questionnaire data on sex, race, height, weight and serum creatinine mg/dl laboratory values at regular intervals before and after PRRT cycles until the end of follow-up.
   [Time Frame: Change in eGFR from baseline to end of follow-up.]

7.2. Secondary Outcomes

1) **Norfolk Carcinoid Symptom Score.** The Carcinoid Symptom Score [49]] contains 13 questions, where question 1 has 3 queries about flushing, with a maximum of 3 points; question 3 has 4 items inquiring about respiratory symptoms, with a maximum score of 4. There are 3 questions about gastrointestinal symptoms for a total of 3 points, 3 questions related to physical functioning for a total of 3 points, and 3 questions related to cardiovascular disease for a total of 3 points; the remaining 2 questions are about family and personal medical history. The answers to the questions are quantified as ''0'' (no symptom) and ''1'' (symptom present), so the higher the score the worse is the symptom burden, from a score of ''0'' to ''18.''
   [Time Frame: Change in score across baseline, 6, 12, and 18 month time points.]
2) **Experiences with cancer care (from CANCORS).** 13 items assess patients' experiences with interpersonal aspects of cancer care [53], including physician communication (five items), nursing care (two items), and coordination and responsiveness of care (six items). The scores in each domain are converted to 100-point scales, with 0 representing the worst possible care and 100 representing optimal care. Patients can also rate the overall quality of their health care since cancer was diagnosed on a 5-point scale ranging from excellent to poor.
   [Time Frame: Change in score across baseline, 6, 12, and 18 month time points.]
3) **Progression-free survival (PFS).** Time to event data will be calculated from the index date (date of diagnosis) to the earliest of disease progression, death from any cause or end of study follow-up (12/31/2023). Acknowledging that patients may have more than one progression over the study period endpoints of median time to first progression (time from initiation of first-line therapy to progression) and time to second progression (time from second-line therapy initiation to progression) will be observed from targeted chart reviews at annual intervals. In collaboration with our clinician group we have discussed the various limitations of the application of the RECIST 1.1 criteria in NETs. These limitations include an overemphasis on tumor progression (given the low proliferation rate of GEP-NETs, monitoring changes in tumor size is suboptimal), and RECIST 1.1 criteria do not reflect overall tumor load or response to therapy in metastatic patients (i.e.: issues with clinical significance of radiologic progressions). Optimizing the management of NET patients therefore requires considering clinical, biological, and pathological aspects of the tumor. We have therefore chosen to categorize disease progression as DISEASE CONTROL (complete or partial response & stable disease), PROGRESSION (with no treatment change), PROGRESSION (with treatment change), and INDETERMINATE. This clinician-anchored approach has been found to be an optimal and valid method (versus RECIST1.1) for evaluating real-world tumor burden endpoints from EMR data [55].
   [Time Frame: median time to progression, assessed annually via chart review]
4) **Overall Survival (OS).** Time to event data will be calculated from the date of diagnosis (index date) to the date of death from any cause, or end of study follow-up (12/31/2023). Death and vital status (death date, cause of death) will be pulled from the death table, and death cause table in the CDM. This data may be supplemented from site linkage to the social security death index or cancer registry sources (where possible). Given the prospective nature of the study we also have potential for passive surveillance/follow-up with participant/next of kin with information collected on our follow-up questionnaires.
   [Time Frame: Up to 5 years]
5) **Adverse toxicities.** We will assess incident acute renal failure, dialysis and liver failure during study follow-up (from diagnosis codes in the CDM). The occurrence of these events will be compared in reference to the treatment regimens received.
   [Time Frame: Up to 5 years]

Table 4: Overview of Primary and Secondary outcomes for NET-PRO by project aims

Primary or Secondary	Name of Outcome	Specific Measure(s)/ Instrument(s) to Be Used	Timepoints (mths)	PROMIS and/or Core Outcome Set ?	Powered Yes/No/NA
Aim 1					
Primary	Health related Quality of Life (HRQoL)	EORTC QLQ-C30 EORTC QLQ-GI.NET21	0, 6, 12, 18	Yes	Yes
Secondary	Symptom inventory	Norfolk Carcinoid Symptom Score [49]Norfolk Carcinoid Symptom Score [49]	0, 6, 12, 18	No	No
Secondary	Experiences of care	Physician communication, coordination and responsiveness of care [62]	0, 6, 12, 18	No	No
Aim 2					
Primary	Sequencing of treatment regimens	-	0-60	No	Yes
Secondary	Progression-free survival	Time to event (Categorization of stable disease, disease progression with no change in treatment, disease progression with changes in treatment, and indeterminate)	0-60	No	Yes
Secondary	Overall survival	Time to event	0-60	No	NA
Secondary	Adverse toxicities	Incident acute renal failure, dialysis and liver failure during follow-up	0-60	No	NA
Aim 3					
Primary	Renal function	Creatinine clearance loss (per/Yr)	0, 6, 12, 18	No	Yes
Secondary	Adverse toxicities	CDM diagnosis codes for acute renal failure, dialysis and liver failure during follow-up	Up to 60	No	No
Secondary	Health related Quality of Life (HRQoL)	Changes in HRQOL and symptom scores	0, 6, 12, 18	No	No
Secondary	Renal toxicity (creatinine clearance) by PRRT isotope	Creatinine clearance loss (per/Yr) 177Lu vs 90Y	Up to 60	No	No
Secondary	Renal toxicity of PRRT by primary tumor location & grade 3 disease	Creatinine clearance loss (per/Yr) GEP-NETs vs lung NETs and G3	Up to 60	No	No

NA: Not applicable

8. COMPARATORS

This section details the main independent variables that will be used to compare outcomes of HRQoL, sequencing of treatment regimens and kidney function.

In all 3 study aims we will be comparing both the frequency of use of first, second and third line and beyond therapies (SSAs, bevacizumab, cytotoxic chemotherapy, everolimus, Interferon alpha, embolization, PRRT, small molecule TKIs) and the effects of their ordering/sequencing on other secondary outcomes (i.e.: symptom burden, survival and adverse toxicity). These interventions have been selected as they are listed as potential biological therapies, liver directed therapies or chemotherapies that are routinely available to NET patients, and for which there is no clear consensus as to the effectiveness of their ordering (or concomitant use).

8.1. Aim 1 (Frequency of treatment regimens)

In this aim we will describe the frequencies of treatment regimens by line of therapy and multi-line sequences. Information from Aim 1 will also be used – with input from the Patient Advocacy Committee (PAC) and Clinician Group – to finalize the comparators for Aims 2 and 3.

8.2. Aim 2 (Treatment selection and outcomes)

With input from the Patient Advocacy Committee (PAC) and Clinician Group we will examine predictors of treatment selection and outcomes of overall survival and disease progression using chosen comparators from aim 1. To do this we will need to carefully pull individual patient level data from the CDM and conduct targeted chart reviews of each patient's EMR.

8.3. Aim 3 (Comparative effectiveness of PRRT regimens)

Comparators will be PRRT with vs. without administration of other systemic therapies and PRRT before vs. after embolization therapy and chemotherapy. Comparisons will be with respect to renal toxicity, disease progression, patient-reported symptoms, and HRQoL. Heterogeneity of treatment effects will be assessed for these comparators in subgroups defined by tumor grade and type (GEP or lung NETs).

9. STATISTICAL ANALYSIS PLAN

9.1. General Statistical Approach

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum and maximum. Categorical variables will be summarized by count and percentage. Group comparisons will be assessed using chi-squared or Fisher's exact tests for categorical variables, and an analysis of variance or Kruskal-Wallis tests for continuous variables where appropriate. Adjustment for covariates listed in Tables 2 and 3 will be explored for each analysis as needed to account for potential confounding effects. Time-dependent covariates will be incorporated to capture changes in covariates across time, as necessary. Inclusion of random effects to account for potential clustering of patients treated at the same study site will be explored. Depending on the rate and pattern of missing data, multiple imputation methods may be considered to account for data missing at random or attributable to non-ignorable drop-out [56]. Planned study outcomes are summarized in Table 4.

9.1.1. Aim 1

Mixed effects regression models will be utilized to assess changes in HRQoL and symptoms within and between groups (i.e.: different treatment regimens) over time. Random effects will be employed to account for the longitudinally correlated nature of repeated questionnaire measurements. Should completion of questionnaires deviate from the planned assessment time points, a spatial power covariance structure will be included to account for the unequal time spacing between assessments within a patient.

9.1.2. Aim 2

Multinomial logistic regression models will be used to identify which patient, clinical, and tumor characteristics (Table 2), and patient attitudes and beliefs (Table 3) influence selection of treatment regimens for each line of treatment. The conditional Cox regression model proposed by Prentice, Williams, and Peterson (PWP) will be used to simultaneously model the gap times between initial diagnosis and first progression and between subsequent progressions as a function of the prognostic factors of interest for progression-free survival. The baseline hazard is expected to differ for first-line therapy and for subsequent lines of therapy, thus event-specific estimates will be obtained. A robust sandwich estimator will be used to account for potential dependencies within patients. Overall survival will be evaluated using a Cox regression model.

9.1.3. Aim 3

Statistical analyses for Aim 3 will mimic those outlined in Aims 1 and 2, but with a special interest in evaluating the effectiveness of PRRT regimens on each of the outcomes. PRRT regimens to be evaluated include: PRRT alone, PRRT ± other biological therapy, PRRT ± prior embolization. Additionally, the PRRT isotope used (177Lu vs 90-Y) will be evaluated.

9.2. Sample Size and Power

For this prospective analysis we will have an estimated sample size of 3,010 patients. The sample size is computed for the population with minimum representation in the total sample. 2019 rates of PRRT were 15% in this population. Using a conservative estimation of 10% PRRT administration, and erring on the side of caution, our sample size and power justification is based on approximately 300 subjects (excluding HRQoL questionnaire completion rates). By the law of the minimum, all other treatment subgroups with representation above 10% will yield greater sample size and consequently higher powers for the below-stated differences

9.2.1. Aim 1

The primary objective of Aim 1 is to evaluate changes in HRQoL over time for each treatment. Calculations are based on using the EORTC QLQ-C30 as the primary HRQoL measure. Conservatively

estimating PRRT to be administered in 10% of patients and further expecting a response rate of 60% in the study, we would expect the PRRT group may have approximately 180 patients with complete HRQoL data. Using a repeated measures design with 1 within-subject factor (time: baseline, 6 months, 12 months, and 18 months), the design achieves the following power (Table 5) to detect a time effect for the corresponding mean change. Calculations are based on assuming an autocorrelation of 0.5 between measurements, a standard deviation of 18, and using a Wilks' Lambda Approximate F Test with a 5% significance level. The power will be higher if PRRT administration amounts to more than 10% of the prospective population.

Table 5: Alternative power for changes in EORTC QLQ-C30 within PRRT treated subgroup

MEAN CHANGE IN HRQOL OUTCOMES AT BASELINE, 6, 12 AND 18 MONTHS (RANGE 0-100)*	**DIFFERENCE IN MEAN HRQOL SCORE** (OVER EACH TIME POINT)	**POWER***
65, 62, 59, 56	3-3-3	100%
65, 63, 61, 59	2-2-2	98.3%
65, 63.5, 62, 60.5	1.5-1.5-1.5	84.3%

*** THE POWER APPLIES EQUALLY TO POSITIVE OR NEGATIVE SCORING SCALES.**

9.2.2. Aim 2

The primary objective of Aim 2 is to evaluate the effect of common treatment sequences on progression-free survival. A lack of historical data on the frequency and number of different variations of treatment sequences, and progression-free survival (PFS) differences by treatment and line of treatment coupled with the likelihood treatment sequences will further differ between the 14 sites taking part in this study make *any realistic and meaningful* sample size and power calculations impossible. Analyses for this aim will be exploratory, and will leverage the use of time-varying covariates in combination with the conditional Cox regression model proposed by Prentice, Williams, and Peterson (PWP) as a means of addressing the heterogeneity evidenced in the data. However, to put into perspective potential PFS differences that may be detected between two treatments using purely hypothetical situations, the below table summarizes power achieved for varying combinations of median PFS differences and number of patients per treatment arm. Calculations are based on the following assumptions: 1:1 treatment allocation, 48 months of uniform accrual and 12 months of follow-up, no loss to follow-up or switching treatments, unadjusted for confounders, and using the Lakatos approximation for a two-sided log-rank test with a 5% significance level.

Table 6: Power determination for changes in median PFS

Median PFS			
Treatment 1	Treatment 2	N Per Treatment Arm	Power
12 months	24 months	45	0.79
		50	0.83
24 months	36 months	175	0.80
		190	0.83

9.2.3. Aim 3

The primary objective of Aim 3 is to evaluate renal toxicity associated with the administration of PRRT as measured by creatinine clearance loss over time. We are expecting 2 mL/min/1.73m^2 annual decline in creatinine clearance based on averaged long-term follow-up with the most common PRRT isotope 177-Lu [34]. The repeated measures design with 180 subjects and 1 within-subject factor (time: baseline, 6 months, 12 months, and 18 months) achieves 100% power to detect creatinine clearance loss of 2 mL/min/1.73m^2 by 6 months, 4 mL/min/1.73m^2 by 12 months and 6 mL/min/1.73m^2 by 18 months, when the Wilks' Lambda approximate F test is used with a significance level of 0.05, and assuming an

autocorrelation of 0.5 from one time point to the next and a standard deviation of 5 mL/min/1.73m^2. Should the standard deviation become unreasonably high in the order of 15 mL/min/1.73m^2, our sample size is large enough to achieve 99% power under the same parameter settings. In order to test Bonferroni-corrected pairwise differences, the individual tests will achieve 99.6% power to detect a clearance loss of 2 mL/min/1.73m^2 between two time points. The Bonferroni-corrected tests will be set at a significance level of 0.05/6.

9.3. Addressing confounding

With a large, proposed sample size of approximately 3,000 patients, we will minimize the effects of confounding on treatment effect estimates by adjusting for factors associated with treatment selection within the context of multivariable models. Known and hypothesized factors associated with treatment selection include but are not limited to the following: sociodemographic (age, sex, race, ethnicity, marital status, income), health status (BMI, smoking history, comorbidities), disease (site, stage, grade, nodal status), prior therapy use (PRRT, everolimus, sunitinib, liver-directed therapies, chemotherapy, surgery), and patient-reported preferences, attitudes, beliefs and experience of care. Determination of confounding factors that may warrant adjustment will be guided by the results from the multinomial logistic regression models evaluating factors associated with selection of treatment regimens (Aim 2). Furthermore, the use of time-dependent variables for treatment and potential confounders (where appropriate) will minimize the effects of survivor treatment selection bias.

As a novel project aimed to evaluate the complex interplay between patient, disease, and treatment factors on toxicity, HRQoL, and survival outcomes, the statistical analysis plan will be refined once descriptive information from Aims 1 and 2 is available for consented patients. For example in Aim 3, PRRT sits amongst a growing number of therapeutic options in metastatic well-differentiated NETs, including pharmacological (i.e.: mTOR inhibitor everolimus and the tyrosine kinase inhibitor sunitinib), hormonal and liver-directed therapies (i.e.: embolization (bland, chemo, radio)), and surgical approaches. Therefore, we need to be mindful of this multimodal treatment algorithm wherein patients may undergo a variety of treatment options at tumor progression(s).

9.4. Addressing clustering of site

Patients seen at the same study site and by the same provider are at increased likelihood to be treated more similarly. Random effects will be included in the multivariable models to account for clustering within the 14 study sites and within provider (assuming a sufficient number of patients are seen by each provider).

9.5. Handling missing data

To minimize the effect of missing data on our ability to adjust for confounding factors, any clinical variable found to be insufficiently populated in the CDM upon evaluation of submitted cohort characterization data, will be abstracted via chart review for consented patients. Moreover, all 14 participating sites have agreed to provide tumor characteristics and NAACCR required variables i.e.: tumor grade, stage, nodal status etc.) as important prognostic covariates. This tumor registry data will be populated in each sites CDM tumor tables, and sites will have the opportunity to engage in data quality curation using sample scripts developed by the GPC network informaticists (enhancing future utilization of cancer registry variables in the CDM), see 10.2 below.

10. DATA MONITORING & QUALITY CONTROL

10.1. Methods to establish validity of the NET Computable Phenotype

We have examined the proportions of NET patients identified through use of our ICD-9/10 coding classifications and the proportions of cases documented by the University of Iowa Hospitals and Clinics (UIHC) institutional tumor registry using ICD-O-3 site/histology codes. The UIHC tumor registry identifies and describes cancer cases using standards developed by NAACCR, which require that cases be documented by certified abstractors, and the resulting data comprises a 'gold standard' for comparison to our phenotype.

For GEP-NETs the ICD-9/10 codes alone identified over 70% of GEP-NET patients identified by the UIHC registry. The most common ICD-code for the 70 patients who were not identified, was C7A.8, a non-specific billable ICD-10-CM code for "other malignant neuroendocrine tumors". Lung NETs account for only 20% of all diagnosed NETs. Of the 82 UIHC lung NET cases ascertained by the tumor registry between 2011-2016, 65% were identified with the ICD codes alone. For the 29 patients (35%) who were not identified with our original ICD code classifications, the most common non-NET lung codes fell into the C34.X grouping that indicates malignant neoplasm of bronchus and lung (excluding small cell lung cancer). The non-specific NET code C7A.8 found for the GEP-NET patients was also often found for these lung NET patients. Therefore, we will improve our GEP and lung-NET phenotypes by including C7A.8 and C34.X in future data specifications, using caution to ensure inclusion of these less specific NET codes are not also identifying non GEP and lung NET phenotypes. Further testing of these modifications at clinical sites beyond Iowa will be important.

Ultimately, our goal is to construct a computable phenotype that relies on structured data from billing and electronic medical record data. We do have another permutation of the algorithm that takes PPV up to 62% (but at a cost, sensitivity goes down to 52%) using additional procedure/treatment codes. We are interested in assessing what the real PPV would be for this version (i.e.: that which would be obtained from a chart review, rather than using the tumor registry as a standard). IRB approval (#: 202107383) has been obtained at Iowa to validate these computable phenotypes against chart reviews, structured data and tumor registry sources. The UICC will test and validate this phenotype at the University of Iowa clinical site and other early adoptive sites as able.

The instance may arise when a provider encounters a patient who appears eligible for the NET-PRO study but who was not identified by the NET computable phenotype. Such patients should still be given the opportunity to enroll in the NET-PRO study (via any of the methods described in 5.5 above), and a note of their missed identification recorded in the local REDCap tracking database and also reported back to the UICC. This will be especially important in the early phases of enrollment when the NET phenotype is still being validated and tested.

10.2. Details on population of tumor table data

All 14 participating sites include the gold-standard, NAACCR-formatted institutional tumor registry data in their research warehouse. Our research plan and schedule of work with each site includes population of their CDM tumor table and participation in data quality curation using scripts developed by GPC network informaticians. Having the PCORnet tumor table at these sites will provide rich, high-quality data (including tumor grade, stage, nodal status, and other pathological characteristics). It will also provide the opportunity to further refine and validate the ICD-based NET computable phenotypes which would facilitate potential future expansion to sites that don't have tumor registry data.

It is recognized that most participating sites have not yet populated the PCORnet CDM Tumor Table. To fulfill Aim 4 which relates to building the PCORnet infrastructure, we request that sites have their tumor tables populated during 2023. Prior to that time, as needed for interim papers or for tuning the

computable phenotype, sites may access side-car NAACCR data in their data warehouse. Similarly, sites unable to fulfill aim 4 by late 2023 may use their side-car data. Most sites will find a direct ETL (extract, transform and load) of all NAACCR data elements is most efficient, however, NAACCR data elements essential to this study will be determined in consultation with the clinician and data groups.

10.2.1. Tumor table quality scripts

The PCORnet CDM tumor table will be populated by each of the 14 participating clinical sites as outlined and agreed upon in the schedule of work (tumor table specifications can be found here). As part of the informatics activities a data quality query will be executed. This will produce a patient-level data-set in a limited data-set format (dates and 5- or 9-digit zip code included, but no other patient identifiers). The query will test code-sets and distributions of key variables – including variables in the PCORnet CDM tumor table. (The UICC will develop all queries and share these with each Institution.) The data-set will be submitted to the UICC. The institutional informatics team will review the data quality report with the UICC. Based on these results, the institutional team will develop a plan for study-specific data quality remediation, as needed, and submit the plan to the UICC. Once study-specific data quality remediation is complete, the data quality query will be re-executed and a new patient-level data-set will be submitted to the UICC. The UICC will provide a second data quality report to the institution. This cycle of data quality remediation will continue until data quality standards have been met, or the institution and UICC agree that no further action is necessary. Again, specific data elements like the tumor table quality scripts will be uploaded to iMeet Central, and if there is interest, we can use PCORnet webinars to disseminate/summarize this workflow cycle (i.e.: query>review>plan>remediation process) to leverage its application in other settings.

10.3. Evaluating and Adapting the NET Patient Health Record (NET PHR)

Participants may be more willing and less burdened to provide information on outcomes and treatments in the context of a tool they already use and find beneficial. Therefore, we plan to directly involve NET patients in evaluating and adapting the Iowa PHR, providing participants with a valuable tool for managing their disease. This account-based PHR platform was designed to be adaptable, web-delivered, un-tethered to, but linkable with EMR data, facilitating enrollment from beyond our 14 diverse PCORnet settings.

We will begin enrollment and standardized data collection to the NET-PRO study with the current PHR portal and evaluate and adapt the portal during the first project year to the custom NET PHR. To do this we plan to engage in a human-centered process for designing the specialized NET PHR features; the primary goal of which will be to understand the information needs of NET patients, and iteratively design PHR features that address these needs. To inform the design of the NET PHR we will closely interact with a group of about 30 NET patients led by Dr. Hourcade, an expert in human-computer interaction who partnered with previous patient groups using these methods (Table 7). These patients will be strategically sampled by age, site and geographic location (selected through our participating NET patient advocacy organizations).

N.B.: Since this set of activities is independent from the main observational study, additional details of these activities will not be included in this protocol.

Table 7: Overview of the human-centered design approaches, and plan of topics and activities to be undertaken with NET patients in the co-production of the NET PHR portal

Step	*Purpose*	*Format*	*n*	*Topic and Activities*
1	Design	2-3 Online focus	Up to 20 (3 groups	Introduction – brainstorming: • Imagine a superhero that can help with their condition – what would the superhero do? (Superhero construct frees patients from perceived

Step	Purpose	Format	n	Topic and Activities
		groups (1hr sessions)	of 5-6 each)	constraints and they identify more types of information if not constrained by if technology can provide it) • Research team compiles a list of potential features from participant drawings What information is most important to track? • Participants individually rank desirable/undesirable features for tracking What feedback is desired? • Participants give ideas for showing, interacting with information e.g. aggregate statistics about common toxicities, symptom management cards
2	Design Validation	Survey	30	Ranking and attitudes • How interested in using each feature/tracking each item? • How important is each type of feedback? • Research team reviews results and identifies 2 types of features to implement in the NET PHR: (1) features that fit the existing capabilities of the PHR – these will be directly implemented as these features have been extensively usability tested; (2) features requiring new development – these will involve more extensive testing in steps 3-5
3	Prototype Validation	Contextual inquiry	Up to 20 (3 groups of 5-6)	• Rapid prototyping with wireframe software (e.g. Balsamiq®) by research team • Patients provide feedback on prototype • Iteratively improve between groups until optimal design reached
4	Prototype Evaluation	Usability (tasks, survey)	30	• Use functional prototype at home • Complete prepared tasks using a test version of the tool • Provide feedback via survey – NASA-TLX (task load index) administered after each task
5	Prototype improvement	Usability (video-recorded)	10	• For any tasks identified as problematic via NASA-TLX responses • Patients share screen, conduct problematic tasks while thinking aloud • 2 rounds may be needed for particularly challenging features

11. NET-PRO TIMELINE

The NET-PRO study period is three years (07/01/2021 to 06/30/2024), with a one-year peer review period. To date the UICC study team has focused concerted efforts on the administrative and regulatory underpinnings of the project including initial IRB approval at UIOWA, and subcontract execution. We have obtained PCORNET study designation, and will soon be in the process of commencing the IRB reliance process and data sharing agreements with collaborating sites so that recruitment can be undertaken. Much effort has gone in to the front-end PHR reprogramming as study enrollment, consent and questionnaire completion hinge on this development.

Figure 4 provides a high-level overview of key milestones and deliverables for the NET-PRO study. A more detailed project timeline in relation to pre-agreed milestones/program deliverables with the study sponsor (PCORI) is outlined in Table 8. Deliverables highlighted in light green indicate completed tasks, those in light orange are currently in progress, those in light red are delayed, and those not color coded await future completion. Additionally, milestones highlighted in blue indicate key deliverables relevant to the data informatics teams, whilst milestones highlighted in purple denote key deliverables and milestones relevant to patient enrollment and recruitment.

Table 8: Detailed Project Timeline

Milestone - Deliverable ID	Milestone - Deliverable Name	Description	Due Date	Completion date	Projected Completion Date
A	Effective Date	Project start date	7/1/2021	7/12/2021	
B1	Initial convening of stakeholder committee	Initial consultation and input from stakeholders to inform research and analysis plan, and agree on subsequent engagement milestones prior to submission of IRB approval and completion of the updated engagement plan.	7/30/2021	8/10/2021	
B2	Specify study governance	Provide governance document/charter to Program Officer outlining structure and roles, and authorities/responsibilities of the PI, other study leads, each committee and the respective members of said committees to PCORI.	8/31/2021	9/1/2021	
B3	Execute all subcontracts	Subcontracts with PCORnet study Coordinating Center (CC), members of the scientific investigator team, rare disease organizations, and participating Clinical Research Networks (CRNs)/ Healthplan Research Networks (HPRNs) executed. Submit notification on completion of subcontracts to Program Officer.	8/31/2021		5/2/2022
B4	Submit updated Recruitment Plan in PCORI Online.	Elements in the recruitment plan should, at a minimum, include the following: a. Timeline b. Total target sample size for primary analysis c. Name and # study sites d. Historical patient volume and estimated eligible N across study sites e. Estimated yield/consent f. Estimated lost to follow up/attrition g. Estimated monthly enrollment	8/31/2021	9/2/2021	
B5	Select and register project at appropriate site for the study design (Clinicaltrials.gov, RoPR, or other as approved by PCORI before study start date).	Submit Study Identification Number and the Primary Completion Date to PCORI. List PCORI as a collaborator so that PCORI's role as the funder (not sponsor) can be identified and tracked.	8/31/2021	9/30/2021	
B6	Submit IRB approval in PCORI Online (Continuing approval submitted annually).	Submit IRB approval of revised study protocol via the PCORI Online system.	9/1/2021	8/16/2021	
B7	Analytic plan	Submit revised analytic plan specifying aims, target population, outcomes	9/30/2021		4/30/2022
B8	Develop, finalize, and submit copy of study protocol in PCORI Online.	Refer to the PCORI Methodology Standards for required elements of the study protocol.	9/30/2021	4/13/2022	
B9	Obtain PCORnet study designation	Obtain and comply with designation requirements.	9/30/2021	6/2/2021	
B10	Refine research questions with rare disease community and other stakeholder input	Submit summary report describing input provided by rare disease community, patient, and other stakeholder partners into the selection and refinement of the research question, including the target population, interventions, and outcomes.	9/30/2021	12/21/2021	
B11	Begin recruitment.	Demonstrate the ability to obtain consent from the target population.	9/30/2021		4/29/2022
B12	Enroll first patient.		9/30/2021		4/29/2022

Milestone - Deliverable ID	Milestone - Deliverable Name	Description	Due Date	Completion date	Projected Completion Date
B13	Program and configure patient health record (PHR) portal for consent and baseline surveys	UICC staff will program consent functionality and baseline surveys in the PHR portal	9/30/2021		4/13/2022
B14	Execute Data Use Agreements (DUAs)	DUAs with institutions owning data are complete.	11/15/2021		5/31/2022
B15	Provide permission to share reporting documents with the PCORnet Coordinating Center (CC) to support a learning network.	Submit memo confirming permission to share approved project, recruitment, and engagement plans, status reports, recruitment, enrollment and retainment numbers (where applicable), and evaluation materials with the PCORnet CC for streamlined coordination and to contribute to the PCORnet dashboard. All study teams will be expected to present to the Steering Committees (SC). Ample notice and specific topics will be given in preparation for any presentation requests.	1/1/2022	12/29/2021	
B16	Submit updated Data Safety and Monitoring Plan to PCORI.	Refer to the PCORI Policy on Data Safety and Monitoring Plans for PCORI-Funded Research.	1/1/2022	12/21/2021	
B17	Submit updated Engagement Plan in PCORI Online.	Elements of the updated Engagement Plan should include: a. Update roster of committee/panel members with short bios b. A Patient and/or Stakeholder Advisory Panel(s) or Committee(s) Governance Schematic c. Planned training for patients and other stakeholder partners on the research process d. Proposed Meeting Schedule e. Tasks or opportunities wherein patients and/or stakeholders will have input via consultation, collaboration or leadership f. Efforts to Evaluate/Assess Engagement	1/1/2022	12/30/2021	
B18	Validation of computable phenotype for cohort identification	Submit evidence of validation of computable phenotype for rare disease cohort; evaluate fit for intended use.	1/1/2022	12/21/2021	
B19	Cohort identification	Participating CRNs will have identified the rare disease cohort for study. Submit evidence of cohort identification. Submit a report on study groups, demographics and other characteristics to PCORI	1/1/2022		5/18/2022
B20	Complete query to identify cohort across non-participating CRNs	Using queries developed by the study and coordinating center programmers, test feasibility of identifying the cohort through the Front Door in non-participating CRNs. Submit report to PCORI via PCORI Online system summarizing number and names of responding network partners, cohort size, and other relevant patient characteristics.	1/1/2022	12/18/2021	
B21	Data linkage assessment	Evaluate whether the quality and quantity of data in the datasets proposed for data linkage is sufficient to meet primary research aims.	1/1/2022	3/11/2022	Need to resubmit
B22	Data linkage plan	Develop a data linkage plan that corresponds with PCORnet Common Data Linkage, if available, in collaboration with the dataset owner(s).	1/1/2022	12/31/2021	
B23	100% of the IRB approvals across sites submitted to PCORI	Update IRB information in PCORI Online	1/1/2022		5/31/2022
B	Report Submission	Submit Interim Progress Report to PCORI via the PCORI Online system accessed through: https://pcori.force.com/engagement	1/1/2022	12/29/2021	
C1	Finalize comparators for Aims 2 & 3	The collection of HRQoL information from Aim 1 will be available for a decent sample of NET patients at this time. Information from Aim 1 will be used – with input from the Patient Advocacy Committee (PAC) and Clinician Group – to finalize the comparators for Aims 2 and 3.	2/28/2022		5/31/2022

Milestone - Deliverable ID	Milestone - Deliverable Name	Description	Due Date	Completion date	Projected Completion Date
C2	Patient enrollment (25%)	25% of participants (N = 753) screened, enrolled, and consented to the study.	3/1/2022		6/30/2022
C3	Validate Study Preliminary Results	Complete validation of sample of events. (Number and type of events will be distributed across the participating CRNs to assure appropriate representation.) Provide a summary of preliminary results of the validation study in interim progress report.	5/1/2022		
C4	Presentation to PCORnet Steering Committee	Annual presentation to PCORnet Steering Committee on progress of study, lessons learned, and recommendations for improvement of PCORnet infrastructure	7/1/2022		
C	Report Submission	Submit Interim Progress Report to PCORI via the PCORI Online system accessed through: https://pcori.force.com/engagement	7/1/2022		
D1	Finalize and submit copy of revised study protocol in PCORI Online.	Refer to the PCORI Methodology Standards for required elements of the study protocol.	7/1/2022		
D2	NET PHR portal finalized	Design parameters and feedback from NET patient sessions is incorporated into the NET PHR, tested, and ready for deployment for existing and future enrollees	7/1/2022		
D3	Submit IRB Continuing approval	Submit IRB approval of revised study protocol via the PCORI Online system.	7/1/2022		
D4	Programmatic evaluation materials due to PCORI.	Submit document that demonstrates study progress and feasibility based on metrics provided by PCORI to awardee. PCORI initiates Programmatic Evaluation. Metrics will include: the validity of cohort identification and its size and characteristic; feasibility of recruitment; generalizability of the sample; feasibility of data linkages (if relevant); validity and completeness of study outcomes; suggestions of needed enhancements or revisions to study protocol, as well as associated timeline. PCORI will provide recommendations about proceeding to next steps of the study within 45 days.	7/1/2022		
D5	Patient enrollment (50%)	50% of participants (N = 1505) screened, enrolled, and consented to the study.	10/1/2022		
D	Report Submission	Submit Interim Progress Report to PCORI via the PCORI Online system accessed through: https://pcori.force.com/engagement	1/1/2023		
E1	Patient enrollment (75%)	75% of participants (N =2258) screened, enrolled, and consented to the study.	6/1/2023		
E2	Submit IRB Continuing approval	Submit IRB approval of revised study protocol via the PCORI Online system.	7/1/2023		
E3	Presentation to PCORnet Steering Committee	Annual presentation to PCORnet Steering Committee on progress of study, lessons learned, and recommendations for improvement of PCORnet infrastructure	7/1/2023		
E	Report Submission	Submit Interim Progress Report to PCORI via the PCORI Online system accessed through: https://pcori.force.com/engagement	7/1/2023		
F1	Develop dissemination plan for rare disease tools and resources	Submit dissemination plan to PCORI via PCORI Online system	1/1/2024		
F	Report Submission	Submit Interim Progress Report to PCORI via the PCORI Online system accessed through: https://pcori.force.com/engagement	1/1/2024		
G1	Patient enrollment (100%)	100% of participants (N = 3010) screened, enrolled, and consented to the study.	2/1/2024		

Milestone - Deliverable ID	Milestone - Deliverable Name	Description	Due Date	Completion date	Projected Completion Date
G2	Submit IRB Continuing approval	Submit IRB approval of revised study protocol via the PCORI Online system.	6/30/2024		
G3	Completion of Data Collection for All Study Aims	Awardee must ensure that all data collection for all study aims as specified in the research plan is completed	6/30/2024		
G4	Completion of Data Analysis for All Study Aims	Awardee must ensure that all analysis and evaluation for all study aims as specified in the Research Plan are completed.	6/30/2024		
G5	Share computable phenotype for target rare disease	Rare disease phenotype submitted to phenotype repository	6/30/2024		
G6	Complete documentation for external use	Final data sets, analytic files and codebooks are made publicly available	6/30/2024		
G7	Dissemination	Complete dissemination of tools and resources to rare disease and research community and other stakeholders.	6/30/2024		
G8	Presentation to PCORnet Steering Committee	Annual presentation to PCORnet Steering Committee on progress of study, lessons learned, and recommendations for improvement of PCORnet infrastructure	6/30/2024		
G9	Primary Completion Date	An estimated Primary Completion Date must be provided when registering the study in Clinicaltrials.gov. For studies that are not clinical trials or non-prospective observational studies registered on ClinicalTrials.gov, the Awardee and PCORI shall agree on a primary completion date as a milestone that precedes the agreed-upon date to submit a Draft Final Research Report.	6/30/2024		
G	Final Progress Report	Submit Final Progress Report to PCORI via PCORI Online system accessed through: https://pcori.force.com/engagement	6/30/2024		
H	Draft Final Research Report Submission	Submit Draft Final Research Report per these instructions.	10/31/2024		
I	Results submitted to ClinicalTrials.gov or other applicable database	Awardee ensures results are submitted to ClinicalTrials.gov or other appropriate database. Results must be submitted to ClinicalTrials.gov no later than one month before submission of the Draft Final Research Report.	1/1/2025		
J	Draft Final Research Report Revisions	Upon receipt of written summary, and as applicable, PI will make revisions and submit revised Draft Final Research Report and disposition of comments table for acceptance in accordance to PCORI policy and process.	4/30/2025		
K	Approval/sign off of the Lay Abstract	No later than 90 days beyond the date PCORI accepts the final report			
L	Contract Term Date				
M	Notification of Publication Acceptance	See Contract for instructions			
*Completion Indicator Key: Deliverables highlighted in light green indicate completed tasks, those in light orange are currently in progress, those in light red are delayed, and those not color coded await future completion.					

12. Engagement and sharing of results customized to local settings of care

This project will provide new information in a rare disease patient population which has a number of treatment regimens available but little evidence regarding their relative effectiveness or safety. Care customization is an important aspect of quality in healthcare – every patient wants to feel that they are getting the care that is tailored to their particular needs. The 14 participating sites in this proposed study are reflective of the diverse clinical environments accessible to NET patients including a mixture of high volume multidisciplinary specialist NET clinics (i.e.: University of Iowa, Vanderbilt University Medical Center, University of North Carolina, Mayo Clinic and Ohio State University) vs. some less specialized healthcare systems (e.g. Allina Health), enabling the examination of the real-world experiences and outcomes of care across a variety of practice settings. It is therefore important that we consider our research findings in the context of current health care delivery at the partnering sites involved in this application.

As study results begin to accrue, stakeholders (i.e.: patients, patient advocates, clinician groups, etc.) will be invited to brainstorm potential dissemination targets and potential modes of providing that information, including ideas for optimally communicating results tailored to different stakeholder groups which may have different messaging needs. Dissemination will begin with a dissemination plan, developed by the stakeholders during the first year of the study. Initial steps of this will include identifying additional stakeholders (i.e.: informal caregivers, cancer center directors, health system marketing and communication, professional societies etc.) and how to engage them. Our team will elicit feedback from stakeholders to advise on implementing optimal communication rubrics that will support engagement of all parties. We will explore and adopt a diversity of communication modalities as informed by our stakeholder groups. We will likewise assess the success of and identify areas for improvement of engagement activities. We will also engage with the PCORnet Coordinating Center for input and guidance on priority dissemination targets, and to ensure we are taking full advantage of the engagement tools, engagement rubric, and engagement strategies already in place within PCORnet. This will include use of the PCORnet resources for sharing of user-friendly communication tools across our stakeholder groups. We will work with patient partner organizations to promote the study findings using their website and online platforms (Facebook/Twitter/Instagram etc.), email lists, and/or newsletters, and patient education conferences as appropriate to communicate study results.

13. STUDY GOVERNANCE AND POLICIES

13.1. Study leadership and Management

Dr. O'Rorke, as principal investigator (PI) of the NET-PRO study, assumes the overall responsibility for the study conduct, and is therefore responsible for ensuring that:

- He provides sufficient oversight over all study activities and tasks delegated to others to ensure that the research is conducted in compliance with all applicable Regulations, Policies and Procedures set forth by the Sponsor (PCORI) and the Institutional Review Board (IRB)
- The study protocol and patient material receive review by stakeholders, and approval by the project steering committee
- IRB approval is obtained before a site starts enrolling subjects
- After the research is approved, all required reports including: progress reports, monthly recruitment updates, protocol deviations - are submitted to the IRB, and the relevant sponsor/funding agency as per their requirements
- No changes are made to the research without first submitting a request to the IRB to amend the study and receiving subsequent IRB approval
- Analyses and study reports adhere to the pre-planned protocol analysis plan and are conducted in accordance with accepted statistical principles and guidelines for reporting observational studies (STROBE Statement)

13.2. University of Iowa Coordinating Center (UICC) Roles and Responsibilities

The University of Iowa serves as the coordinating center (UICC) for the NET-PRO study. The UICC plays a critical role in keeping all project tasks on track, and implementing and supervising most of the field methods employed. The UICC must be responsive to the feedback of the NET-PRO Steering Committee. The UICC is therefore responsible for:

1) Coordinating all aspects of the study conduct across clinical sites
2) Training site staff on implementation of the research protocol
3) Tracking enrollment status of patients who visit the PHR website or return paper study packets, and communicating this patient-level information to sites
4) Communicating Institutional Review Board (IRB) approvals, continuing reviews, and modifications to sites
5) Providing templates for all study materials
6) Providing hard copy materials when needed and appropriate (i.e.: to support paper-based enrollment by sites).
7) Answering patient questions pre- and post-enrollment
8) Administering the study website (PHR)
9) Maintaining security and integrity of collected data

13.3. NET-PRO Steering Committee

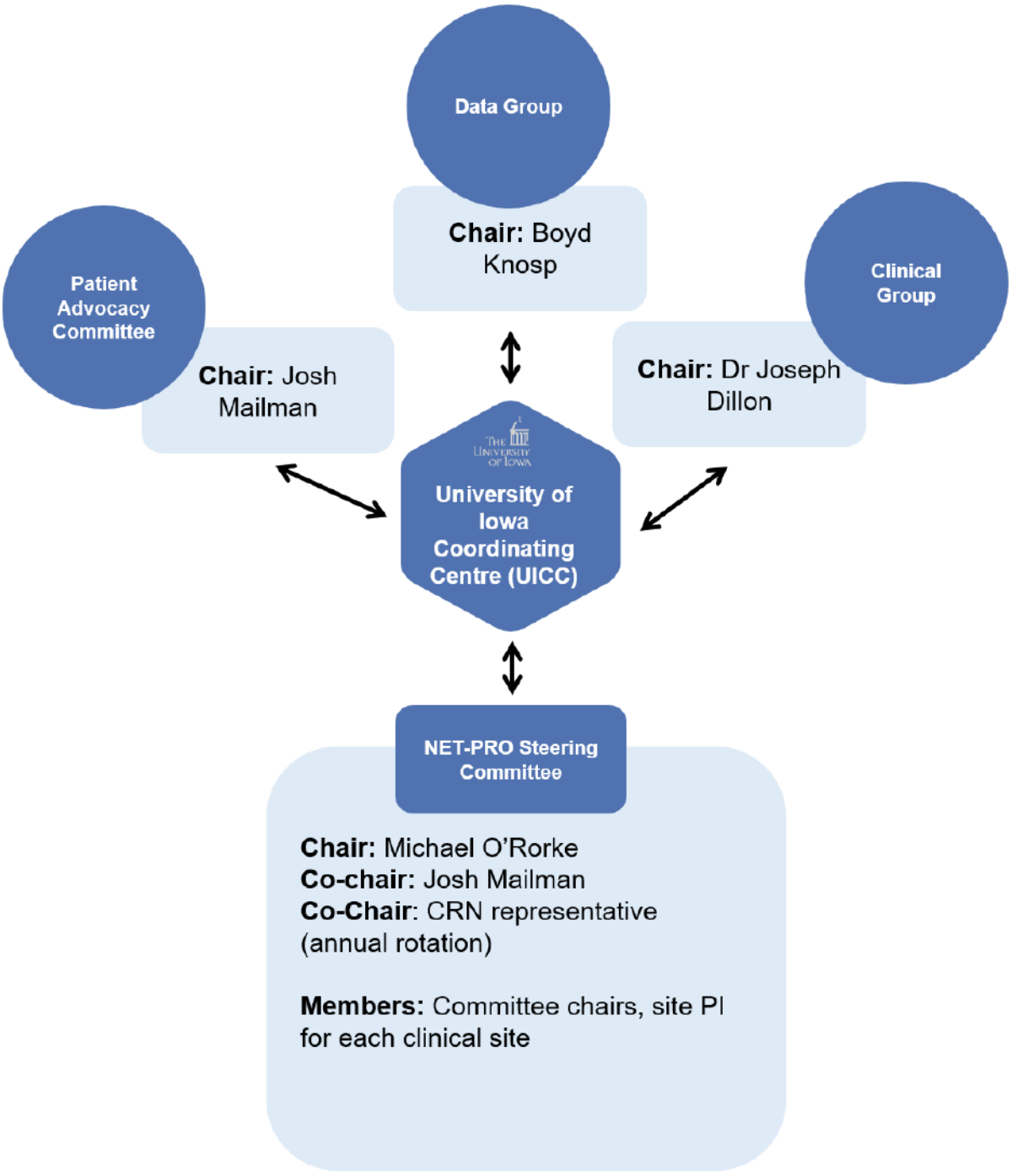
The Steering Committee for the NET-PRO study is responsible for the direction, coordination, oversight, feasibility and successful completion of the NET-PRO study. The steering committee is co-chaired by the PI (Dr. O'Rorke), Mr. Mailman (lead patient advocate), and an annual rotating co-chair from a non-GPC site (i.e.: OneFlorida, PaTH, and STAR). The Steering Committee membership includes the chair of each stakeholder group, and all of the participating PCORnet partner site PIs (or representatives) (Figure 5).

13.3.1. Primary functions of the Steering Committee

The steering committee members advise on long-term strategies in support of program objectives, ensuring program objectives are being adequately addressed, and that the project remains under control. In practice these responsibilities are carried out by performing the following functions:

- Reviewing and providing final sign-off on major project elements such as key study documents, including but not limited to, the protocol, site materials (i.e.: patient materials, consent documentation, newsletters and updates to study partners etc.), Data Management Plan, the Statistical Analysis Plan, and the study accrual and retention metrics in compliance with Sponsor requirements
- Prioritization of project objectives and outcomes as identified in the study protocol
- Monitoring and review of project status, including oversight of project milestones over the course of the study to ensure progress on specific aims, objectives and deliverables are being met
- Ensuring that strategies to address potential threats to the project's success have been identified, and ameliorated, and that these risks are regularly assessed (i.e.: project management and quality assurance practices, study accrual, retention and attrition, aspects of data quality, data transfers and safeguarding of the same)
- Providing assistance to the project when required including resolution of project conflicts and disputes, reconciling differences of opinion and approach
- Ensuring stakeholder committee engagement in essential study functions
- Reviewing joint activities, leveraging lessons learned, and planning dissemination activities
- Reviewing and approving final draft manuscripts prior to submission to peer-review journals

Figure 5: Overall governance structure of the NET-PRO study


Data Group
Chair: Boyd Knosp
Patient Advocacy Committee
Chair: Josh Mailman
Clinical Group
Chair: Dr Joseph Dillon
University of Iowa Coordinating Centre (UICC)
NET-PRO Steering Committee
Chair: Michael O'Rorke
Co-chair: Josh Mailman
Co-Chair: CRN representative (annual rotation)
Members: Committee chairs, site PI for each clinical site

13.4. Role and Purpose of the Stakeholder Committees

To ensure participation and input from a full range of stakeholders into the design and conduct of the NET-PRO study, several committees and groups have been convened to serve as the project decision-making bodies, with patient advocates serving on or interacting with each (Figure 4).

NET-PRO Stakeholder Committees – Summary of Responsibilities

Steering Committee	
Authorities/responsibilities	Responsible for providing guidance and oversight for the overall conduct of the study.
Leadership	Co-chaired by Dr. O'Rorke, Mr. Mailman, and an annual rotating co-chair from OneFlorida, PaTH, and STAR.
Membership	Site PIs from the 14 enrolling sites Chairs of the patient, clinician, and data groups UICC reps: Gryzlak, Rudzianski, McDowell, Riley
Structure	Periodic webinars as needed (every 1-2 months); agenda is drafted by the UICC but reviewed and approved by leadership prior to sending to membership.
Interaction with other decision-making bodies	Provides input to and reports feedback from the committees or groups they respectively chair.
Patient Advocacy Committee (PAC)	
Authorities/responsibilities	Provide input and advice on study design and protocol, sampling for focus groups and recruitment, informs and reviews patient and study materials, and advises on developed features and functionality of the NET PHR.
Leadership	Chaired by Josh Mailman
Membership	Leadership and staff from each of the four patient advocacy organizations UICC reps: O'Rorke, Chrischilles, Gryzlak, Rudzianski
Structure	Periodic webinars as needed (every 1-2 months); agenda is drafted by the UICC but reviewed and approved by the chair prior to sending to membership.
Interaction with other decision-making bodies	UICC provides relevant updates to the PAC and is advised by the PAC on aspects of the study described above.
Clinician Group	
Authorities/responsibilities	Reviews the study protocol to ensure feasibility and to optimize efficiencies around standardizing data items for disease progression and chart extraction.
Leadership	Chaired by Joe Dillon
Membership	Clinical leads and support staff from each enrolling site UICC reps: O'Rorke, Chrischilles, Gryzlak, Rudzianski, McDowell
Structure	Periodic webinars as needed (every 1-2 months); agenda is drafted by the UICC but reviewed and approved by the chair prior to sending to membership.
Interaction with other decision-making bodies	UICC provides relevant updates to the Clinician Group and is advised by the Clinician Group on aspects of the study described above.
Data Group	
Authorities/responsibilities	Develop protocols in support of data extraction and data sharing activities.

Leadership	Chaired by Boyd Knosp
Membership	Informatics leads and support staff from each enrolling site UICC reps: O'Rorke, Chrischilles, Gryzlak, Rudzianski, McDowell
Structure	Periodic webinars as needed (every 1-2 months); agenda is drafted by the UICC but reviewed and approved by the chair prior to sending to membership.
Interaction with other decision-making bodies	UICC provides relevant updates to the Data Group and is advised by the Clinician Group on aspects of the study described above.
UI Coordinating Center (UICC)	
Authorities/responsibilities	Maintaining study timelines, troubleshooting emergent issues, compliance with established agreements and Institutional Review Board (IRB) guidance and oversight, communications amongst all parties, including PCORnet, production of study materials, implementation of data collection protocols, development and testing of the NET PHR tool, and development and dissemination of periodic study progress reports to all stakeholders.
Leadership	Chaired by O'Rorke
Membership	Chrischilles, McDowell, Gryzlak, Rudzianski, Riley, Zamba, Hourcade, Knosp, Mueller, Ortman, Crooks, Dillon
Structure	Weekly calls; agenda is set by Gryzlak with input from others.
Interaction with other decision-making bodies	UICC provides administrative support for all other groups and committees; maintains communications between and across all stakeholders. Implements decisions of each respective group.
Interaction with other decision-making bodies	UICC provides administrative support for all other groups and committees; maintains communications between and across all stakeholders. Implements decisions of each respective group.

13.4.1. NET-PRO Stakeholder Committees – Membership and Affiliations

Steering Committee		
Affiliation	**Forename**	**Surname**
University of Iowa Coordinating Center	Betsy	Chrischilles
University of Texas Southwestern Medical Center	Lindsay	Cowell
Vanderbilt University Medical Center	Satya	Das
Medical University of South Carolina	Toros	Dincman
University of Michigan	Tobias	Else
University of Pittsburgh Medical Center	David	Geller
University of Florida	Yi	Guo
University of Kansas Medical Center	Mei	Liu
NorCal CarciNET Community	Josh	Mailman
University of Iowa Coordinating Center	Michael	O'Rorke
University of North Carolina at Chapel Hill	Hanna	Sanoff
University of Utah	Heloisa	Soares
Ohio State University	Vineeth	Sukrithan
Medical College of Wisconsin	Bradley	Taylor

Patient Advocacy Committee (PAC)		
Affiliation	Forename	Surname
Healing NET Foundation	Cindy	Lovelace
University of Iowa Coordinating Center	Betsy	Chrischilles
Neuroendocrine Cancer Awareness Network (NCAN)	Maryann	Wahmann
Neuroendocrine Tumor Research Foundation	Elyse	Gellerman
NorCal CarciNET Community	Josh	Mailman
University of Iowa Coordinating Center	Michael	O'Rorke

Clinician Group		
Affiliation	Forename	Surname
University of Texas Southwestern Medical Center	Muhammed	Beg
University of Iowa	Chandrikha	Chandrasekharan
Ohio State University	Gwen	Christenson
Medical University of South Carolina	Toros	Dincman
University of Michigan	Tobias	Else
Medical College of Wisconsin	Thomas	Gamblin
University of Pittsburgh Medical Center	David	Geller
Vanderbilt University Medical Center	Kamran	Idrees
University of Florida	Brian	Ramnaraign
University of North Carolina at Chapel Hill	Hanna	Sanoff
University of Utah	Heloisa	Soares
University of Kansas Medical Center	Weijing	Sun
Allina Health	Michaela	Tsai

Data Group		
Affiliation	**Forename**	**Surname**
Informatics Leads		
University of Florida	Jiang	Bian
University of Kansas Medical Center	Sravani	Chadaka
University of Iowa Coordinating Center	Mark	Crooks
Vanderbilt University Medical Center	Hillary	Duckham
University of Utah	Ram	Gouripeddi
University of North Carolina at Chapel Hill	Michael	Kappelman
University of Michigan	Sarah	Maidlow
Allina Health	Narayana	Mazumder
University of Pittsburgh Medical Center	Richard	Morgan
Medical College of Wisconsin	Kristen	Osinski
University of Texas Southwestern Medical Center	Phillip	Reeder
Medical University of South Carolina	Patricia	Rudisill
Informatics Staff		
University of Texas Southwestern Medical Center	Shiby	Antony
University of Kansas Medical Center	Kelechi	Anuforo
University of Michigan	John	Brussolo
University of Texas Southwestern Medical Center	Suleyman	Goksu
University of Michigan	David	Hanauer
University of Utah	Reid	Holbrook
University of Michigan	Siqing	Hu
University of North Carolina at Chapel Hill	Kellie	Walters
University of Iowa	Michael	Wright

13.5. Voting at committee meetings

During the course of committee meetings, the need may arise to vote on a particular issue. For issues requiring a vote, one vote per member will be allowed. Voting by e-mail will be allowed at the discretion of the Co-Chairs (i.e.: in the event that a quorum is not present during the committee meeting, or a key member is absent). Voting by representatives of the absentee (i.e.: project managers/study coordinators of the PI) are not permissible.

13.6. Attendance at committee meetings

13.6.1. Co-Chairs

On committees with more than one Chair, both Chairs are expected to be at all meetings. In the event that one of the Co-Chairs is unable to attend, the other Co-Chair will preside over the meeting. In the event that both Chairs are unable to attend a meeting, an alternate Chair may be appointed at the discretion of the Co-Chairs, or the meeting will be cancelled.

13.6.2. Members

It is expected that members will attend all scheduled committee meetings. Committee meetings will be held via ZOOM, allowing for maximum participation. However, in the event that a member is not able to attend, s/he should inform the chair(s). A designee may attend the meetings in place of the member at the discretion of the chair(s).

13.7. Resolution of disputes

The Steering Committee will facilitate any disputes arising from other stakeholder groups. If disputes arise within the Steering Committee, all members will have the opportunity to address their concerns and if a decision cannot be mutually agreed to, the Steering Committee will vote. If a dispute arises in any of the stakeholder groups, these disputes will be communicated to the Steering Committee for discussion. Any member of the stakeholder group can present their concerns to the Steering Committee, who will vote on the issue as appropriate.

14. STUDY RESPONSIBILITIES

14.1. Investigator Responsibility/Performance

The UICC agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with the protocol; accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of this prospective cohort study. The UICC will provide current copies of the study protocol to all clinical sites and other site personnel responsible for study conduct.

14.2. Site communications

There will be monthly written communications (NET-PRO newsletter) and a monthly Zoom call between study site investigators, the UICC study coordinator and PI, and other relevant personnel. These site meetings will be in parallel with our quarterly steering committee calls and weekly UICC meetings.

14.3. Study documentation

Study documentation includes all electronic and paper forms, data entry and monitoring forms (i.e.: REDCap pro forma or baseline survey), sponsor-investigator correspondence, and regulatory documents (i.e.: signed protocol and amendments, IRB correspondence and approval, invoices and budget records). By signing the protocol, the PI acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to UI appropriate parties by the UICC investigator upon request. It will also be made available at the investigator's site by UICC upon request for inspection, copying, review, and audit at reasonable times by representatives of UICC or responsible government agencies as required by law.

14.4. Protocol Deviations

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the study according to the investigational plan.
Investigators are required to obtain approval from the UI PI before initiating deviations from the investigational plan or protocol. Such approval will be documented in writing and maintained in study files. No deviations from the protocol of any type will be made without complying with all the IRB's established procedures. Planned deviations will be reported to the UICC and IRB amendments/modifications sought as appropriate.

14.5. Publication policies

The PCORnet Publications Policy applies to all scientific publications based on data from the PCORnet CDM. As such, this policy will be applied to the NET-PRO study and all publications, abstracts, and presentations associated with the project. All authors must meet the criteria for authorship as outlined by the International Committee of Medical Journal Editors (ICJME). First and last authors will be determined before any work begins on the paper. Any study manuscript that might also be considered a foundational or PCORnet-wide publication will be shared with the PCORnet Steering Committee in advance, and members invited to join as co-authors.

14.5.1. General guidance for the assignment of authorship:

•For papers that include both clinical and data expertise, each site will get to select one contributing author and one collaborator
•Papers that are data-focused will include one author per site (the site Informatics lead or other selected data personnel)

15. PROTECTION OF HUMAN SUBJECTS

We will follow the Department of Health and Human Services (DHHS) regulations for the Protection of Human Research Subjects based on established, internationally recognized ethical principles, to safeguard the rights and welfare of participants in the NET-PRO study.

15.1. Risk to Human Subjects

15.1.1. Study Procedures, Materials and Potential Risks

A potential risk to subjects is to their privacy and confidentiality should our efforts to protect this be inadvertently breached. There is the potential that participants will experience some discomfort from responding to questions about their health and health care. Any unauthorized disclosure of identifiable data may also induce the feeling of distress. However, this is not an intervention study, and study subjects may choose to not answer any questions or withdraw from the study at any time.

15.1.2. Adequate Protection against Risks

Several approaches to minimizing risks to subjects will be implemented:
To mitigate against feeling of discomfort when responding to survey questions:

- Subjects will be advised that they are free to skip any survey questions they prefer not to answer (online survey questions also have a radial 'reset' button, so respondents can change their mind, and remove/change their response for any particular question).
- Subjects are free to withdraw from the study at any time.
- Subjects will be provided time to read the consent form fully, and discuss any questions with the research staff, their family and their doctor.

To mitigate against unauthorized disclosures:

- All investigators are committed to the protection of confidentiality and privacy in all studies and data management functions.
- All sites appreciate the unique aspects of rare diseases that require extra attention in protecting the confidentiality of subjects as related specifically to their data.
- The study PHR portal is secured with a certificate issued by ITS. Portal accounts are only accessible with unique credentials.
- All portal data are stored in a IT-managed database, only accessible to IT administrators and select members of the research team who need such access
- Study data will be maintained on password protected IT managed databases and network drives and research staff will be directed to not download data onto any laptops or mobile devices.
- Data sharing between the UICC and study sites will occur via an institutionally supported secure platform (like OneDrive).

15.1.3. Potential Benefits to Patients

There is no direct benefit to the participants of the study. However, the results of this study will permit the development of comparative effects of different treatment regimens (and combinations) for patients with NETs, and may highlight optimal care pathways from the patient's perspective. This evidence is currently lacking. Data from this project will therefore establish the patient perspective on managing NETs, and provide clinicians helpful information to guide treatment recommendations on which treatments to use first, and how that may affect future treatment options, and their comparative effectiveness in real-world care settings; all of which have been deemed important by patients.

15.1.4. Representativeness of the diversity of the patient population

The Surveillance Epidemiology and End Results (SEER) database currently provides the most representative, population-based, demographic data on NETs in the United States. A recent retrospective analysis from this database examining the geographic (rural vs urban) and sociodemographic features of 53,034 NET patients (all ages and stages) diagnosed between 1973 to 2015[61] identified that 90% (47,517) of these individuals resided in urban vs rural areas. The mean age of patients at diagnosis was 58 years (60 years amongst rural patients) and the majority (34,963/66%)

were non-Hispanic white race (83% rural vs 64% urban). There were also higher proportions of advanced stage disease (regional vs distant metastases) in rural versus urban patients [57].
The baseline demographic characteristics of NET patients in this planned PCORnet study are relatively consistent with those previously reported in population-based registries. As can be seen in Table 9, across the 14 participating PCORnet datamarts in our planned prospective cohort analysis (including 4 geographically dispersed CRN's STAR, OneFlorida, GPC and PATH), the majority of patients we will recruit will be non-Hispanic white (2595/3010 or 86%). Whilst this proportion is perhaps higher than what would be expected nationally, it is not dissimilar from the 86% Caucasian NET population (mean age 56 years) observed in an earlier analysis of 7 National Comprehensive Cancer Network institutions [58], which is perhaps not surprising given 12 out of our 14 PCORnet partners are affiliated with an NCI-designated comprehensive Cancer Center and many include a rural catchment area. Women and men will be recruited into the study in proportion to their frequency in the affected patient groups. This means that slightly more women will be recruited than men. We will work with our affiliated CTSAs and NCI-designated cancer center clinical research cores to implement rigorous coordination and navigation support to encourage participation by disadvantaged individuals. It is our intention to also enroll NET patients through our established five NET patient advocacy organizations across North America to boost the ethnic diversity of the NET patients our cohort will likely enroll.

Table 9: Estimated Final Racial/Ethnic and Gender Enrollment Table

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	-	-	-
Asian	6	8	14
Black/African American	135	159	294
Hawaiian/Pacific Islander	-	-	-
White	1194	1401	2595
Multirace	-	-	-
Other	49	58	107
Ethnicity	Male (N)	Female (N)	Total (N)
Hispanic (Latino/Latina)	41	49	90
Non-Hispanic	1343	1577	2920

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APPENDIX A: NET diagnosis codes (ICD-9/10), ICD-O-3 codes, and histology codes

ICD-O-3 Site Codes

SITE	CODE	DESCRIPTION
GEP	C16.0	Cardia, NOS
GEP	C16.1	Fundus of stomach
GEP	C16.2	Body of stomach
GEP	C16.3	Gastric antrum
GEP	C16.4	Pylorus
GEP	C16.5	Lesser curvature of stomach NOS
GEP	C16.6	Greater curvature of stomach NOS
GEP	C16.8	Overlapping lesion of stomach
GEP	C16.9	Stomach, NOS
GEP	C17.0	Duodenum
GEP	C17.1	Jejunum
GEP	C17.2	Ileum
GEP	C17.3	Meckels diverticulum
GEP	C17.8	Overlapping lesion of small intestine
GEP	C17.9	Small intestine, NOS
GEP	C18.0	Cecum
GEP	C18.1	Appendix
GEP	C18.2	Ascending colon
GEP	C18.3	Hepatic flexure of colon
GEP	C18.4	Transverse colon
GEP	C18.5	Splenic flexure of colon
GEP	C18.6	Descending colon
GEP	C18.7	Sigmoid colon
GEP	C18.8	Overlapping lesion of colon
GEP	C18.9	Colon, NOS
GEP	C19.9	Rectosigmoid junction
GEP	C20.9	Rectum, NOS
GEP	C25.0	Head of pancreas
GEP	C25.1	Body of pancreas
GEP	C25.2	Tail of pancreas
GEP	C25.3	Pancreatic duct
GEP	C25.4	Islets of Langerhans
GEP	C25.7	Other specified parts of pancreas
GEP	C25.8	Overlapping lesion of pancreas
GEP	C25.9	Pancreas, NOS
GEP	C26.0	Intestinal tract, NOS
GEP	C26.8	Overlapping lesion of digestive system
GEP	C26.9	Gastrointestinal tract, NOS
LUNG	C34.0	Main bronchus
LUNG	C34.1	Upper lobe, lung
LUNG	C34.2	Middle lobe, lung

LUNG	C34.3	Lower lobe, lung
LUNG	C34.8	Overlapping lesion of lung
LUNG	C34.9	Lung, NOS

ICD-O-3 Histology Codes

CODE	DESCRIPTION
8150	Pancreatic endocrine tumor, malignant
8151	Insulinoma, malignant
8152	Glucagonoma, malignant
8153	Gastrinoma, malignant
8155	Vipoma, malignant
8156	Somatostatinoma, malignant
8157	Enteroglucagonoma, malignant
8240	Carcinoid tumor, NOS
8241	Enterochromaffin cell carcinoid
8242	Enterochromaffin-like cell tumor, malignant
8246	Neuroendocrine carcinoma, NOS
8249	Atypical carcinoid tumor

ICD-9 and -10 Codes

TYPE	SITE	CODE	DESCRIPTION
ICD-9	GEP	209.00	Malignant carcinoid tumor of the small intestine, unspecified portion
ICD-9	GEP	209.01	Malignant carcinoid tumor of the duodenum
ICD-9	GEP	209.02	Malignant carcinoid tumor of the jejunum
ICD-9	GEP	209.03	Malignant carcinoid tumor of the ileum
ICD-9	GEP	209.10	Malignant carcinoid tumor of the large intestine, unspecified portion
ICD-9	GEP	209.11	Malignant carcinoid tumor of the appendix
ICD-9	GEP	209.12	Malignant carcinoid tumor of the cecum
ICD-9	GEP	209.13	Malignant carcinoid tumor of the ascending colon
ICD-9	GEP	209.14	Malignant carcinoid tumor of the transverse colon
ICD-9	GEP	209.15	Malignant carcinoid tumor of the descending colon
ICD-9	GEP	209.16	Malignant carcinoid tumor of the sigmoid colon
ICD-9	GEP	209.17	Malignant carcinoid tumor of the rectum
ICD-9	GEP	209.23	Malignant carcinoid tumor of the stomach
ICD-9	GEP	209.25	Malignant carcinoid tumor of foregut, not otherwise specified
ICD-9	GEP	209.26	Malignant carcinoid tumor of midgut, not otherwise specified
ICD-9	GEP	209.27	Malignant carcinoid tumor of hindgut, not otherwise specified
ICD-9	GEP	157.4	Malignant neoplasm of islets of langerhans
ICD-10	GEP	C7A.01	Malignant carcinoid tumors of the small intestine
ICD-10	GEP	C7A.010	Malignant carcinoid tumor of the duodenum
ICD-10	GEP	C7A.011	Malignant carcinoid tumor of the jejunum
ICD-10	GEP	C7A.012	Malignant carcinoid tumor of the ileum

ICD-10	GEP	C7A.019	Malignant carcinoid tumor of the small intestine, unspecified portion
ICD-10	GEP	C7A.020	Malignant carcinoid tumor of the appendix
ICD-10	GEP	C7A.021	Malignant carcinoid tumor of the cecum
ICD-10	GEP	C7A.022	Malignant carcinoid tumor of the ascending colon
ICD-10	GEP	C7A.023	Malignant carcinoid tumor of the transverse colon
ICD-10	GEP	C7A.024	Malignant carcinoid tumor of the descending colon
ICD-10	GEP	C7A.025	Malignant carcinoid tumor of the sigmoid colon
ICD-10	GEP	C7A.026	Malignant carcinoid tumor of the rectum
ICD-10	GEP	C7A.029	Malignant carcinoid tumor of the large intestine, unspecified portion
ICD-10	GEP	C7A.092	Malignant carcinoid tumor of the stomach
ICD-10	GEP	C7A.094	Malignant carcinoid tumor of the foregut, unspecified
ICD-10	GEP	C7A.095	Malignant carcinoid tumor of the mid-gut, unspecified
ICD-10	GEP	C7A.096	Malignant carcinoid tumor of the hindgut, unspecified
ICD-10	GEP	C25.4	Malignant neoplasm of endocrine pancreas
ICD-9	LUNG	209.21	Malignant carcinoid tumor of the bronchus and lung
ICD-10	LUNG	C7A.090	Malignant carcinoid tumor of the bronchus and lung
ICD-9	AMBIGUOUS	209.20	Malignant carcinoid tumor of unknown primary site
ICD-9	AMBIGUOUS	209.29	Malignant carcinoid tumor of other sites
ICD-9	AMBIGUOUS	209.30	Malignant poorly differentiated neuroendocrine carcinoma, any site
ICD-10	AMBIGUOUS	C7A.00	Malignant carcinoid tumor of unspecified site
ICD-10	AMBIGUOUS	C7A.098	Malignant carcinoid tumors of other sites
ICD-10	AMBIGUOUS	C7A.1	Malignant poorly differentiated neuroendocrine tumors
ICD-10	AMBIGUOUS	C7A.8	Other malignant neuroendocrine tumors

APPENDIX B: NET Computable Phenotype – technical specification (SAS code)

NET-PRO Computable Phenotypes and Approaches for Recruitment

Overview

The NET-PRO recruitment approach is similar to the ADAPTABLE pragmatic clinical trial. Teams at each site will contact potentially eligible patients by electronic/ground mail or will approach them in person at the clinic. Understandably, each site may have a preference for a particular form of contact that will optimize their enrollment.

In order to accommodate these varied approaches, we have developed a multi-pronged approach that leverages existing data sources to identify potential enrollees. They include:

- Phenotypes that use diagnosis codes in electronic health record (EHR) data in clinical data research warehouses or most recent PCORnet Common Data Model (CDM) refresh.
    - A phenotype is provided for using these data for low-touch recruitment: 'High positive predictive value phenotype'
    - A phenotype is provided for use when resources can confirm eligibility first, e.g. chart review or in clinic recruitment: "High sensitivity phenotype"

- Phenotypes that use data from institutional tumor registries
    - These data have a typical lag time of one year (depending on the institution), but an excellent phenotype is provided for using this data source as part of a low-touch recruitment strategy

This document describes the advantages and disadvantages of each data source and provides technical specifications for computable phenotypes that are appropriate for different recruitment strategies. For example, study sites that plan to recruit from their clinics or conduct chart reviews before recruiting may find it most effective to use a highly sensitive phenotype to identify potential participants and verify eligibility through chart review or in the context of a clinic visit; staff could screen out the false positives that would be flagged with such a phenotype. Sites that plan to recruit by 'low-touch' via e-mail or ground mail *without prior chart review to confirm eligibility*, however, will need a phenotype with high positive predictive value (PPV) to maximize the possibility that contacted patients actually have a neuroendocrine/carcinoid tumor (NET) diagnosis. (There is generally a trade-off between PPV and sensitivity; higher PPV is associated with lower sensitivity and higher sensitivity is associated with lower PPV.)

The validity of each computable phenotype is also discussed. Where available, results from validation studies performed at the University of Iowa Coordinating Center (UICC) are provided. Each site is encouraged to conduct its own validation studies, and the UICC can provide assistance for this based on its experience.

It is useful to remember that prospective enrollees will confirm their eligibility by responding to eligibility questions early in the enrollment process. This will serve as a final check in case the phenotype mistakenly identifies someone as having a qualifying NET. The recruiting materials have been worded carefully to minimize the possibility that a potential enrollee is alarmed to be contacted for a study focused on NETs.

Following the ADAPTABLE example, the UICC will continue to develop and refine these computable phenotypes to maximize their performance. This will happen through the life of the project.

Phenotypes that use diagnosis codes in electronic health record (EHR) data (research warehouse or CDM)

Many research institutions maintain medical record and billing data in a clinical research data warehouse (CRDW) that contains structured information on diagnoses and procedures. The PCORnet Common Data Model (CDM) is often populated by this source data. Computable phenotypes can be applied to the CDM or the underlying CRDW (which may be updated more frequently than the CDM).

An advantage of CRDW data is that patient data are structured by clinical or billing staff in real-world settings using the International Classification of Diseases (ICD) system (9th and 10th editions). While data are generally high quality, errors can occur. Also, diagnoses can change or be refined over time, and these changes are not always clearly documented. Some ICD codes are ambiguous with regard to tumor site (see the ICD codes labeled AMBIGUOUS in the Appendix). It is also important to note that the date a cancer ICD diagnosis code first appears on an encounter cannot necessarily be considered to be the date of cancer diagnosis; it generally lags behind the true diagnosis date. That lag in time can be substantial, especially if a patient was originally diagnosed or treated at another institution.

Phenotype for low-touch recruitment (without prior chart review or clinic visit): 'High positive predictive value phenotype'

- This phenotype was designed to maximize positive predictive value so it would be appropriate for recruitment via electronic or ground mail without prior confirmation of eligibility through chart review or clinic visit.
- The phenotype identifies patients with at least one ICD code in their electronic medical record (EMR)/billing records that specifies a GEP or lung NET. To mitigate the effect of incidental coding errors, at least two NET codes (which may or may not specify the site of the NET; see code descriptions in the Appendix) must be present, and the patient's first and last NET code must be more than 30 days apart.
- The first NET code for a patient is presently required to be dated on or after 01JAN2019. This increases the likelihood that the patient's NET diagnosis will be in the required 2019-2023 study window.
- This phenotype should be applied for all patients who are not known to have died.
- The lung NET High PPV phenotype had a PPV of 92% and the GEP NET High PPV phenotype had a PPV of 90-98% when compared with chart review at The University of Iowa. The estimated sensitivity was 59.0% and 45.2%, respectively (see Technical Details Box 1 for further information)

Technical Details Box 1. Performance of Phenotypes that use Diagnosis Codes in EHR Data (research warehouses or CDM)

1. High PPV Phenotype

Estimating the Positive Predictive Value of the High PPV Phenotype

The University of Iowa (UI) team conducted a chart review to validate a 15% random sample of cases identified with this phenotype over a five-year period. This was done separately for lung (N = 13) and GEP NETs (N = 51).

- Of the 13 cases identified by the phenotype as having lung NETs, 12 had diagnoses that were unequivocally confirmed on chart review (i.e., the chart described pathological confirmation of a lung NET). This corresponds to a PPV of 92%. The single case that was not confirmed had a pancreatic NET.
- Of the 51 cases identified by the phenotype as GEP NETs, 46 had diagnoses that were unequivocally confirmed on chart review. This corresponds to a PPV of 90%. There were two other cases that had pathological evidence of a NET with an unknown primary location. An additional two cases had a suspected NET with no pathological confirmation on the chart. If these four cases are considered "hits", PPV increases to 98%. For the one remaining case, the chart contained contradictory and ambiguous information about the patient's tumor.

Estimating the Sensitivity of the High PPV Phenotype

The UI team used the University of Iowa Hospitals and Clinics (UIHC) institutional tumor registry to identify cohorts of patients with confirmed GEP and lung NETs (N = 166 and N = 39, respectively). These cases were diagnosed over a two-year period. The phenotype was applied to these cohorts to obtain a measure of sensitivity.

- Of the 39 cases with lung NETs, 23 cases were identified with the phenotype. This corresponds to sensitivity of 59.0%.
- Of the 166 cases with GEP NETs, 75 cases were identified with the phenotype. This corresponds to sensitivity of 45.2%.

2. High Sensitivity Phenotype

Estimating the Sensitivity of the High Sensitivity Phenotype

As above, the UI team used the UIHC institutional tumor registry to identify separate cohorts of patients with confirmed GEP and lung NETs (N = 166 and N = 39, respectively). The high sensitivity phenotype was applied against these cohorts to obtain a measure of sensitivity.

- Of the 39 cases with lung NETs, 33 cases were identified with the phenotype. This corresponds to sensitivity of 84.6%.
- Of the 166 cases with GEP NETs, 148 cases were identified with the phenotype. This corresponds to sensitivity of 89.2%.

Implementation for high PPV phenotype

Definitions

```
%LET GEPCODES10 =
'C7A.01','C7A.010','C7A.011','C7A.012','C7A.019','C7A.020','C7A.021','C7A.022','C7A.023',
'C7A.024','C7A.025','C7A.026','C7A.029','C7A.092','C7A.094','C7A.095','C7A.096','C25.4';
%LET GEPCODES09 = '209.00','209.01','209.02','209.03','209.10','209.11','209.12','209.13','209.14',
'209.15','209.16','209.17','209.23','209.25','209.26','209.27','157.4';

%LET LUNGCODES10 = 'C7A.090';
%LET LUNGCODES09 = '209.21';

%LET ambiguousNET10 = 'C7A.00','C7A.098','C7A.1','C7A.8';
%LET ambiguousNET09 = '209.20','209.29','209.30';
```

Criterion	Logic/Notes	Defined
1. At least one ICD code that specifies a GEP or lung NET	Basis: CDM DIAGNOSIS table or source data equivalent	At least one record for each patient: Lung NETs (DX_TYPE = '09' AND (DX IN (&LUNGCODES09))) OR (DX_TYPE = '10' AND (DX IN (&LUNGCODES10))); GEP NETs (DX_TYPE = '09' AND (DX IN (&GEPCODES09))) OR (DX_TYPE = '10' AND (DX IN (&GEPCODES10)));

2. Patient's first NET code dated on or after 01JAN2019	Basis: CDM DIAGNOSIS table or source data equivalent	Define first_net_dt: <u>Lung NETs</u> [set of lung/ambiguous site NET records] → (DX_TYPE = '09' AND (DX IN (&LUNGCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&LUNGCODES10,&ambiguousNET10))); <u>GEP NETs</u> [set of GEP/ambiguous site NET records] → (DX_TYPE = '09' AND (DX IN (&GEPCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&GEPCODES10,&ambiguousNET10))); first_net_dt = of the set of lung/GEP NET records for each patient, min(admit_date) *** first_net_dt >= '01JAN2019'd
3. Days between patient's first and last NET code is greater than 30 days	Basis: CDM DIAGNOSIS table or source data equivalent	Define first_net_dt and last_net_dt: <u>Lung NETs</u> [set of lung/ambiguous site NET records] → (DX_TYPE = '09' AND (DX IN (&LUNGCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&LUNGCODES10,&ambiguousNET10))); <u>GEP NETs</u> [set of GEP/ambiguous site NET records] → (DX_TYPE = '09' AND (DX IN (&GEPCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&GEPCODES10,&ambiguousNET10))); first_net_dt = of the set of lung/GEP NET records for each patient, min(admit_date) last_net_dt = of the set of lung/GEP NET records for each patient, max(admit_date) ***

		if intck('day',first_net_dt,last_net_dt) > 30

Phenotype for use when resources can confirm eligibility first, e.g. chart review or in clinic recruitment: "High sensitivity phenotype"

- This phenotype was designed to maximize sensitivity so it would be appropriate for clinic recruitment or chart confirmation prior to e-mail or ground mail recruitment.
- The phenotype relaxes the criteria described above and identifies patients with at least one ICD code in their EMR/billing records that specifies a NET (see codes in the Appendix).
- Relaxing the number of codes required resulted in a sensitivity of 84.6% (lung) and 89.2% (GEP)(See Technical Details Box 1).

Implementation for high sensitivity phenotype

Criterion	Logic/Notes	Defined
1. At least one ICD code that specifies a NET	Basis: CDM DIAGNOSIS table or source data equivalent	At least one record for each patient: Lung NETs (DX_TYPE = '09' AND (DX IN (&LUNGCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&LUNGCODES10,&ambiguousNET10))); GEP NETs (DX_TYPE = '09' AND (DX IN (&GEPCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&GEPCODES10,&ambiguousNET10)));
2. Patient's first NET code dated on or after 01JAN2019		Lung NETs [set of lung/ambiguous site NET records] → (DX_TYPE = '09' AND (DX IN (&LUNGCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&LUNGCODES10,&ambiguousNET10))); GEP NETs [set of GEP/ambiguous site NET records] → (DX_TYPE = '09' AND (DX IN (&GEPCODES09,&ambiguousNET09))) OR (DX_TYPE = '10' AND (DX IN (&GEPCODES10,&ambiguousNET10)));

		first_net_dt = of the set of lung/GEP NET records for each patient, min(admit_date) *** first_net_dt >= '01JAN2019'd

Adding Data from Institutional Tumor Registries to Expand Low-Touch Recruitment

All hospitals at NET-PRO participating sites are accredited by the American College of Surgeons' Commission on Cancer (CoC). To maintain this accreditation, they are required to maintain a tumor registry. These registries identify tumors with malignant behavior and abstract their clinical characteristics, patient demographics, and treatment. This work is performed in compliance with the standards developed by the North American Association of Central Cancer Registries (NAACCR). Tumor registries document incident, primary cancers. Cases are documented by trained abstractors who gather information directly from patient medical records. The information is considered to be of high quality; **registry records of NETs can be regarded with high confidence**. Patients identified through this source could be approached for recruitment through e-mail or similar methods without necessitating prior chart review or clinic visit to confirm eligibility . Documentation is extensive and complies with NAACCR standards. Cancer site and histology are coded according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). These standards allow for implementation of consistent case criteria across study sites.

When present in tumor registries, the diagnosis can be considered confirmed. However, there is usually a lag between diagnosis and case abstraction; cases are typically abstracted 4-6 months after diagnosis, and it can take more than a year before a registry abstracts all eligible cases for a given diagnostic year. Another limitation is that tumor registries generally abstract only those cancers that are diagnosed or treated at their respective institutions. Patients who are seen for tests only, a "second opinion", or other consultation may not be abstracted. So although documentation of a case can be regarded with high confidence, there are likely other eligible cases whose records are not abstracted. At the University of Iowa Hospitals and Clinics (UIHC), we have found that about two-thirds of eligible NET cases are found in tumor registry records. We have also found that about 45-59% of patients detected with the EHR High PPV phenotype (described in the previous section) are found in the tumor registry records. Hence, tumor registry data can be potentially useful to increase the number of patients for low touch recruitment, and this phenotype could be used in conjunction with the High PPV phenotype to increase eligible cases

<u>Phenotype for using tumor registry data as part of a low-touch recruitment strategy</u>

- This computable phenotype selects those patients with primary lung or GEP NETs diagnosed between 2019 and 2023 who are 18 years of age and older at diagnosis.
- Cases have been documented by trained abstractors who gather information directly from patient medical records. The information is considered to be of high quality.
- The unique patients identified by the tumor registry algorithm can be directly recruited without need for chart confirmation or clinic visit.

Implementation

Criterion	Logic/Notes	Defined
1. Lung/GE	Basis: CDM	Lung tumor site PRIMARY_SITE_N400 in ('C340','C341','C342','C343','C348','C349');

Criterion	Logic/Notes	Defined
P tumor site	TUMOR table or source data equivalent (NAACCR #400 - Primary Site) Sites that use the PCORnet tumor table must establish a link to a table with the identifying data that is necessary for recruitment; the tumor table itself is deidentified. Tumor registries generally do not store the decimal in the ICD-O-3 site codes, but this may vary between hospitals.	GEP tumor site PRIMARY_SITE_N400 in ('C160','C161','C162','C163','C164','C165','C166','C168','C169','C170','C171','C172','C173','C178', 'C179','C180','C181','C182','C183','C184','C185','C186','C187','C188','C189','C199','C209','C250','C251', 'C252','C253','C254','C257','C258','C259','C260','C268','C269');

Criterion	Logic/Notes	Defined
2. NET histology	Basis: CDM TUMOR table or source data equivalent (NAACCR #522) Some sites may store histology in the first four characters of the morphology variable (NAACCR #521 Morph--Type&Behav ICD-O-3). This variable is not included in Version 1.2 of the PCORnet tumor table.	HISTOLOGIC_TYPE_ICD_O3_N522 in ('8150','8151','8152','8153','8155','8156','8157','8240','8241','8242','8246','8249');
3. Diagnosed between 01/01/2019-12/31/2023	Basis: CDM TUMOR table or source data equivalent	substr(DATE_OF_DIAGNOSIS_N390,1,4) in ('2019', '2020', '2021', '2022', '2023');

Criterion	Logic/Notes	Defined
	(NAACCR #390)	
4. Aged ≥18 years at diagnosis	Basis: CDM TUMOR table or source data equivalent (NAACCR #230)	input(AGE_AT_DIAGNOSIS_N230,3.) >= 18;

Other Recruitment Methods

Direct recruitment of eligible patients attending clinic (i.e., recently diagnosed), or at a routine follow-up appointment (i.e., prevalent cases) (see Protocol 4.3.1).
This approach will require a liaison with the practice clinics to assess patient appointments and coordinate with the clinical team to introduce the study in-person and supply a study packet/e-mail invitation. Provision of specific guidance on this is difficult, as the process will differ according to the logistics of each site. Further guidance on this route will be disseminated and discussed with study coordinators and the recruitment monitoring workgroup.

APPENDIX C: Pre- and Post-Consent Contacts

Activity (Responsible Entity)	Contact	Mode(s)	Timing
Pre-Consent Contacts **(Sites)** *Population:* • *Did not consent, and* • *Did not decline, and* • *Is not deceased, and* • *Did not identify as ineligible, and* • *Did not indicate they need more time*	Invitation Contact #1	Email, EMR messaging, in-person (letter or study packet), mailed letter	N/A
	Invitation Contact #2	Email, EMR messaging, in-person (letter, study packet, or continued interest query), mailed letter, phone	7 days after Invitation Contact #1
	Invitation Contact #3		7 days after Invitation Contact #2
	Invitation Contact #4		7 days after Invitation Contact #3
	Invitation Contact #5		7 days after Invitation Contact #4
	Invitation Contact #6		7 days after Invitation Contact #5
Post-Consent Info **(Sites)** *Population:* • *Consented, and* • *Did not withdraw, and* • *Is not deceased, and* • *[Email not provided in Step 3, or* • *phone or address info not provided in Step 4)]*	N/A	Site to provide email, phone, address info in UICC REDCap for UICC to contact subject	7 days after Consent was signed
Post-Consent Reminder Contacts **(UICC)** *Population:* • *Consented, and* • *Did not withdraw, and* • *Is not deceased, and* • *Did not complete Survey #1*	Reminder #1	Email, mailed letter, phone	7 days after Consent was signed
	Reminder #2		7 days after Reminder #1
	Reminder #3		7 days after Reminder #2
	Reminder #4		7 days after Reminder #3
	Reminder #5		7 days after Reminder #4
	Reminder #6		7 days after Reminder #5
Survey #2/3/4 Contacts **(UICC)** *Population:* • *Consented, and* • *Did not withdraw, and* • *Is not deceased, and* • *Completed Survey #1*	Reminder #1	Email, mailed letter, phone	(6/12/18 months minus 3 days) after completion of Survey #1
	Reminder #2		7 days after Contact #1
	Reminder #3		7 days after Contact #2
	Reminder #4		7 days after Contact #3
	Reminder #5		7 days after Contact #4
	Reminder #6		7 days after Contact #5