Protocol Title

Prospective study of 18F-AlF-NOTA-Octreotide PET-CT or PET-MR in diagnosis, treatment and prognosis for Neuroendocrine Neoplasms

Version Information

Version Number: 2.0

Release Date: November 16, 2024

Research Institution: The First Affiliated Hospital, Zhejiang University School of Medicine

Principal Investigator: Chen Donghe

Protocol Amendment History

Version	Date	Revision Summary
1.0	2024-09-07	Initial Draft
2.0	2024-11-16	Revision 1

Protocol Synopsis

Item	Details
Study Title	18F-Octreotide PET/CT or PET/MR for Diagnosis, Therapeutic Response, and Prognosis in Neuroendocrine Neoplasms

Item	Details
Design	Prospective, single-center, cross-sectional study
Centers	1
Sample Size	152
Indication	Patients with suspected/confirmed NEN
Objective	Evaluate diagnostic efficacy, therapeutic response assessment, and prognostic prediction of 18F-Octreotide PET/CT or PET/MR using pathology as the gold standard.
Primary Endpoint	Completion of multimodal imaging + pathological confirmation
Inclusion Criteria	1. Clinical diagnosis of neuroendocrine neoplasms;2.Supected of neuroendocrine neoplasms
Exclusion Criteria	1. Inability to undergo biopsy/surgery. 2. Active malignancy/history within 5 years. 3. Severe uncontrolled comorbidities/active infection. 4. Unable to provide informed consent.
Termination Criteria	1. Study objectives met. 2. Occurrence of SAEs.
18F-Octreotide QC	Produced per *Chinese Pharmacopoeia*; passed rodent safety studies; facility holds Type IV Radioactive Pharmaceutical License.
Follow-up Plan	Internal patients: Data extracted from electronic medical records. External patients: Telephone follow-up for pathological results.
Analysis Plan	SPSS 17.0 for: - Sensitivity/specificity/NPV/PPV (2×2 tables) - AUC/optimal SUV cutoff (ROC curves) - Kappa test (imaging vs. pathology concordance) - Significance: p<0.05

Item	Details
Quality Management	AE surveillance system; anonymized data storage; regulatory audit compliance; no identifiable data in publications.

Abbreviations

Abbreviation	Full Term
PET	Positron Emission Tomography
CT	Computed Tomography
ROC	Receiver Operating Characteristic Curve
SSTR	Somatostatin Receptors

1. Research Background

Neuroendocrine neoplasms (NEN) are heterogeneous tumors. Neuroendocrine cells are distributed throughout multiple organs and tissues, enabling NEN to arise in various sites, commonly the gastrointestinal tract, pancreas, and lungs. Symptoms may relate to hormone secretion and bioactive peptides entering systemic circulation [1]. Beyond these sites, NEN can also occur in other endocrine organs (e.g., thymus, adrenal glands, pituitary, thyroid, and parathyroid). Over the past decade, NEN incidence and prevalence have increased [2]. Amidst the rise of precision oncology, solid tumor treatment has entered an era dominated by genetic testing and targeted therapy. Although NEN incidence is growing, treatment selection and prognosis prediction rely on clinicopathological factors (staging, grading, differentiation), lacking precision biomarkers or assays for guiding therapy.

Ultrasound, CT, and MRI—common imaging modalities—struggle to accurately diagnose and assess NEN. Thus, a highly sensitive diagnostic tool is urgently needed to address clinical demands.

Nuclear medicine plays a fundamental role in NEN diagnosis and research, particularly in somatostatin receptor (SSTR) imaging. As most NEN express SSTR, SSTR analogs serve as targets for radionuclide imaging [3]. ^{111}In-DTPA-D-Phe1-octreotide (Octreoscan) SPECT is a classic method for diagnosing SSTR-positive NEN [4]. However, ({68})Ga-labeled DOTA-SSTR PET/CT (e.g., DOTA-Tyr(^3)-octreotate [DOTATATE], DOTA-Nal(^3)-octreotide [DOTA-NOC], DOTA-Tyr(^3)-octreotide [DOTATOC]) reduces scan time, enhances spatial resolution, detects more lesions [5]. Different 68Ga-DOTA-SSTR tracers exhibit subtype-specific affinity: 68Ga-DOTATATE targets SSTR2; 68Ga-DOTA-NOC prefers SSTR3/SSTR5; 68Ga-DOTATOC has lower SSTR5 affinity [6]. Recent studies [7–11] confirm 68Ga-DOTA-SSTR PET/CT's high diagnostic value for localizing primaries, guiding clinical strategy, detecting occult metastases, and improving staging/prognosis. Thus, Nordic/U.S. guidelines endorse SSTR PET/CT for NEN diagnosis.

18F (97% β(+), T({1/2})=109.7 min) is ideal for peptide-based PET imaging due to favorable physicochemical properties [12]. 18F-FDG, the most common PET tracer, is preferred for aggressive/poorly differentiated NEN but lacks sensitivity/specificity for indolent/well-differentiated cases [13–14]. Compared to 68Ga tracers, 18F-labeled SSTR offers superior resolution potential, making it clinically valuable.

18F-AlF-NOTA-octreotide 18F-Octreotide) enables rapid peptide synthesis, accumulates markedly in NEN, and exhibits excellent safety/dosimetry. Versus 18F-FDG, 18F-Octreotide provides better tumor-to-background contrast in well-differentiated NEN imaging [15].

2. Research Objectives and Content

2.1 Objectives

This study utilizes 18F-Octreotide PET/CT or PET-MR in suspected/confirmed NEN patients to evaluate diagnostic efficacy (via postoperative pathology), therapeutic response, and prognosis prediction. It aims to clarify the role of 18F-Octreotide imaging in tumor localization, treatment planning, prognosis, and peptide receptor radionuclide therapy (PRRT) selection. The technique also holds promise for lesion segmentation, grading, survival prediction, and genotyping.

2.2 Research Content

(1) Primary diagnosis cohort: Multimodal imaging 18F-Octreotide PET/CT or PET-MR + contrast-enhanced CT/MR) followed by biopsy/surgical pathology (gold standard, including grading, Ki-67, SSTR2, TP53/Rb status).

(a) Diagnostic efficacy: Calculate sensitivity, specificity, NPV, PPV, AUC-ROC; assess concordance between imaging and pathology.

(b) TNM staging: Compare lesion detection rates of 18F-Octreotide imaging vs. CT/MR; evaluate staging accuracy.

(c) Tumor heterogeneity: Quantify intratumoral heterogeneity via 18F-Octreotide PET; develop quantitative methods and compare with radiomics for predicting pathological complete response (pCR).

(2) Recurrence cohort: Post-treatment (surgery/endocrine therapy/chemotherapy) multimodal imaging.

Assess response per PERCIST criteria, explore dynamic imaging parameters for recurrence risk prediction.

Combine radiomics/AI to identify prognostic parameters.

3. Tracer Characteristics, Mechanism, and Scope

3.2 Tracer Characteristics

Quality control per Chinese Pharmacopoeia (2015 edition), Radiopharmaceutical Testing:

Appearance: Colorless, transparent, sterile, pyrogen-free aqueous/ethanol (15%) solution.

pH: Within specified range (tested via pH strip/meter).

Specific activity: ≥37 × 10(^3) MBq/mol (measured by activimeter).

Radionuclide purity: γ-spectrometry shows only 0.511 MeV and 1.02 MeV peaks.

Radiochemical purity: ≥95% (TLC/HPLC).

Chemical purity: ≥95% (HPLC).

Microbiology: Sterile, apyrogenic.

Endotoxin: Below threshold.

Acetonitrile: ≤0.01%

K222: ≤50 ng/mL.

3.3 Mechanism and Scope

18F's properties make it ideal for peptide-based PET [12]. While 18F-FDG suits aggressive NEN, it underperforms in indolent cases [13–14]. 18F-labeled SSTR tracers offer higher resolution than })Ga analogs, promising broad clinical utility.

4. Indications, Contraindications, and Precautions

4.1 Indications: Suspected or confirmed NEN patients.

4.2 Contraindications:

Inability to undergo biopsy/surgery.

Active malignancy or history within 5 years.

Severe uncontrolled comorbidities/active infections.

Inability to provide informed consent.

4.3 Precautions:

Pregnant/lactating women require medical guidance and signed consent.

5. Overall Design

5.1 Research Methodology

This prospective, single-center, cross-sectional study evaluates the diagnostic efficacy of 18F-Octreotide PET/CT in patients with neuroendocrine neoplasms (NEN). A total of 152 subjects will be enrolled from the First Affiliated Hospital, Zhejiang University School of Medicine.

5.2 Bias Minimization Measures

5.2.1 Blinding: Not applicable (open-label).

5.2.2 Clinical Endpoint Determination: Biopsy or surgical pathology serves as the gold standard.

5.3 Subject Selection

5.3.1 Inclusion Criteria:

(1) Clinical diagnosed of NENs.

(2) Suspected of NENs.

5.3.2 Exclusion Criteria:

(1) Inability to undergo biopsy/surgical treatment.

(2) Concurrent active malignancy.

(3) Severe uncontrolled comorbidities/active infections.

(4) Inability to provide informed consent.

5.3.3 Criteria and Procedures for Subject Withdrawal:

Subjects not meeting inclusion criteria (verified via medical history/electronic records) will be excluded. Subjects may withdraw during the procedure due to hypoglycemia, tremor, pain, or severe abdominal discomfort.

5.3.4 Loss to Follow-up:

• Defined as incomplete follow-up without formal withdrawal.

• For subjects receiving biopsy/surgery elsewhere, ≥3 phone attempts will be made. Unresponsive cases after 3 calls + certified mail will be deemed "lost to follow-up."

• Lost subjects are excluded from diagnostic efficacy analysis but included in safety assessment if data are available.

5.3.5 Enrollment Period: December 2024 to December 2027 (3 years).

5.3.6 Sample Size: 152 cases.

5.4 Study Endpoints:

Study completion is defined as completion of multimodal imaging and acquisition of pathological results.

---

6. Research Procedures and Protocols

6.1 Ethics and Informed Consent

• The study commences after ethics committee (EC) approval. Protocol amendments require re-approval.

• EC approval (including consent forms) must be documented with version/date.

• Written informed consent is mandatory before enrollment.

6.2 Subject Screening

• Consent is obtained after explaining risks/benefits. Subjects receive time to consider participation.

• Baseline data (general exams, labs, history from within 1 week pre-consent) are collected. Adverse events/concomitant medications are recorded post-consent.

6.3 Medical History Collection

Comprehensive documentation of:

• Symptoms, signs, and history (tumors, surgeries, biopsies, radiotherapy, chemotherapy, allergies, octreotide/PRRT history).

• Lab tests: Fasting insulin, CgA, proinsulin/C-peptide, NSE, VIP, Syn, VMAT-2, CD56.

• Prior imaging (X-ray, US, CT, MRI, 18F-FDG PET/CT/MR).

• Recent pathology (grading, Ki-67 index).

6.4 Patient Preparation

Pregnancy: Avoid unless benefits outweigh risks.

Hydration: Encourage water intake pre/post-injection to reduce radiation exposure and improve image quality. Void bladder pre-scan; catheterize if incontinence occurs.

IV Access: Use a cannula to prevent tracer extravasation.

Fasting/Fasting Medications: Not required. Withhold short-acting octreotide ≥24h and long-acting analogs 3–4 weeks pre-scan if feasible (evidence inconclusive).

6.5 Radiopharmaceutical Administration

• Dose: 18F-Octreotide (3.7 MBq/kg, range 3.7–4.44 MBq; obese patients may receive higher doses).

• Administration: IV injection separate from parenteral nutrition lines.

6.6 Image Acquisition

• Patient Positioning: Arms at sides for whole-body scans; arms raised for chest/abdomen.

• CT Protocol: For attenuation correction/anatomic localization. Use low-dose principles where feasible.

• PET Protocol:

Optimal imaging: 45–60 min post-injection.

Scan range: Skull base to mid-thigh (adjust per clinical needs).

Acquisition time varies by dose, BMI, scanner.

• Interventions: Hydration ± diuretics/catheterization to reduce urinary tracer activity.

• Reconstruction: Iterative reconstruction + time-of-flight (if available); parameters optimized per patient/scanner.

6.7 Image Interpretation

• Normal Biodistribution: Spleen (highest), kidneys, liver, adrenals, pituitary, salivary glands. Minimal uptake in brain/lungs/muscle; excreted via kidneys.

• Pathologic Uptake: Focal uptake in non-physiologic sites (vs. diffuse bowel uptake = non-pathologic).

• Malignancy Criteria: Uptake > liver = SSTR-positive malignancy. Correlates with tumor grade/SSTR expression.

6.8 Reporting Standards

Objectives: Address referring physicians' clinical queries and justify necessity/diagnostic value of })-Octreotide imaging.

Procedure Flow:

Registration → 2. Preparation (fast ≥4h) → 3. History/consent → 4. 18F-Octreotide injection → 5. Uptake period (60 min) → 6. Scan (20–30 min).

7 Statistical Considerations

7.1 Total Sample Size

Assuming a sensitivity of 0.90, specificity of 0.88, and disease prevalence of 0.25 from literature, with a margin of error of 0.1 and $\alpha = 0.05$:

For sensitivity calculation:

$$N_1 = \frac{1.96^2 \times 0.9 \times (1-0.9)}{0.1^2 \times 0.25} = 138$$

For specificity calculation:

$$N_2 = \frac{1.96^2 \times 0.88 \times (1-0.88)}{0.1^2 \times (1-0.25)} = 54$$

The theoretical sample size is estimated at 138 cases. Accounting for a 10% expected dropout rate (based on prior studies), the adjusted total sample size is 152 cases.

7.2 Significance Level and Power

Significance level: $\alpha = 0.05$

Power: 0.95

7.3 Statistical Methods

Analysis performed using SPSS 17.0:

Sensitivity, specificity, and positive/negative predictive values calculated via 2×2 contingency tables.

ROC curves used to determine AUC and optimal cut-off values (e.g., SUV thresholds).

Kappa test evaluated consistency between 18F-Octreotide PET/CT and pathological diagnoses.

Statistical significance: $p < 0.05$.

---

8 Data Recording and Management

8.1 Investigator Data Recording

Detailed records of all eligible subjects, including laboratory results.

Two nuclear medicine physicians (≥5 years' experience) independently interpret imaging; discrepancies resolved by a senior consultant.

Original data signed and dated by the investigator.

All adverse events (AEs) documented; serious adverse events (SAEs) reported per protocol.

---

9 Expected Timeline

Recruitment period: 36 months

Follow-up: Ends upon completion of 18F-Octreotide PET/CT and pathological confirmation.

---

10 Adverse Event Assessment and Reporting

10.1 Definition

Any untoward medical occurrence related to imaging/radiopharmaceuticals during/after the study, including symptoms, signs, or lab abnormalities.

10.2 Major Adverse Events

PET/CT risks: Potential radiation exposure.

18F-Octreotide risks: Rare mild reactions (rash, pruritus); severe reactions (shock) not reported in literature.

10.3 Documentation of AEs

Use standardized medical terminology.

Include:

Start/end dates

Severity

Causality assessment

Action taken

Outcome

10.4 Reporting of SAEs

Immediate actions taken.

Written reports submitted within 24 hours to:

Institutional Ethics Committee

Provincial regulatory authorities

Contact:

Affiliated Hospital 1, Zhejiang University School of Medicine

Su Xinhui: 13806071262

Chen Donghe: 13777452235

10.5 AE Follow-up

All AEs followed until resolution.

---

11 Quality Control (QC) & Assurance (QA)

11.1 Laboratory QC

18F-Octreotide prepared per Chinese Pharmacopoeia 2015.

Batch testing: pH, specific activity, radiochemical/radionuclide purity, endotoxin, sterility.

Reports signed and dated.

11.2–11.4 Staff & Procedures

Investigators: Certified, GCP-trained, and experienced.

Pre-study training on protocols.

QA ensures compliance with Good Practice for Radioactive Pharmaceuticals.

12–14 Data Confidentiality & Storage

Confidentiality: Subject identities protected; data anonymized (ID codes only).

Storage: Original records retained for 10 years post-study.

---

15 Study Termination & Reporting

Summary report prepared by lead unit and submitted to regulatory authorities.

Results may be published or used for regulatory submissions.

16–18 Responsibilities

Sponsors:

Training, protocol adherence, data auditing.

Investigators/Sites:

Obtain informed consent.

Report AEs/SAEs within 24 hours.

Protect subject safety; halt study if necessary.

Maintain certification and site facilities (e.g., radioprotection, waste management).

Pre-study training on radiopharmaceutical handling/imaging protocols.

Refrences：

[1].Barakat MT, Meeran K, Bloom SR．Neuroendocrine tumours．Endocr Relat Cancer, 2004, 11(1): 1-18．

[2]. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol.2017, 3: 1335-1342.

[3]. BozkurtMF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with (68) Ga-DOTA–conjugated somatostatin receptor targeting peptides and (18)F-DOPA.Eur J Nucl Med Mol Imaging.2017; 44:1588–1601.

[4]. Kwekkeboom DJ, Kooij PP, BakkerWH, et al. Comparison of 111In-DOTATyr3-octreotide and 111In-DTPA-octreotide in the same patients: biodistribution, kinetics, organ and tumor uptake. J Nucl Med.1999; 40: 762–767.

[5]. Sadowski SM, Neychev V, Millo C, et al. Prospective study of 68Ga-DOTATATE positron emission tomography/computed tomography fordetecting gastro-entero-pancreatic neuroendocrine tumors and unknown primary sites.J Clin Oncol.2016; 34: 588–596.

[6]. Putzer D，Kroiss A，Waitz D，et a1．Somatostatin receptor PET in neuroendocrine tumours：68 Ga-DOTA-Tyr3-octreotide versus" Ga-DOTAolanreotide．Eur J Nucl Med Mol Imaging．2013; 40 (3): 364-372．

[7]. Yamaga LYI, Cunha ML, Campos Neto GC, et a1. 68Ga DOTATATE PET/CT in recurrent medullary thyroid carcinoma: A lesion-by-lesion comparison with"1 In-octreotide SPECT/CT and conventional imaging. Eur J Nucl Med Mol Imaging，2017,44 (10)：1695-1701．

[8]. Sadowski SM．Millo C，Cottle-Delisle C，et a1．Results of 68Gallium-DOTATATE PET/CT scanning in patients with multiple endocrine neoplasia type 1. J Am Coil Surg，2015，221 (2)：509-517．

[9].Bodei L, Ambrosini V, Herrmann K, et al Current concepts in 68 Ga-DOTATATE imaging of neuroendocrine neoplasms: Interpretation, Biodistribution, Dosimetry, and Molecular Strategies.J Nucl Med. 2017 Nov; 58(11):1718-1726.

[10] Barrio M, Czernin J, Fanti S, et a1. The impact of somatostatin receptor-directed PET/CT on the management of patients with neuroendocrine tumor: A systematic review and Meta-snalysis. J Nucl Med, 2017, 58(5): 756-761．

[11]. Conry BG, Papathanasiou ND, Prakash V, Kayani I, Caplin M, Mahmood S, Bomanji JB. Comparison of (68) Ga-DOTATATE and (18)F-fluorodeoxyglucose

PET/CT in the detection of recurrent medullary thyroid carcinoma.Eur J Nucl Med Mol Imaging. 2010 Jan;37(1):49-57.

[12]. Coenen HH, Elsinga PH, Iwata R, et al. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences.Nucl Med Biol. 2010; 37:727–740.

[13]. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTADPhe1, Tyr3-octreotate) and 18F-FDG.Cancer.2008; 112: 2447–2455.

[14]. Krenning EP, Valkema R, Kwekkeboom DJ, et al. Molecular imaging as in vivomolecular pathology for gastroenteropancreatic neuroendocrine tumors: implications for follow-up after therapy. J Nucl Med. 2005; 46(Suppl 1): 76S–82S.

[15]. Long T, Yang N, Zhou M, Chen D, Li Y, Li J, Tang Y, Liu Z, Li Z, Hu S. Clinical Application of 18F-AlF-NOTA-Octreotide PET/CT in Combination With 18F-FDG PET/CT for Imaging Neuroendocrine Neoplasms. Clin Nucl Med. 2019 Jun; 44 (6):452-458.

[16]. Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, Papathanasiou ND, Pepe G, Oyen W, De Cristoforo C, Chiti A. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE.Eur J Nucl Med Mol Imaging. 2010 Oct; 37 (10):2004-10.

Informed Consent Form for Clinical Research Project

Protocol Title: Prospective study of ^{18}F-AlF-NOTA-Octreotide PET-CT or PET-MR in diagnosis, treatment and prognosis for Neuroendocrine Neoplasms

Protocol Number:

Protocol Version: 2.0 (November 16, 2024)

Informed Consent Version: 2.0 (November 16, 2024)

Research Institution: First Affiliated Hospital, Zhejiang University School of Medicine

Principal Investigator: Chen Donghe

Subject Name:

Subject Initials:

Subject Address:

Subject Phone:

We invite you to participate in this clinical research. This informed consent form provides information to help you decide whether to join. Please take time to read it carefully. If you have questions or need clarification, discuss them with the study physician.

Participation is completely voluntary. This study has been reviewed and approved by the Hospital Clinical Research Ethics Committee—IIT Ethics Review Panel.

Background

Neuroendocrine neoplasms (NEN) are heterogeneous tumors arising from neuroendocrine cells distributed throughout the body. Common sites include the gastrointestinal tract, pancreas, and lungs. Symptoms may relate to hormone secretion

and vasoactive peptides entering circulation. Over the past decade, NEN incidence and prevalence have increased. Precision oncology emphasizes genetic testing and targeted therapies, yet NEN lacks precise biomarkers for prognosis or treatment selection.

Current imaging (ultrasound, CT, MRI) struggles to accurately diagnose or assess NEN. Thus, a highly sensitive diagnostic tool is urgently needed. Nuclear medicine, particularly somatostatin receptor (SSTR) imaging, plays a key role. As most NENs express SSTR, SSTR analogs serve as targets for radionuclide imaging. The FDA-approved ^{68}Ga-DOTA-SSTR PET/CT outperforms traditional methods by reducing scan time and improving lesion detection. However, ^{18}F-labeled SSTR tracers (e.g., ^{18}F-Octreotide) offer superior resolution and tumor-to-background ratios.

Research Objectives

This study uses ^{18}F-Octreotide PET-CT/PET-MR to:

1. Evaluate diagnostic accuracy (sensitivity, specificity, NPV, PPV, AUC) using pathology (Ki-67, SSTR2, P53, Rb) as the gold standard.

2. Assess TNM staging accuracy and lesion detection rates compared to contrast CT/MRI.

3. Quantify tumor heterogeneity via radiomics/AI, predicting postoperative pCR and recurrence risk.

4. Explore dynamic imaging parameters (PERCIST criteria) for prognosis and peptide receptor radionuclide therapy (PRRT) efficacy prediction.

Study Procedures

- Newly Diagnosed Patients: Multimodal imaging (^{18}F-Octreotide PET-CT/PET-MR + contrast CT/MRI), followed by pathology.

- Recurrent Patients: Post-treatment multimodal imaging for efficacy assessment.

Risks and Discomforts

- Radiation: Minimal risk from PET-CT; procedures comply with Radiation Protection Requirements for X-ray Computed Tomography.
- Tracer: ^{18}F-Octreotide may cause mild reactions (rash, pruritus); severe reactions (e.g., shock) are rare. Emergency SOPs are in place.

Potential Benefits

You may benefit from precise tumor localization. Results may advance care for future patients with similar conditions.

Costs and Compensation

- ^{18}F-Octreotide is provided without charge. PET-CT scan fees are self-paid.
- No financial compensation.

Privacy and Confidentiality

Your identity will be coded and protected. Study data may be published anonymously. Regulatory authorities may review records for quality assurance.

Contact Information

For questions, contact:

- Dr. Chen Donghe or Su Xinhui: 87236432
- Ethics Committee: 0571-87233418, 79 Qingchun Road, Hangzhou

_____

Consent Statement

I confirm that:

1. I understand this research, its risks, and have had my questions answered.

2. Participation is voluntary; refusal will not affect my medical care.

3. I permit access to my records by study staff, the institution, and ethics committees under confidentiality safeguards.

4. I agree to participate.

Subject Signature: _____ Date: _____

Subject Contact: _____

If subject lacks capacity:

Guardian Signature: _____ Date: _____

Guardian Contact: _____ Relationship: _____

If subject cannot read this form:

Witness Signature: _____ Date: _____

Witness Contact: _____

Investigator Signature: _____ Date: _____

Investigator Contact: _____