RESEARCH PROTOCOL

Title:

The clinical utility of [^{68}Ga]-labelled fibroblast activation protein inhibitor (FAPI) positron emission tomography and computed tomography (PET/CT) in patients with resectable or borderline resectable pancreatic ductal adenocarcinoma (PDAC) undergoing neoadjuvant chemotherapy.

Short Title:

Clinical utility of [^{68}Ga] FAPI PET/CT in patients with potentially resectable PDAC.

Statement of Compliance:

This document is a protocol for a research project assessing the clinical utility of [^{68}Ga] FAPI PET/CT in managing patients with PDAC. The study will be conducted in accordance with all stipulations of this protocol, the conditions of the Human Research Ethics Committee (HREC) approval, the National Health and Medical Research Council (NHMRC) *National Statement on Ethical Conduct in Human Research (2007)–Updated 2018*, NHMRC and Universities Australia, the *Australian Code for the Responsible Conduct for Research (2007)* and the *Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).*

Adjustments in the Protocol:

The final approved protocol will not be adjusted without the ethics committee's prior written approval of the amendment, except when necessary to eliminate immediate danger to the patients, or changes involving logistics or administration only.

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Study Synopsis

Title	The clinical utility of [^{68}Ga]-labelled fibroblast activation protein inhibitor (FAPI) positron emission tomography and computed tomography (PET/CT) in patients with resectable or borderline resectable pancreatic ductal adenocarcinoma (PDAC) undergoing neoadjuvant chemotherapy.
Short Title	Clinical utility of [^{68}Ga] FAPI PET/CT in patients with potentially resectable PDAC.
Study Design	Single-centre prospective, single-arm study.
Duration	18 months.
Site	Princess Alexandra Hospital, Woolloongabba, Brisbane.
Sample Size	Approximately 20 patients with newly diagnosed resectable or borderline resectable PDAC undergoing neoadjuvant chemotherapy.
Primary Objective	To assess whether [^{68} Ga] FAPI PET/CT provides clinical benefit in patients with resectable or borderline resectable PDAC who have been referred for neo-adjuvant chemotherapy.
Aims	1. To compare the SUVmax of [^{68} Ga] FAPI PET/CT to [^{18}F] FDG PET/CT in patients diagnosed with resectable or borderline resectable PDAC pre- and post-neoadjuvant chemotherapy. 2. To assess the percentage of fibroblast activation protein (FAP) expression in the pre-treatment biopsy specimen and the resected specimen and correlate this with [^{68} Ga] FAPI PET/CT SUVmax results pre- and post-neoadjuvant chemotherapy. 3. To assess the change in SUVmax on [^{68} Ga] FAPI PET/CT post neoadjuvant chemotherapy and correlate it with tumour response to chemotherapy determined on contrast enhanced CT scan and the resection specimen.
Research Questions	1. Is [^{68} Ga] FAPI PET/CT more accurate than [^{18}F] FDG PET/CT in determining tumour burden before and after neoadjuvant chemotherapy in patients with potentially resectable PDAC? 2. Does FAPI tracer uptake correlate with FAP expression on immunohistochemical evaluation of biopsy and resection specimens? Does higher FAP expression result in poorer response to chemotherapy? 3. Does the change in SUVmax on [^{68} Ga] FAPI PET/CT following chemotherapy correlate with response to treatment in patients with potentially resectable PDAC? Is this correlation stronger than it is for [^{18}F] FDG PET/CT?
Anticipated Outcomes	1. [^{68} Ga] FAPI PET/CT will be superior to [^{18}F] FDG PET/CT in assessing tumour burden and its response to neoadjuvant chemotherapy. 2. Higher FAP expression in the tumour stroma will result in higher FAPI tracer uptake and is associated with a poorer response to neoadjuvant chemotherapy. 3. The change in SUVmax on [^{68} Ga] FAPI PET/CT following chemotherapy will correlate with response to treatment observed on contrast enhanced CT and pathological specimens. This correlation will be stronger than it is for [^{18}F] FDG PET/CT.

Glossary of Abbreviations

CAFs	Cancer-associated fibroblasts
EUS	Endoscopic ultrasound
FAP	Fibroblast activation protein
FAP	Fibroblast activation protein
FAPI	Fibroblast activation protein inhibitor
FDG	Fluorodeoxyglucose
HIRF	Herston Imaging Research Facility
HPB	Hepato-pancreato-biliary
HREC	Human Research Ethics Committee
MDT	Multidisciplinary team meeting
MRCP	Magnetic resonance cholangiopancreatography
NHMRC	National Health and Medical Research Council
PAH	Princess Alexandra Hospital
PDAC	Pancreatic ductal adenocarcinoma
PET/CT	Positron emission tomography and computed tomography
R0 resection	Microscopically margin-negative resection
RBWH	Royal Brisbane and Women's Hospital
SUV	Standardised uptake value
SUVmax	Maximum standardised uptake value within a specific region of interest
TME	Tumour microenvironment
TRI	Translational Research Institute

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is becoming an increasingly common cause of cancer mortality, with a five-year survival rate of <10% (1). At the time of diagnosis, approximately 80–85% of patients present with either unresectable or metastatic disease. Even in the small subset of patients who present with a localised, resectable tumour, prognosis remains poor, with approximately 30% of patients in this group surviving five years post-surgery (2).

Accurate diagnosis and assessment of tumours at an early stage have important implications for treatment decisions and prognosis (3). Unfortunately, over the past decade, advances in diagnostic approaches and peri-operative management of PDAC have made minimal improvements in patient outcomes, and survival remains poor. It is, therefore, necessary to investigate new diagnostic tools in the hope of improving patient outcomes (4).

2. Background

The current ‘standard of care’ investigation for a patient with clinical suspicion of PDAC is a contrast-enhanced CT scan using a dual-phase pancreatic protocol. Adjunctive imaging modalities include transabdominal ultrasound, endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) (5). Patients at high risk of locally advanced or metastatic disease often have an additional PET/CT in an attempt to accurately stage their disease (6).

The glucose analogue, fluorodeoxyglucose (FDG), is the radio-isotype most commonly used for detecting and staging malignant tumours on PET/CT (7). [^{18}F] FDG PET/CT, however, is not an ideal imaging agent for PDAC due to its variable detection of lymph node metastases, possible false-positive findings, e.g. inflammation, and decreased sensitivity in detecting peritoneal metastases (8).

Recent studies have explored alternative radio-isotypes in the initial staging of many solid tumours. Of specific interest is the use of [^{68} Ga] FAPI PET/CT targeting fibroblast activation proteins expressed on the membrane of cancer-associated fibroblasts (9, 10).

Cancer-associated fibroblasts (CAFs) and FAP expression

Malignant tumours comprise neoplastic cells surrounded by non-malignant stromal cells that shape and create the tumour microenvironment (TME). CAFs are a heterogeneous population of fibroblast-like cells accounting for a large percentage of tumour stroma and are key modulators of tumour progression (11, 12).

FAP is a type II transmembrane glycoprotein expressed on the surface of CAFs and is upregulated in more than 90% of human epithelial malignancies. CAFs with high FAP expression are associated with a poorer prognosis as they promote local tumour invasion, angiogenesis, microenvironmental immune suppression and increased risk of metastases (13). FAP is, therefore, a promising target for both diagnostic and therapeutic approaches in many solid tumours, including PDAC.

FAPI and its use as a radionuclide

FAP-specific inhibitors (FAPI) are small molecules coupled to chelators that bind specifically to membrane-bound FAP. Most tumours show high uptake of FAPI with very low accumulation in normal tissues. This depicts tumour-stromal interaction, which cannot be visualised by morphologic imaging and can assist in monitoring treatment responses (14).

[^{68} Ga] FAPI PET/CT compared with [^{18}F]FDG PET/CT imaging

Recent studies have shown that the radio-isotype [^{68} Ga] FAPI PET/CT is more sensitive than [^{18}F] FDG PET/CT in the initial staging of many solid tumours (15,16). A study performed by Pang et al. compared [^{68} Ga]FAPI PET/CT to [^{18}F]FDG PET/CT, specifically in patients with PDAC. This study demonstrated that [^{68} Ga] FAPI PET/CT is superior to [^{18}F] FDG PET/CT in the initial TNM staging of the tumour (17). However, there are no studies evaluating the utility of [^{18}F] FAPI PET/CT in assessing treatment responses to chemotherapy.

Evaluation of response to chemotherapy in PDAC

The evaluation of PDAC response after neoadjuvant treatment is complex as there are few studies on the subject with a lack of consensus and recommendations. Studies have shown that CT evaluation of PDAC after neoadjuvant chemotherapy has a low diagnostic performance in predicting R0 resectability. After chemotherapy, tumour cells within the tumour microenvironment tend to disappear, but fibrosis of the stroma persists. It is impossible to determine whether tumour fibrosis was pre-existing or developed in response to treatment on current morphological imaging (18).

A study performed by Choi et al. evaluated the use of [^{18}F] FDG PET/CT in assessing response to neoadjuvant therapy in PDAC. This study showed that a decrease of more than 50% of standardised uptake value (SUV) on PET-CT was strongly predictive of R0 resection (19).

Ultimately, there is very little literature about the use of PET-CT scan for this indication. This raises the interest in evaluating [^{68} Ga] FAPI PET/CT as a marker of tumour response to neoadjuvant therapy in PDAC.

3. Aims/Objectives

The primary objective of this study is to assess whether [^{68} Ga] FAPI PET/CT provides clinical benefit in patients with resectable or borderline resectable PDAC who have been referred for neoadjuvant chemotherapy.

The specific aims of this study are as follows:

1. To compare the SUVmax of [^{68} Ga] FAPI PET/CT to [^{18}F] FDG PET/CT in patients diagnosed with resectable or borderline resectable PDAC pre- and post-neoadjuvant chemotherapy.
2. To assess the percentage of fibroblast activation protein (FAP) expression in the pre-treatment biopsy specimen and the resected specimen and correlate this with [^{68} Ga] FAPI PET/CT SUVmax results pre- and post-neoadjuvant chemotherapy.
3. To assess the change in SUVmax on [^{68} Ga] FAPI PET/CT post neoadjuvant chemotherapy and correlate it with tumour response to chemotherapy determined on contrast enhanced CT scan and the resection specimen.

4. Hypotheses

For patients with potentially resectable PDAC this study sets out to prove that:

1. [^{68} Ga] FAPI PET/CT will be superior to [^{18}F] FDG PET/CT in assessing tumour burden and its response to neoadjuvant chemotherapy.
2. Higher FAP expression in the tumour stroma will result in higher FAPI tracer uptake and is associated with a poorer response to neoadjuvant chemotherapy.
3. The change in SUVmax on [^{68} Ga] FAPI PET/CT following chemotherapy will correlate with response to treatment observed on contrast enhanced CT and pathological specimens. This correlation will be stronger than it is [^{18}F] FDG PET/CT.

5. Methods

a. Study Design

This study is a single-centre, prospective study evaluating the utility and clinical benefit of [^{68}Ga] FAPI PET/CT in 20 patients deemed to have resectable or borderline resectable PDAC on initial clinical evaluation and are considered suitable for neoadjuvant chemotherapy with FOLFIRINOX. The FOLFIRINOX regimen is a currently accepted standard of care chemotherapy for resectable or borderline resectable PDAC. Patients will undergo FDG-PET/CT which is also accepted care in the work up of a patient with potentially resectable pancreatic cancer. Because [^{68}Ga] FAPI PET/CT remains an experimental imaging modality, any findings on [^{68}Ga] FAPI PET/CT that could alter patients' clinical decision making will be confirmed through biopsy or another established imaging modality and discussed at the HPB MDT meeting.

b. Study Site

This study will take place at Princess Alexandra Hospital (PAH), Woolloongabba, QLD, Australia. Metro South Health will be the primary sponsor for this study. The [^{68}Ga] FAPI isotype will be obtained from the Radiology department at the Royal Brisbane and Women's Hospital and couriered to PAH Radiology department in accordance with the "Code for the Safe Transport of Radioactive Material' guidelines.

Should there not be adequate recruitment of patients at PAH, feasibility to extend this study to include the Royal Brisbane and Women's Hospital will be considered.

c. Study Population

i. Sample Size

This study aims to recruit approximately 20 patients who have been referred to any hepato-pancreato-biliary (HPB) surgeon or medical oncologist within the PAH catchment. Any patient who fulfils the inclusion criteria, and is willing to participate in the study, will be included.

ii. Inclusion Criteria

- Age > 18 years
- Able to give informed consent
- Histological specimen from the primary pancreatic lesion confirming the diagnosis of PDAC.
- Patients need to have either a resectable or borderline resectable pancreatic lesion after imaging review at the HPB multidisciplinary (MDT) meeting
- No metastatic disease
- Eastern Cooperative Oncology Group performance status ≤ 1
- No contraindications to neoadjuvant chemotherapy.

iii. Exclusion Criteria

- Patients not medically fit for peri-operative chemotherapy with FOLFIRINOX or surgery
- Patients with known or suspected metastatic disease
- Pregnant or breastfeeding patients (if a female patient is pre-menopausal, she will require a negative urine pregnancy test prior to enrolment)
- Patients with allergies to or contraindications to [^{68} Ga] FAPI or [^{18}F] FDG tracer
- Patients who have had surgery or chemotherapy prior to 1st PET/CT imaging.

iv. Recruitment of Participants

Participants will be recruited from the HPB MDT and Cancer Services at PAH. Screening for eligibility will take place upon initial referral. The coordinating investigator will be alerted if a patient is believed to be a potential candidate and will confirm eligibility with the treating clinician.

v. Informed Consent

This study will be conducted in compliance with the National Statement on Ethical Conduct in Humans: General requirements for consent (2.2).

A potential candidate for the study will be approached by one of the study investigators and invited to participate in the research. Study investigators will explain the aims, methods, anticipated benefits, and potential hazards to each candidate in simple English. This will be done either in person at a clinic appointment or over the telephone.

Potential participants will be provided with a Participant Information Sheet and Consent Form. Patients will be given up to a week to review the written information and have their questions answered to their satisfaction. The study investigator will then confirm their admission to the study.

For patients who do not speak fluent English, the consent form will require counter signing by an interpreter who has been accredited and appointed by Queensland Health to interpret a language

the patient speaks fluently. The interpreter's signature will indicate that all verbal and written information provided regarding the study has been adequately translated.

An explanation will also be provided to the participant that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The participant's willingness to participate in the trial will be documented in writing on the Participant Information Sheet and Consent Form and signed by the participant with the date and time documented. The study investigator will sign and date the information and consent form indicating they have provided the required written and verbal explanation to the participant. The original consent form will be kept, and a copy given to the participant.

6. Study Procedures

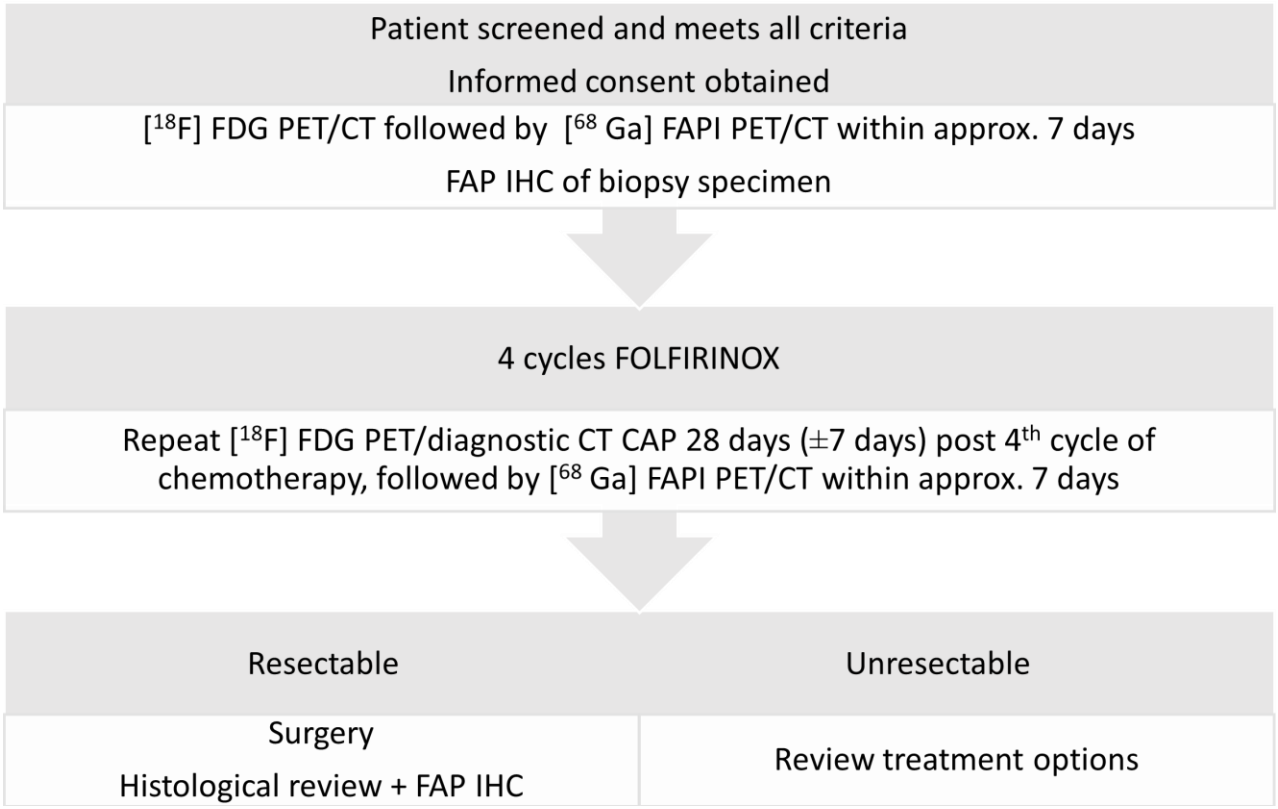

Fig 1: Summary of the study procedure

a. Imaging Protocol

All patients fulfilling inclusion criteria will be referred for PET/CT scanning as arranged by the coordinating investigator. Patients will first undergo [^{18}F] FDG PET as part of pre-treatment workup, followed by [^{68} Ga] FAPI PET/CT within approximately seven days.

Imaging procedures are as follows:

[^{18}F] FDG PET: PET/CT imaging will be conducted after >6 hours of fasting and among patients with normal blood glucose levels. The dose of [^{18}F] FDG is calculated according to the patient's weight, 3.7MBq/kg. Static PET/CT imaging will be performed using the Siemens PET/CT scanner 60 minutes after intravenous injection and will include the skull base to upper thighs.

[^{68} Ga] FAPI PET/CT: No specific preparation is required for [^{68} Ga] FAPI PET/CT. The specific radio-isotype used is the [^{68} Ga]-FAPI-46 variant, and the dose is calculated according to the patient's weight, 1.8–2.2 MBq/kg. Static PET/CT imaging will be performed using the Siemens PET/CT

scanner 60 minutes after intravenous injection and includes the base of the skull to the upper thighs.

b. Chemotherapy Protocol

Patients will receive four cycles of FOLFIRINOX within approximately seven days of completing both PET/CT scans at the PAH medical oncology unit. The FOLFIRNOX regimen is defined as follows:

Day 1 Oxaliplatin 70mg/m^2 IV over two hours
Irinotecan 150mg/ m^2 IV over 90 mins
Leucovorin 300mg/m^2 IV over 90mins
Flurouracil 300mg/m^2 IV bolus
Followed by
Days 1–2 Flurouracil 2.4g/m^2 IV continuous infusion over 46 hours

Repeat cycle every two weeks for 4 cycles

Approximately 28 days after the patient has completed their fourth cycle of chemotherapy, patients will repeat a [^{18}F] FDG PET/diagnostic CT chest, abdomen and pelvis as part of their standard of care imaging, followed by a [^{68} Ga] FAPI PET/CT within approximately 7 days.

c. Histological Analysis

After diagnostic requirements have been completed, pre-treatment biopsy specimens will undergo FAP immunohistochemistry (IHC). Tissue samples will be acquired from Queensland Pathology at PAH laboratory. FFPE blocks or slides will be transferred to Translational Research Institute (TRI) histology core facility for staining and analysis. Tissue samples will be stored in secure PC2 laboratory.

All patient data will be de-identified, and laboratory staff will not have access to clinical information or re-identifiable patient data. Re-identifiable patient data will be analysed within the PAH Medical Oncology department. Tissue samples will only be collected as part of a participant's usual management. No invasive tissue sampling will take place solely for the purpose of the study.

Following repeat PET/CT scanning, the patient's response to chemotherapy will be discussed at the HPB MDT meeting and evaluated for surgery. If still deemed resectable, the patient will proceed to surgery. Resection specimens will undergo routine histological evaluation as per standard guidelines. After diagnostic requirements have been completed, IHC for FAP expression will be performed at TRI histology core facility as per the above procedure.

If the patient is deemed unresectable, the patient will be evaluated, and treatment options will be offered as per the standard of care for metastatic or unresectable PDAC.

d. Study Measures

A qualified nuclear medicine physician will interpret the results from the [^{18}F] FDG and [^{68} Ga] FAPI PET/CTs. The following measures will be obtained from the images produced:

- SUVmax of [^{68} Ga] FAPI uptake in tumour deposits pre-chemotherapy at 60 minutes post-radio-isotype injection
- SUVmax of [^{18}F] FDG uptake in tumour deposits pre-chemotherapy at 60 minutes post-radio-isotype injection
- SUVmax of [^{68} Ga] FAPI and [^{18}F] FDG post four cycles of chemotherapy at 60 minutes post-radio-isotype injection.

The response to chemotherapy will be evaluated at the HPB MDT meeting, where decisions about surgical resection are determined. Any discussions regarding change of management will be discussed with the treating clinician. No changes in management will be based on [^{68} Ga] FAPI-PET/CT results. These decisions will be made based on the results of standard of care investigations.

Histological analysis of the pre-treatment biopsy specimen and the resected specimen will be performed by a qualified pathologist at PAH. IHC for FAP staining will be performed on the specimens after routine histological evaluation has been completed according to standard protocols.

Measures from each tissue sample will include:

- Proportion of stromal cells stained.
- Intensity of staining for stromal cells.
- Proportion of neoplastic cells stained.
- Intensity of staining for neoplastic cells.
- Dominant pattern of staining (i.e., stromal cells only, neoplastic cells only, or mixed).

7. Data Analysis and Statistical Methods

Descriptive statistics (frequencies and percentages) will be reported for categorical variables and interquartile range (IQR) will be reported for continuous variables.

We will compare the SUVmax response using a paired t-test or Wilcoxon rank-sum test for the following:

- [^{68} Ga] FAPI PET/CT and [^{18}F] FDG PET/CT pre-chemotherapy
- [^{68} Ga] FAPI PET/CT pre- and post-chemotherapy
- [^{18}F] FDG PET/CT pre- and post-chemotherapy

We will plot receiver operating characteristic (ROC) curves and calculate areas under the curve (AUCs) for each parameter to determine cut-points with optimal sensitivity and specificity. A two-sided P-value of <0.05 will be considered significant throughout.

For the patients' tissue analysis, we will perform linear regression, adjusting for potential confounders to determine if proportion and intensity of staining is related to SUVmax of primary pancreatic lesions. We will do this separately for both stromal and neoplastic expression. For each pattern of FAP expression (i.e., stromal cells only, neoplastic cells only, or mixed) we will determine median e SUVmax-p and IQR. We will compare groups using parametric or non-parametric tests depending on distribution of absolute SUVmax-p.

8. Data Management

a. Data Collection

Information required for this study will be collected directly from the participants and their medical records. Only the study investigators assigned to this research will have access to the patients' personal and medical information, pathology and initial imaging results and imaging data collected as part of the study.

b. Patient Confidentiality

Personal information and data collected will be treated in line with the Office of the Australian Information Commissioner's health privacy guidelines. In this study, data will be in re-identifiable form because data analysis and interpretation depend on patients' medical characteristics.

Participants in the study will have an identification code number allocated at enrolment. Patient data collected will be recorded under the participant's identification code. A code list linking the participant's identification number to their name will be kept by the Coordinating Principal Investigator in a password protected file in the Queensland Health secure server.

c. Data Security

Participant imaging results reported by the nuclear medicine clinicians will be stored in computer files under password protection on secure servers. Only investigators in the research team have access to these files.

Clinical data will be recorded onto an electronic data capture system in a password-secured, firewall-protected network within Metro South Health. Only investigators in the research team have access to this, and all access will be audited by the Coordinating Principal Investigator.

Medical information or records in paper copies will be securely stored in locked facilities. All study-related documents and data collection forms will be archived in a secure environment for a minimum of 15 years. After this time, study data will be destroyed according to institutional policies.

9. Participant Safety/Risk Management

Additional procedures that a participant would receive in this study are [^{68} Ga] FAPI PET/CT scans pre- and post-chemotherapy.

a. Generic Risks

The risks and complications of the PET/CT procedure can include the following:

- Minor pain, discomfort and bruising as a result of the insertion of an intravenous cannula
- Physical discomfort related to positioning for the PET-CT scan
- A small amount of radiation to produce the PET images (details below)
- Infection from intravenous cannula site, which may require treatment with antibiotics
- An allergic reaction to injected tracer requiring further treatment.
- Death resulting from this procedure has not been reported

b. Risks Associated with Radiation Exposure

The dose of radiation a patient receives from a [^{18}F] FAPI PET/CT at the PAH is approx. 10 millisieverts (mSv) and from [^{68} Ga] FAPI PET/CT is approx. 6.5mSv. The participants in this study will receive two [^{18}F] FDG PET/CT scans, which is part of their standard of care therapy, and two [^{68} Ga] FAPI PET/CT scans. This equates to 23 mSv in total.

The annual occupational radiation exposure limit is 50 mSv per year, and even at this level, the increased cancer risk is so low that it cannot be measured against the normal incidence of cancer. It is, therefore, anticipated that participants will be at no increased risk of harmful effects from the PET/CT scans they receive.

c. Risks Associated with Injection of FAPI Ligand

Variations of the FAPI ligand, including [^{68} Ga]-FAPI-46, have been used in several human clinical trials to date. No adverse effects from an intravenous injection of radio-labelled FAPI have been identified.

d. Risk Management

Safety monitoring and reporting will be performed in accordance with the NHMRC safety monitoring and reporting in clinical trials involving therapeutic goods guidelines. An annual safety report will be provided to the approving HREC for safety review and study continuation approval.

Potential risks are included in the participant information and consent forms. Participants are free to choose to participate based on their preference and assessment of potential risks. No study activity will take place until consent has been obtained.

The less common risks of infection from intravenous cannula site and reaction to injected tracer can be minimised by following standard operating procedures.

e. Adverse Event Reporting

Adverse events are unlikely but may occur due to reaction to the tracer or complications resulting from infection of the intravenous cannula site. Any adverse events will be reported to HREC as per routine reporting.

10. Ethical Considerations

This study is to be conducted in full conformance with all stipulations of the protocol, the conditions of the HREC approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007), the principles of the "Declaration of Helsinki" and Good Clinical Practice. Study conduct will not commence until all necessary HREC, and Institutional Governance approvals and authorisations have been received.

11. Outcomes and Significance

Successful outcomes of this study could potentially:

1. *Guide clinical decisions in the early management of patients with PDAC*:
   We anticipate that [^{68} Ga] FAPI PET/CT will be superior to [^{18}F] FDG PET/CT in determining initial tumour burden and tumour response to chemotherapy. This will better guide clinicians' decisions concerning surgical or further treatment options resulting in decreased patient morbidity. This will also help determine the most cost-effective treatment plan.

2. *Promote future trials looking at the use of [^{68} Ga] FAPI PET/CT as a screening tool:*
   Should [^{68} Ga] FAPI PET/CT show high sensitivity in defining malignant pancreatic lesions, its use as a possible screening tool in high-risk patients could be investigated. This would lead to earlier intervention, improving clinical outcomes and decreasing mortality in patients with PDAC.

3. *Promote theranostic trials:*
   The FAPI molecule is a good therapeutic candidate because of its high uptake in pancreatic malignancies with negligible uptake in normal tissue. FAPI can therefore be used as an isotype to carry radioactive nuclides directly to the pancreatic tumour delivering a high dose of cytotoxic radiation and potentially overcome treatment resistance

Ultimately, this study will hopefully guide further research to bring about the clinical translation of this novel tracer. It will also allow our collaborative to establish FAPI manufacture locally, give our clinicians experience in the use of this PET tracer and enhance our track record in this research field to attract

future larger grants. Subsequent studies based off this study will only be undertaken once appropriate ethics and governance approvals have been sought.

12. Publication and Reporting

Data collected during this study is confidential, and no data identifying any participant will be published. The primary manuscript of this study will be presented to the academic community through posters and presentations at relevant forums. It will also be submitted to a suitable peer-review journal for consideration for publication. Participants will be given access to the manuscript at their request.

Should an incidental finding been discovered by [68Ga] FAPI PET/CT, it will be raised at the HPB MDT meeting and cross referenced with standard of care investigations. Decisions/ discussion points from the HPB MDT will be conveyed to the patient's treating clinician. No clinical decisions will be made from [68Ga] FAPI PET/CT alone. The patients treating clinician can then discuss further management of incidental findings with the patient.

13. References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021 May;71(3):209–49.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians. 2020 Jan;70(1):7–30.

3. Peng D, He J, Liu H, Cao J, Wang Y, Chen Y. FAPI PET/CT research progress in digestive system tumours. Vol. 54, Digestive and Liver Disease. Elsevier B.V.; 2022. p. 164–9.

4. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Vol. 395, The Lancet. Lancet Publishing Group; 2020. p. 2008–20.

5. Zins M, Matos C, Cassinotto C. Pancreatic adenocarcinoma staging in the era of preoperative chemotherapy and radiation therapy. Vol. 287, Radiology. Radiological Society of North America Inc.; 2018. p. 374–90.

6. Al-Hawary M, Behrman SW, Benson III AB, Lurie RH, Cardin DB, Gabriela Chiorean E, et al. NCCN Guidelines Version 1.2022 Pancreatic Adenocarcinoma Continue NCCN Guidelines Version 1.2022 Pancreatic Adenocarcinoma [Internet]. 2022. Available from: https://www.nccn.org/home/member-

7. Yang T, Ma L, Hou H, Gao F, Tao W. FAPI PET/CT in the Diagnosis of Abdominal and Pelvic Tumors. Vol. 11, Frontiers in Oncology. Frontiers Media S.A.; 2022.

8. Rohrich M, Naumann P, Giesel FL, Choyke PL, Staudinger F, Wefers A, et al. Impact of 68ga-FAPI pet/ct imaging on the therapeutic management of primary and recurrent pancreatic ductal adenocarcinomas. Journal of Nuclear Medicine. 2021 Jun 1;62(6):779–86.

9. Altmann A, Haberkorn U, Siveke J. The latest developments in imaging of fibroblast activation protein. Vol. 62, Journal of Nuclear Medicine. Society of Nuclear Medicine Inc.; 2021. p. 160–7.

10. Chen H, Zhao L, Ruan D, Pang Y, Hao B, Dai Y, et al. Usefulness of [68Ga]Ga-DOTA-FAPI-04 PET/CT in patients presenting with inconclusive [18F]FDG PET/CT findings. European Journal of Nuclear Medicine and Molecular Imaging. 2021 Jan 1;48(1):73–86.

11. Zi F, He J, He D, Li Y, Yang L, Cai Z. Fibroblast activation protein α in tumor microenvironment: Recent progression and implications (Review). Molecular Medicine Reports. 2015 May 1;11(5):3203–11.

12. Kelly T, Huang Y, Simms AE, Mazur A. Fibroblast Activation Protein-α. A Key Modulator of the Microenvironment in Multiple Pathologies. In: International Review of Cell and Molecular Biology. Elsevier Inc.; 2012. p. 83–116.

13. Cohen SJ, Alpaugh RK, Palazzo I, Meropol NJ, Rogatko A, Xu Z, et al. Fibroblast Activation Protein and Its Relationship to Clinical Outcome in Pancreatic Adenocarcinoma.

14. Rohrich M, Naumann P, Giesel FL, Choyke PL, Staudinger F, Wefers A, et al. Impact of 68ga-FAPI pet/ct imaging on the therapeutic management of primary and recurrent pancreatic ductal adenocarcinomas. Journal of Nuclear Medicine. 2021 Jun 1;62(6):779–86.

15. Chen H, Pang Y, Wu J, Zhao L, Hao B, Wu J, et al. Comparison of [68Ga]Ga-DOTA-FAPI-04 and [18F] FDG PET/CT for the diagnosis of primary and metastatic lesions in patients with various types of cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2020 Jul 1;47(8):1820–32.

16. Hicks RJ, Roselt PJ, Kallur KG, Tothill RW, Mileshkin L. FAPI PET/CT: Will It End the Hegemony of 18F-FDG in Oncology? J Nucl Med. 2021 Mar 1;62(3):296–302.

17. Pang Y, Zhao L, Shang Q, Meng T, Zhao L, Feng L, et al. Positron emission tomography and computed tomography with [68Ga]Ga-fibroblast activation protein inhibitors improves tumor detection and staging in

patients with pancreatic cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2022 Mar 1;49(4):1322–37.

18. Cassinotto C, Sa-Cunha A, Trillaud H. Radiological evaluation of response to neoadjuvant treatment in pancreatic cancer. Vol. 97, Diagnostic and Interventional Imaging. Elsevier Masson SAS; 2016. p. 1225–32.

19. Choi M, Heilbrun LK, Venkatramanamoorthy R, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using 18 F Fluorodeoxyglucose Positron Emission Tomography (FDG PET) to Monitor Clinical Outcomes in Patients Treated with Neoadjuvant Chemo-Radiotherapy for Locally Advanced Pancreatic Cancer. Am J Clin Oncol. 2010 Jun;33(3):257-61.