BEFAST STUDY:
[^{68}Ga]Ga-FAPI total body PET/CT for Better and Faster imaging in cancer

Protocol: [^{68}Ga]Ga-FAPI PET/CT for response evaluation during immune checkpoint inhibitor therapy in malignant melanoma

General Information

EudraCT information:

EU trial number: 2023-509549-11-00
Sponsors protocol number: 4
Study protocol version: 4

Sponsor

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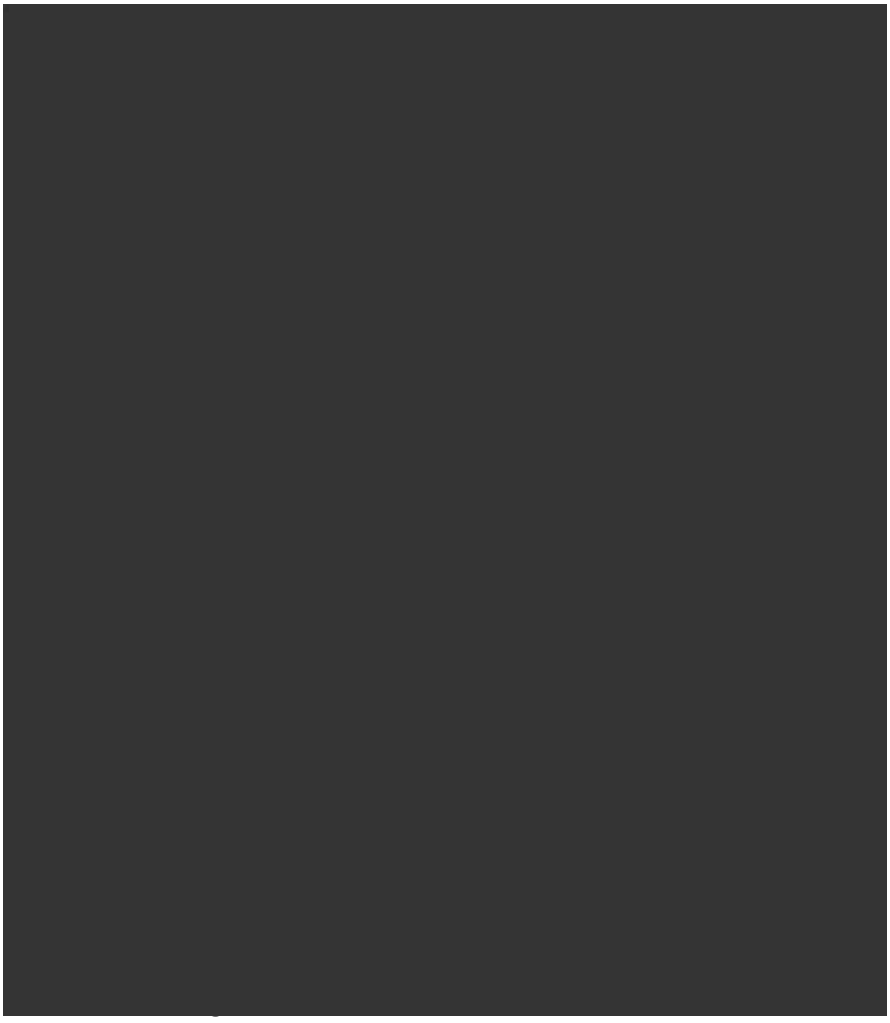
Principal Investigator (PI):

The information of the current PI is available on the European clinical trial information system (CTIS) website: https://euclinicaltrials.eu/. Information on this trial can be retrieved by using the EU trial number (2023-509549-11-00) as a search criteria.

List of advisors:



Localization of the trial:

The localization of the trial is available at the CTIS website: https://euclinicaltrials.eu/. Information on this trial can be retrieved by using the EU trial number (2023-509549-11-00) as a search criteria.

Collaborating departments

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GCP-monitoring:

The GCP-unit of Copenhagen University Hospital will monitor the trial.
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Statement:

The presented trials will be conducted in accordance with the protocol and laws and regulations on clinical trials provided by the Danish state and the European Union.

Timeframe:

The inclusion of patients is expected to start in the spring of 2025, and inclusion period is expected to last for 1 year. All patients have a follow-up period of 6 months. The trial will end 6 months after the last participant has completed their second [^{68}Ga]Ga-FAPI-46 PET/CT. Data will be stored for 25 years.

Signature

Glossary of Abbreviations

Abbreviation	Definition
ICT	immune checkpoint inhibitor therapy
IrAE	immune-related adverse events
PET	Positron Emission Tomography
CT	Computed Tomography
[^{18}F]FDG	2-[^{18}F]fluoro-2-deoxy-D-glucose (chemical name)
FAP	Fibroblast Activation Protein
FAPI	Fibroblast Activation Protein inhibitor
[^{68}Ga]	Gallium-68
[^{68}Ga]Ga-FAPI-46	[^{68}Ga]gallium (S)-2,2',2''-(10-(2-(4-(3-((4-(2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethylcarbamoyl)-quinolin-6-yl)(methyl)amino)-propyl)piperazin-1-yl)-2-oxoethyl) 1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (chemical name)
TME	Tumor microenvironment
TNM	Tumor, Node, Metastasis
CAF	Cancer Associated Fibroblasts
mSv	Millisievert
mBq	Megabecquerel
ECM	extra-cellular matrix
MMP	Matrix metalloprotease
ELISA	enzyme-linked immunosorbent assay
CRF/eCRF	Case Report Form/Electronic Case Report Form
PI	Principal Investigator
IMPD	Investigational medicinal product dossier
SUV	Standardized Uptake Value
CTIS	Clinical Trial information System
AE	Adverse Event
AR	Adverse Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected unexpected serious Adverse Reaction
RECIST	Response Evaluation Criteria in Solid Tumors
RSI	Reference safety information
GCP-unit	Good Clinical Practice-unit
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice

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1. Purpose:

The purpose of the study is to evaluate positron emission tomography/computed tomography (PET/CT) combined with the tracer [^{68}Ga]Gallium (S)-2,2',2''-(10-(2-(4-(3-((4-(2-(2-cyano-4,4-difluoropyrrolidin-1-yl)-2-oxoethylcarbamoyl)-quinolin-6-yl)(methyl)amino)-propyl)piperazin-1-yl) 2-oxoethyl) 1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid (**[^{68}Ga]Ga-FAPI-46**) for response evaluation during immune checkpoint inhibitor therapy (ICT) in patients with advanced stage malignant melanoma.

2. Background:

Malignant melanoma is one of the most common types of cancers in Denmark. The incidence is 5.7% for women and 6.6% for men, and has increased over the past 10 years (1). The cancer is highly aggressive and treatment resistant especially in advanced stages. The introduction of immunotherapy and especially immune checkpoint inhibitor therapy (ICT) have improved survival rates for malignant melanoma patients with advanced stages (2, 3). In addition, ICT has also proven to be useful in an adjuvant and neoadjuvant setting for patients with low stages(4).

Immune checkpoint inhibitors stimulate the patient's own immune system by blocking regulators that normally downregulate and fine-tune T-cell activation (5). Blocking these regulators cause the T-cells to recognize foreign cells such as cancer cells. The therapy causes an indirect effect on cancer cells by generating an immune response towards the malignant tumor with immune-cell infiltration followed by inflammation and cytotoxicity. This effect induces a different tumor response compared to chemotherapy (6). ICT can cause a delayed tumor-response, and the responses can be preceded by initial worsening (pseudo-progression) (7). A downside to ICT is the immune-related adverse events (IrAE). IrAEs result from inflammatory damage in healthy tissue. Blocking the naturally occurring regulation of T-cells generates overactive immune cells, which causes the autoimmune reaction in addition to the desired reaction towards cancer cells. Most common IrAEs are diarrhea, pruritus, rash, colitis vitiligo and endocrine IrAEs

such as thyroiditis and hypophysitis (7). It is estimated that IrAE will occur in 15-90% of patients treated with ICT. More severe events can occur in 15-30% of patients, depending on the type of ICT used (5).

Positron emission tomography (PET) with the radioactive tracer 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) combined with computed tomography (CT) is a scanner modality that plays a key-role in staging, response evaluation and follow-up in malignant melanoma(8-11). The radioactive tracer is an isotope fluorine 18 (^{18}F) bound to the glucose analogue 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG). Patients are injected with the tracer prior to the scan, and cells will take up the radioactive glucose analogue. The basis for imaging with [^{18}F]FDG PET is the increased glucose uptake and metabolic trapping in cancer cells(12). The CT component helps to visualize the anatomical location of the increased metabolism (13).

Even though [^{18}F]FDG PET/CT is a sensitive diagnostic tool, it still lacks specificity in some settings; [^{18}F]FDG PET/CT has limited specificity in discriminating between inflammation and cancer, which is due to an unspecific uptake of [^{18}F]FDG in inflammatory and infectious processes(8). This pitfall is especially evident in response evaluation of malignant melanoma treated with ICTs, as the inflammatory damage on the malignant lesions and the IrAEs can be confused with progressive disease (7).

In recent years, researchers have focused on developing diagnostic tracers that targets the tumor microenvironment (TME). The TME is composed of non-malignant cells and has been recognized as an important part of tumor development (14). Cancer associated fibroblasts (CAFs) are a group of hyperactive stromacells within the TME, which can promote inflammation, tumor growth, angiogenesis and drug resistance. In vitro and in vivo studies have shown that CAFs promote melanoma cell proliferation and invasion (15, 16). CAFs express a variety of targetable factors, including the transmembrane glycoprotein called fibroblast activation protein (FAP). FAP is a known marker for CAFs and is upregulated in 90% of epithelial neoplasms and malignant melanoma (17). The presence of FAP on CAFs is also associated with tumor growth and migration(14). The so-called FAPI is a specific enzyme inhibitor that binds to FAP on CAFs (18). FAPI can be combined with different radioactive components to create radioactive tracers for use in PET imaging. Especially FAPI-variants bound to gallium-68 ([^{68}Ga]Ga-FAPI) have been evaluated. Unlike [^{18}F]FDG, [^{68}Ga]Ga-FAPI does not reflect characteristics of the tumor and inflammatory cells (increased glucose metabolism), but the pro-carcinogenic microenvironment with CAFs (16).

PET/CT imaging with [^{68}Ga]Ga-FAPI variants has shown high sensitivity in diagnosing primary tumor (estimated pooled sensitivity of 1.0), as well as distant metastasis (estimated pooled sensitivity of 0.93) in different cancer types(19). This tracer is unique as it offers low uptake in most normal tissue and high uptake in malignant lesions (20, 21), thus improving tumor-to-background-ratio (TBR) compared to standard [^{18}F]FDG PET/CT. One case study demonstrated increased uptake of [^{68}Ga]Ga-FAPI compared to [^{18}F]FDG in metastatic lesions in a patient with malignant melanoma (22). Especially, the liver metastases had increased uptake and improved TBRs on [^{68}Ga]Ga-FAPI PET compared to [^{18}F]FDG PET.

The potential of [^{18}Ga]FAPI PET in detecting malignant lesions in malignant melanoma patients have primarily been demonstrated in case reports. Larger studies on the use of [^{68}Ga]FAPI-46 PET or other FAPI tracer variants in malignant melanoma patients have not been identified in the peer reviewed literature.

[^{68}Ga]Ga-FAPI-PET could also play a potential role in response evaluation of ICT, as CAFs has been recognized as emerging key-players in immune regulation of the TME, promoting local

immunosuppression(23-25). Interestingly, normal stromal fibroblasts inhibit invasion of malignant melanoma by recruiting immune cells and studies have shown that melanoma cells secrete regulating factors, which transform normal fibroblasts into CAFs (15). [^{68}Ga]Ga-FAPI PET has also been suggested as a modality to detect or predict side effects of ICT. FAP-expression is also seen in non-cancerous tissue during physiological and pathological processes such as inflammation and fibrosis. As such, one pilot study found [^{68}Ga]Ga-FAPI PET to be potentially useful in detecting early signs of ICT-associated myocarditis(26). Case studies have also reported increased FAPI-uptake in organs with an inflammatory reaction caused by ICT such as immunotherapy-related thyroiditis(27) and immuno-therapy related polyarthritis(28).

Imaging with [^{68}Ga]Ga-FAPI offers several potential advantages for patient comfort and logistics. No fasting or any other preparation prior to [^{68}Ga]Ga-FAPI PET imaging is required. In addition, preliminary studies suggest that imaging can be performed as early as 10 min post injection (29). Thus, [^{68}Ga]Ga-FAPI-46 could improve logistics and patient comfort. Current PET/CT with [^{18}F]FDG requires patients to fast for 4-6 hours and wait for 60 mins after tracer injection before scanning. This adds to the relatively complex logistics and patient stress associated with a [^{18}F]FDG PET/CT scan. This is especially evident for patients with melanoma, who undergo repeated [^{18}F]FDG PET/CT scans during treatment and during the surveillance period. With [^{68}Ga]Ga-FAPI-46 the time a patient needs to spend at the hospital for a PET/CT scan could potentially be reduced from approx. 2 hours to 1 hour by moving from [^{18}F]FDG-PET/CT to [^{68}Ga]Ga-FAPI-46 PET/CT.

[^{68}Ga]Ga-FAPI PET/CT has proven to be safe, with no tracer-related adverse events in adult cancer patients with various diagnoses (30-33). More than 1000 patients have been scanned with this tracer without any other reporting of side effects. In addition, a recently published paper by Hirmas et al presented data on 303 patients scanned with [$_{68}$Ga]Ga-FAPI-46(34) .The effective radiation dose of different types of FAPI-ligands bound to ^{68}Ga varies between 0.008-0.016 millisieverts (mSv)/megabecquerel(MBq), which is lower than the effective dose of the standard [^{18}F]FDG, 0.020 mSv/MBq (35).
For the variant [^{68}Ga]Ga-FAPI-46, administration of 200 MBq will cause a total body effective radioactive dose of 1,56+/-0.26 mSV (30).

Based on the current knowledge, we believe that the tracer [^{68}Ga]Ga-FAPI-46 can improve PET/CT for response evaluation for patients with melanoma treated with ICT. Furthermore, it has the potential to improve logistics and patient comfort for these patients. We do not believe any other studies have evaluated the use of the tracer [^{68}Ga]Ga-FAPI-46 in response evaluation during ICT in this patient group.

2.1 Evaluation of FAP-biomarkers in liquid biopsies

Expression of FAP has been shown to be involved in extra-cellular matrix (ECM) remodeling and fibrogenesis. Excessive ECM degradation, e.g., from matrix metalloprotease (MMP) mediated cleavage during tumor progression, results in protein fragments that are released into the circulation. These fragments can be assessed non-invasively as a liquid biopsy and quantified as a disease-biomarker. As FAP has been shown to cleave ECM components including type I and III collagen, it can be expected that fragments from these cleavages would appear in circulation (36). Zhang et al. have identified multiple potential FAP cleavage sites in various ECM-associated proteins, including ^{1069}AGPSGAPGPA^{1078} on mouse type III collagen (37).
Nordic Bioscience has developed a competitive enzyme-linked immunosorbent assay (ELISA) targeting fragments of the alpha-1 chain of human type III collagen. This fragment is generated by cleavage of the

alpha-1 chain between amino acid residues P^{1069} and A^{1070} (C3F (the human equivalent to the previously mentioned cleavage site on mouse type III collagen)) by FAP. As such, these fragments can serve as a biomarker of FAP activity in the ECM.
Nordic bioscience has also confirmed the specificity of the ELISA assay to the FAP cleaved type III collagen. They have also measured the levels of C3F in a lung cancer cohort and compared the levels in patients with adenocarcinoma and squamous cell carcinoma to healthy subjects. In this cohort, the levels of C3F were elevated in the patients with lung cancer (data not published).

As C3F reflects FAP activity, we expect that it would correlate to the quantification of signal detected from the FAPI-tracer on [^{68}Ga]Ga-FAPI-46 PET/CT of patients with cancer. In this study, we plan on exploring this correlation and generate preliminary evidence, which can support this hypothesis. In the future, these liquid biopsies of FAP activity biomarkers could be a potential screening tool for selecting the right patients to receive a PET/CT scan and to provide a way to monitor the patients between PET/CT scans.

3. Trial Objectives

The aim of the study is to evaluate [^{68}Ga]Ga-FAPI-46 PET/CT as a non-invasive diagnostic tool for response evaluation during ICT in patients with advanced stage malignant melanoma.

3.1 Study Hypothesis

- [^{68}Ga]Ga-FAPI-46 PET/CT can improve response evaluation in patients suffering from advanced stage malignant melanoma treated with ICT and potentially serve as a biomarker.

3.2 Primary objectives

1) Evaluate [^{68}Ga]Ga-FAPI-46-uptake in malignant lesions on [^{68}Ga]Ga-FAPI-46 PET/CT.
2) Evaluate changes in [^{68}Ga]Ga-FAPI-46-uptake in malignant lesions on [^{68}Ga]Ga-FAPI-46 PET/CT during ICT.
3) Compare the changes in malignant lesions on [^{68}Ga]Ga-FAPI-46 PET/CT with changes on standard [^{18}F]FDG PET/CT and clinical response during ICT.

Changes in FAPI-uptake in both primary tumour and metastases between the baseline [^{68}Ga]Ga-FAPI-46 PET/CT and [^{68}Ga]Ga-FAPI-46 PET/CT after 3 months of ICT will be estimated qualitatively. This will be compared with changes on a standard [^{18}F]FDG PET/CT and the clinical response (please refer to section 4.9 and 4.10).

3.3 Secondary objectives

1) Evaluate if changes in [^{68}Ga]Ga-FAPI-46 uptake during ICT in healthy tissue can be used as a predictor of potential side effects.
2) Compare changes on [^{68}Ga]Ga-FAPI-46 PET/CT in healthy tissue with changes on standard [^{18}F]FDG PET/CT.

Differences in tracer-uptake in healthy tissue between the baseline [^{68}Ga]Ga-FAPI-46 PET/CT and [^{68}Ga]Ga-FAPI-46 PET/CT after 3 months of ICT treatment will be evaluated. These changes will be compared to any side effect that the patients may experience during ICT. The FAPI-uptake on [^{68}Ga]Ga-FAPI-46 PET/CT will

also be compared to findings on the routine follow-up [^{18}F]FDG PET/CT (please refer to section 4.9 and 4.10).

3.4 Exploratory objectives:

1) Correlation between [^{68}Ga]Ga-FAPI-46-uptake on [^{68}Ga]Ga-FAPI-46 PET/CT and levels of FAP activity biomarkers in serum blood samples.
2) Correlation between [^{68}Ga]Ga-FAPI-46-uptake on [^{68}Ga]Ga-FAPI-46 PET/CT and levels of other biomarkers (e.g. ECM remodeling biomarkers) in serum blood samples.
3) Correlation between levels of biomarkers in serum blood samples and treatment outcome.

Blood samples from the participants included will be analyzed by Nordic Bioscience. Results from this analysis will be correlated to the disease activity measured quantitatively on the [^{68}Ga]Ga-FAPI-46 PET/CT. In addition, we will correlate results from the biomarker analysis with treatment outcome of immunotherapy after 6 months using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

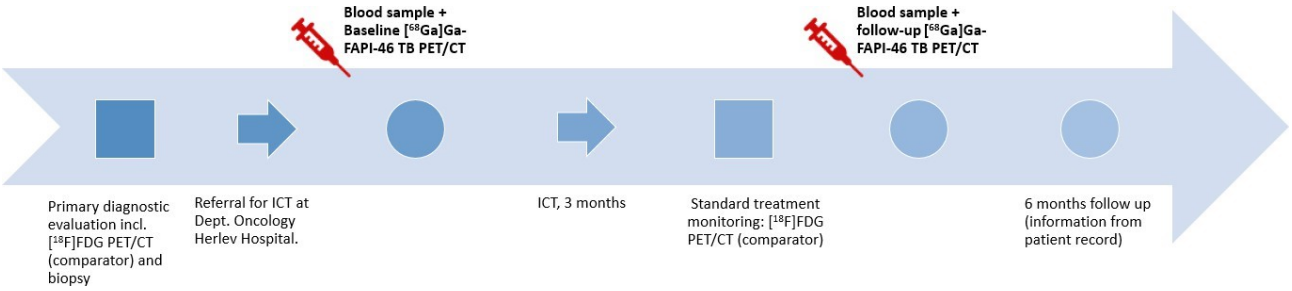
4. Methods and Design:

4.1 Study Design

The study is a phase II nonrandomized clinical trial evaluating [^{68}Ga]Ga-FAPI-46 PET/CT for response evaluation during ICT in patients with advanced stage malignant melanoma with visible target lesions on standard [^{18}F]FDG PET/CT. The study will be regarded as a pilot study and include 20 patients.

The included participants will undergo two scans in addition to their standard imaging (diagnostic [^{18}F]FDG PET/CT). At baseline the patients will undergo a [^{68}Ga]Ga-FAPI-46 PET/CT (the project scan). This will be performed before initiation of ICT. In addition to the scan, a blood sample will be collected prior to injection of the tracers. After 12 weeks of treatment, the participant will undergo the same project scan ([^{68}Ga]Ga-FAPI-46 PET/CT) and a second blood sample in addition to their standard imaging (diagnostic [^{18}F]FDG PET/CT). Thus, participants will be included for 2 [^{68}Ga]Ga-FAPI-46 PET/CT, two blood samples and passive follow-up for 6 months after the last [^{68}Ga]Ga-FAPI-46 PET/CT scan.
For details on procedure, dose and frequency of injection of the tracer during the PET/CT scan please refer to section 4.5. All eligible participants will receive the standard treatment and standard surveillance of their cancer, no matter their participation status.

4.2 Trial procedure



4.3 Test group

Patients with advanced stage malignant melanoma with visible lesions on [^{18}F]FDG PET/CT referred for ICT at the Dept. of Oncology Herlev Hospital will be sought enrolled. The study will include 20 patients with two evaluable [^{68}Ga]Ga-FAPI-46 PET/CT.

4.3.1 Inclusion criteria

1) Male or female, ≥18 years old
2) Histological verified metastatic or locally advanced malignant melanoma
3) Visible malignant lesions on [^{18}F]FDG PET/CT or CT
4) Subjects must be considered inoperable
5) Subjects must be considered medically suitable for ICT
6) Subjects must be able to read and understand the patient information in Danish to give informed consent

4.3.2 Exclusion criteria

1) Ocular or mucosal melanoma
2) Other concurrent cancer disease
3) Previous systemic oncological treatment with ICT
4) Pregnancy or lactation
5) Weight more than the maximum limit of a PET/CT-scanner bed (140 kg)
6) History of allergic reaction due to compounds similar to the chemical composition of [^{68}Ga]Ga-FAPI-46

If the patient is fertile, the patient will be asked about potential pregnancy and a urinary pregnancy test will be performed before inclusion. If the patient is postmenopausal (defined by the Danish Medical Agency as having absence of menstruation in at least 12 months before inclusion (38)) or infertile due sterilisation no pregnancy test will be performed. The result of the pregnancy test will be documented in the electronic case report form (eCRF). The reason for not performing the pregnancy test will also be documented in the eCRF.

If the patient exhibits signs of severe allergic reaction after injection of the tracer, the patient will be excluded from the study.

If the PET/CT scan reveals that the tracer has been injected subcutaneously, the patient will be excluded from the trial.

4.3.3 Withdrawal of participants:

Patients must be withdrawn from the trial if the following occurs:

1) The participant withdraws his/hers consent.
2) The participant does not start the planned treatment with ICT.
3) The participant stops ICT before 3 months of treatment.
4) The participant cannot go through with the first [^{68}Ga]Ga-FAPI-46 PET/CT.
5) The investigator decides to withdraw the participant, in case the investigator finds it necessary for the safety of the individual participant.

All data on participants, including excluded and withdrawn participants will be stored for 25 years.
Data on participants who are excluded or withdrawn before the first [^{68}Ga]Ga-FAPI-46 PET/CT will not be used for the final analysis. However, the data will be used to document total amount of excluded and withdrawn participants and reasons for this. Participants who are excluded after they have undergone the first project scan [^{68}Ga]Ga-FAPI-46 PET/CT will be used for specific analysis, however, not the comparative analysis between the first and second [^{68}Ga]Ga-FAPI-46 PET/CT scan.
Participants who are excluded or withdrawn after the project scan will be observed for adverse reaction and events during and after the scan the same way as patients, who are included.

The study will be terminated by the sponsor/principal investigator (PI) in case of unexpected or unacceptable side effects. However, we do not expect to end the trial prematurely due to safety, as no serious adverse reaction or events have been reported in previous trials.

4.3.4 Compensation for potential dropouts and excluded and withdrawn patients

Only patients with evaluable [^{68}Ga]Ga-FAPI-46 PET/CT scans are accounted for in the final sample size. Thus, patients excluded or withdrawn from the study before the project scans will be replaced until at total number of 20 patients with two evaluable [^{68}Ga]Ga-FAPI-46 PET/CT are met.

4.4 Recruitment of Patients

The recruitment arrangements are described in the document “Recruitment arrangements” in part II of the application dossier.

4.5 [^{68}Ga]Ga-FAPI-46 PET/CT scan

Information on production, preparation and handling of the tracer [^{68}Ga]Ga-FAPI-46 is described in the investigational medicinal product dossier (IMPD). The tracer is produced and finalized for administration at the Dept. of Clinical Physiology and Nuclear Medicine, Cyclotron section and Radiochemistry, Rigshospitalet, who will comply with directions described in the IMPD. The precursor FAPI-46 acetat salt (GMP) (which is used to produce the tracer) is produced by the firm ABX in Dresden, Germany and delivered via SOFIE Bioscience.

[^{68}Ga]Ga-FAPI-46 is a sterile solution for intravenous injection. All incoming raw materials will be registered and tested. For each synthesis raw materials used will be documented in a dedicated batch record ensuring full traceability. The investigational medicinal product (IMP) is accounted for in the "IMP accountability log", where used IMPs as well as destructed IMPs are accounted for. Methods for quality control are validated. [^{68}Ga]Ga-FAPI-46 will only be released when all quality control tests are within specifications. The released product will be accompanied with a dose sheet containing information about the batch number, the volume, the calibration time, and the available doses at different time points within the shelf-life of the product. Final release will be performed by a person qualified to do so by The Danish Medicines Agency (Qualified Person). The Dept. of Clinical Physiology and Nuclear Medicine will handle the bookkeeping regarding the use of the compound. The tracer has proven to be safe, and no adverse reactions have been reported (30-32).

When the [^{68}Ga]Ga-FAPI-46 is administered, the batch number, the injected/administered dose and the time of injection/administration will be documented on a PET administration sheet ("PET arbejdsseddel"), which is correlated to each individual participant with their CPR number. This sheet will be saved, which also will secure full traceability. Any excess tracer not administered to the subjects will be destroyed.

Prior to initiation of ICT, participants will undergo an [^{68}Ga]Ga-FAPI-46 PET/CT scan at the Department of Clinical Physiology and Nuclear Medicine, PET section 3982, Rigshospitalet.
Upon arrival, the participant will be placed in a bed in a relaxed prone position. The participant will be informed about the outline of the scan, and questioned about relevant conditions (allergies, potential pregnancy etc.). If the participant is female and fertile, and if the pregnancy test from the inclusion consultation is more than 48 hours old, we will perform another urinary pregnancy test. If the pregnancy test is negative, the patient can go through with the project scan. The test result will be documented on the PET administration sheet by the scanning personnel and afterwards documented in the eCRF. A peripheral venous catheter is placed the cubital fossae for tracer injection.

The participant will then be injected with 1-2MBq/kg of [^{68}Ga]Ga-FAPI-46, with a minimum dose of 100 MBq and a maximum dose of 246 MBq (30, 39). The content of FAPI-46 in each batch of [^{68}Ga]Ga-FAPI-46 is limited to 50 µg. The patient will only get a fraction of the full batch of the tracer. This means that the dose of [^{68}Ga]Ga-FAPI-46 for each participant never will exceed 50 µg (please refer to the IMPD quality page 24).

The patient will then rest for 30-40 min, to let the tracer be distributed within the body. The participant will then undergo a PET scan of 10-20 min. The PET scan will cover an area from vertex to mid-thighs as standard. However, if the patient has distant metastases on the lower part of the legs/or feet, this will be included in the scan. The patient will receive a low dose CT scan, which will be performed prior to the PET scan. The radiation dose of the [^{68}Ga]Ga-FAPI-46 PET/CT is approximated to 6 mSv.
After 12 weeks of ICT, patients will undergo another [^{68}Ga]Ga-FAPI-46 PET/CT, and the same procedure will be followed.

Patients will be observed during both scanning sessions. After 24 hours of the first scan, the patient will be contacted by co-investigators or delegated research personnel to check the patients' condition. Any adverse event will be recorded, and the reporting standards stated in section 7 will be followed.

4.6 Standard imaging [^{18}F]FDG PET/CT (Comparator)

Included patients will have undergone a standard [^{18}F]FDG PET/CT for routine clinical purposes before entering the trial and starting treatment with ICT. Included patients will also undergo a standard [^{18}F]FDG PET/CT for monitoring the disease during treatment. This is standard monitoring procedure for all patients with malignant melanoma in treatment with ICT regardless of the inclusion in the trial. These scans will be done at Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital or at the Department of Clinical Physiology and Nuclear Medicine at Rigshospitalet.

[^{18}F]FDG is a marketed product. Information regarding handling of the tracer [^{18}F]FDG is described in the product resume. The tracer is produced and finalized for administration at the Dept. of Clinical Physiology and Nuclear Medicine, Cyclotron section and Radiochemistry, Rigshospitalet, or at Dept. of Clinical Physiology and Nuclear Medicine Herlev Hospital, who will comply with directions described in the product resume.

[^{18}F]FDG is a sterile solution for intravenous injection. All incoming raw materials will be registered and tested. For each synthesis raw materials used will be documented in a dedicated batch record ensuring full traceability. Methods for quality control are validated. [^{18}F]FDG will only be released when all quality control tests are within specifications. The Dept. of Clinical Physiology and Nuclear Medicine at Herlev Hospital or Rigshospitalet will handle the bookkeeping regarding the use of the compound.

When the [^{18}F]FDG is administered, the lot number or batch number, the injected dose and the time of injection will be documented. This information will be available in the electronical medical record (Sundhedsplatformen) of each participant. The information will be documented in the eCRF. As the information is available from the personal electronical medical record, the information will be fully traceable to the individual participant. At Rigshospitalet, this information will also be documented on a PET administration sheet ("PET arbejdsseddel"), which is correlated to each individual participant with their CPR number. This sheet will also be saved electronically, which also will secure full traceability.

The procedures of the scans will be done in accordance with local guidelines (please refer to appendix 3). In general, the scans will proceed as follows: Before arrival the participant will have to fast for minimum 4 hours and limit hard physical activity 24 hours before the scan. If the participant suffers from diabetes, specific preparation is needed. This is described in detail in local guidelines (please refer to the appendix 3). Upon arrival at the Department of Clinical Physiology and Nuclear Medicine at either Herlev Hospital or Rigshospitalet, the participant will be placed in a bed in a relaxed prone position. The participant will be informed about the outline of the scan, and questioned about relevant conditions (e.g., allergies and diabetes) and if the patient has fasted. If the participant is female and fertile, a urinary pregnancy test will be performed. If the pregnancy test is negative, the patient can go through with the scan. A peripheral venous catheter is placed the cubital fossae for tracer injection. The participant will then be injected with 3-4 MBq/kg of [^{18}F]FDG, with a maximum dose of 400 MBq. The participant will then rest for 45-60 min to let the tracer be distributed in the body. The patient will then be placed in a PET/CT scanner, and undergo a combined PET and CT scan for 15-20 min.

4.7 Blood sample

One 4 ml serum blood sample will be taken prior to each of the [^{68}Ga]Ga-FAPI-46 PET/CT. Blood samples will be transferred to the Department of clinical biochemistry Research Section Rigshospitalet immediately after the sample has been taken. Trained personnel at the department will handle and store the blood samples in a biobank until collected by Nordic bioscience. The blood samples will then be analyzed by Nordic bioscience, using an in house competitive ELISA. For more information on blood sample storage and analysis please refer to section 8.

4.8 List of medicinal products:

4.8.1 Investigational medicinal products

Product name	Active ingredient	Type of medicinal product	Regulatory status	Reference Safety information (RSI)
[^{68}Ga]Ga-FAPI-46	[^{68}Ga]Ga-FAPI-46	A positron emission tomography (PET) radioligand for detecting Fibroblast Activation Protein (FAP)	No marketing authorization	Investigators Brochure and IMPD

4.8.2 Comparator

Product name	Active ingredients	Purpose in the study	Regulatory status	Reference Safety information (RSI)
[^{18}F]FDG	[^{18}F]FDG	[^{18}F]FDG is indicated for diagnostic use with PET	Marketing authorization	Product resume, see appendix 1.

4.9 Interpretation of project scans

The baseline and the follow-up [^{68}Ga]Ga-FAPI-46 PET/CT scan will be evaluated using a standardised method by a team of experienced specialists in clinical physiology and nuclear medicine. The uptake of [^{68}Ga]Ga-FAPI-46 in selected lesions and in normal tissue will also be evaluated. Differences in uptake between the baseline project scan and the follow-up project scan will be estimated. Results from the scan assessments will be documented in the eCRF.

If any condition is visible on the project scans that requires urgent medical attention (e.g. pulmonary embolism), the participants' primary physician will be contacted by the co-investigator. In this context, the primary physician will most likely be an oncologist from Herlev Hospital. The participants will be informed of the condition and treated according to local guidelines by their primary physician.

4.10 Interpretation of clinical scans

The clinical standard imaging [^{18}F]FDG PET/CT scans will be used to assess treatment response in the study. Treatment response will be evaluated retrospectively using the RECIST criteria (40). The most recently updated version of the guideline will be used. The standard imaging will also be evaluated clinically as part of the normal treatment monitoring, and patients will get the description of the scan from their primary physician, which will be an oncologist from the Department of Oncology at Herlev Hospital.

4.11 Endpoint assessment:

4.11.1 Primary Objectives

1) *Evaluate changes in [^{68}Ga]Ga-FAPI-46 uptake in malignant lesions on [^{68}Ga]Ga-FAPI-46 PET/CT.*
2) *Evaluate changes in [^{68}Ga]Ga-FAPI-46-uptake in malignant lesions on [^{68}Ga]Ga-FAPI-46 PET/CT during ICT.*
3) *Compare the changes in malignant lesions on [^{68}Ga]Ga-FAPI-46 PET/CT with changes on standard [^{18}F]FDG PET/CT and clinical response during ICT.*

Specified malignant lesions will be defined and evaluated by a team of specialists on the baseline [^{68}Ga]Ga-FAPI PET/CT scan and the uptake of the FAPI tracer in the lesions will be quantified (please refer to section 4.9). The evaluation of the malignant lesions on [^{68}Ga]Ga-FAPI PET/CT will also be compared with a similar lesion evaluation on the [^{18}F]FDG PET/CT (standard imaging). The FAPI-uptake will be reassessed after 12 weeks of ICT by the same team of specialists. Changes in uptake of malignant lesions after 12 weeks of ICT on the [^{68}Ga]Ga-FAPI-46 PET/CT will be compared to changes on the [^{18}F]FDG PET/CT and the clinical response. The clinical response will be assessed using the patients' medical record.

4.11.2 Secondary objectives

1) *Evaluate if changes in [^{68}Ga]Ga-FAPI-46-uptake during ICT in healthy tissue can be used as a predictor of potential side effects.*
2) *Compare changes in uptake on [^{68}Ga]Ga-FAPI-46 PET/CT in healthy tissue with changes on standard [^{18}F]FDG PET/CT.*

Tracer-uptake in healthy tissue and benign lesions on [^{68}Ga]Ga-FAPI-46 PET/CT will be evaluated using the same method as described in "Primary Objectives". A similar evaluation of standard [^{18}F]FDG PET/CT will be performed. FAPI-uptake in healthy tissue on [^{68}Ga]Ga-FAPI-46 PET/CT will be compared to the findings on [^{18}F]FDG PET/CT. To verify the [^{68}Ga]Ga-FAPI-46 PET/CT assessment (including evaluation of healthy tissue, malignant lesions and benign lesions), the assessment will be compared to the findings from a composed reference standard. This consist of all available imaging, biopsy results, blood tests, and information on hospitalization and changes in patient management up to 6 months after the [^{68}Ga]Ga-FAPI PET/CT.

Changes in FAPI-uptake on the [^{68}Ga]Ga-FAPI PET/CT and FDG-uptake on the standard [^{18}F]FDG PET/CT in normal tissue after 3 months of ICT will be evaluated. Changes in FAPI-uptake will also be compared to any side effect (IrAE) that the patients may experience during ICT. The presence of IrAE will be determined by an expert in oncology, who is blinded from the project scans. The expert will evaluate the patients' clinical records, using all available imaging, biopsy results, information on hospitalization and changes in patient management up to 6 months after the baseline [^{68}Ga]Ga-FAPI PET/CT.

4.11.3 Exploratory objectives:

1) *Correlation between [^{68}Ga]Ga-FAPI-46-uptake on [^{68}Ga]Ga-FAPI-46 PET/CT and levels of FAP-activity biomarkers in serum blood samples during ICT.*
2) *Correlation between [^{68}Ga]Ga-FAPI-46-uptake on [^{68}Ga]Ga-FAPI-46 PET/CT and levels of other biomarkers(e.g. ECM remodeling biomarkers) in serum blood samples.*
3) *Correlation between levels of biomarkers in serum blood samples and treatment outcome.*

Blood samples from the included participants will be analyzed by Nordic Bioscience (please refer to section 2, Background). Results from this analysis will be correlated to the disease activity evaluated on the [^{68}Ga]Ga-FAPI-46 PET/CT. Results from the serum blood sample analysis will also be correlated with treatment outcome after 6 months of treatment. Treatment outcome will be defined using the RECIST criteria (40). This analysis will be done retrospectively on routine clinical scans (PET/CT). The updated guideline and definitions of the RECIST criteria will be used.

5. Statistics:

5.1 Sample size:

[^{68}Ga]Ga-FAPI-46 PET/CT has not previously been tested in patients with malignant melanoma in this specific setting. The study will be regarded as a pilot study, and we plan to include 20 patients with an interim analysis when the first 10 patients have undergone the baseline [^{68}Ga]Ga-FAPI-46 PET/CT (please refer to section 6).

5.2 Statistical analyses:

All statistical analyses will be conducted using the statistical analysis programs SPSS or R.
Descriptive statistics will be performed to evaluate patient characteristics and tumor characteristics. For description of FAPI-measurements from the scan, the arithmetic mean, standard deviation and median will be used. Comparison between [^{68}Ga]Ga-FAPI-46 and [^{18}F]FDG evaluation of malignant lesions (primary tumor and metastases) and normal tissue will be performed with a paired non-parametric test or a paired student's t-test. Changes on the [^{68}Ga]Ga-FAPI-46 will be correlated to the result from the response assessment using a non-parametric test (e.g. Kruskal Wallis test). A similar method will be used to evaluate FAPI-uptake changes in normal tissue and the correlation to IrAE.

Correlation between FAPI-uptake and results from the blood samples will be compared using statistical correlation-tests (e.g. Spearman rank correlation). The correlation between treatment outcome and levels of FAP-activity biomarkers/other relevant biomarkers in the blood will be evaluated using a paired student's t-test or paired non-parametric test. The test could also be performed with a Point Bisereal correlation test.

Two-tailed p-value of <0.05 will be considered significant. If any substantial changes in the original statistical plan are made (e.g. change in sample size), this will be reported as an amendment. In the Clinical Trial Regulation, substantial amendments are named substantial modifications, and a substantial modification (amendment) will be submitted via Clinical trial information system (CTIS) to the Danish Medicines Agency and the Danish Medical Research Ethics Committee. Data from the included patients will be used for all the statistical analyses. Data on participants, who have been excluded after having undergone one of the two [^{68}Ga]Ga-FAPI-46 PET/CTs, will be used for selected analyses. Data that turns out to be incorrect or false will not be used in the final analysis. Data not used will be stored in the eCRF.

6. Interim analysis:

An interim analysis will be performed after 10 baseline [^{68}Ga]Ga-FAPI-46 PET/CT scans to evaluate quality and usefulness of the scans. This will be done by the sponsor/PI and a co-investigator.
A qualitative analysis of the first 10 scans will be performed. This analysis will determine if the scans have the quality to be used for interpretation and evaluation of lesions suspicious of malignancy and also if quality of the scans allow readings of uptake-values in suspected lesions. If less than 5 of the first 10 patients demonstrate FAPI-uptake in known tumors the study will not continue. Otherwise, we will continue until 20 evaluable patients (undergoing baseline as well as 3 months follow-up scan) has been included. In addition, the sponsor/PI will evaluate the safety of the study. If any unexpected serious adverse reactions or serious adverse events after the [^{68}Ga]Ga-FAPI-46 PET/CT scan have occurred at that time point, the trial will be stopped. We do not expect to end the trial prematurely due to safety, as no serious adverse reaction or events have been reported in previous trials.

7. Side effects and Risks

7.1 Side effects of the investigational medicinal product

[^{68}Ga]Ga-FAPI-46 tracer: No adverse reaction or events have been reported in the first radiation dosimetry and biodistribution studies of [^{68}Ga]Ga-FAPI-46 (30, 41, 42) and in later phase II studies (31, 32). More than 1000 patients have been scanned with this tracer without any other reporting of side effects. There is, however, always a risk of unexpected side effects or allergic reactions as with all other medications.

7.2 Side effects of the comparator

[^{18}F]FDG tracer: [^{18}F]FDG is a standard tracer used for PET/CT in diagnostic cancer imaging, including for monitoring and diagnosing patients with malignant melanoma. There is a low probability of side effects after administration of [^{18}F]FDG. The tracer is contraindicated in patients with hypersensitivity reaction to any active substance or excipients in the solution. The sensitivity of the [^{18}F]FDG PET examination can be compromised by medicinal products that affect blood glucose levels (e.g. corticosteroids) and insulin levels, which should be taken into consideration before the examination (please refer to product resume, appendix 1, section 4.5 and 4.8). The [^{18}F]FDG PET/CT scan is a standard evaluation scan, which will be conducted as a part of the routine clinical examinations for the included patients, and will be done regardless of the inclusion in the trial.

7.3 Risks during the study

The participants receive radiation from radioactive component of the tracer [^{68}Ga]Ga-FAPI-46 and from the low-dose CT scans. The radiation dose is approximated to 6 mSv for the [^{68}Ga]Ga-FAPI-46 PET/CT with low dose CT. Thus, the total radiation burden for both [^{68}Ga]Ga-FAPI-46 PET/CT scans is 12 mSv. This is equivalent to 4 times the annual background radiation in Denmark (3mSv). The accumulative radiation dose increases the life-time risk of untreatable cancer per scan with 5% * 0.006 Sv = 0.03% compared to the rest of the population(43). The participants will undergo two scans during the trial, why the increased lifetime risk will be 0.03%*2 = 0.06%. The lifetime risk of dying from untreatable cancer for the general population is 25%. Thus, the two additional sets of scans ([^{68}Ga]Ga-FAPI-46 PET/CT) will increase the lifetime risk from 25% to 25.06%.

The radiation burden from the standard [^{18}F]FDG PET/CT is approximately 12-15 mSv. This scan will be done regardless of the inclusion of the trial.

Other risks during PET/CT scans include claustrophobia and fear of needles. During the insertion of the needle, there is a minimal risk of infection and hematoma. These risks are also present during the blood sample prior to the PET/CT.

7.4 Safety

A qualified medical doctor will be present in the department during the [^{68}Ga]Ga-FAPI-46 PET/CT scans and at the routine [^{18}F]FDG PET/CT. Emergency equipment is available in accordance with current procedures of the department, including cardiopulmonary resuscitation (CPR) and oxygen supply/suction. The staff of the department is trained to handle emergencies and the applicable standard procedures will be followed in case of anaphylaxis or other allergic reactions.

In case the participants experience an adverse reaction or show signs of an adverse reaction or allergic reaction during the [^{68}Ga]Ga-FAPI-46 PET/CT, the participant will be appointed and, if necessary, treated by local staff until the participant no longer has clinical signs of adverse reactions. The patient will be admitted at Rigshospitalet through the Trauma Center.

If the participant experience any side effects during the routine [^{18}F]FDG PET/CT scan, the patient will be treated in accordance with local guidelines at the hospital where the participant undergoes the scan.

7.5 Registration of side effects and events

Participants will be observed during the [^{68}Ga]Ga-FAPI-46 PET/CT scan for adverse reaction and events, and will be contacted one time, 24 hours after they've been injected with the tracer [^{68}Ga]Ga-FAPI-46 and undergone the first [^{68}Ga]Ga-FAPI-46 PET/CT and questioned on adverse reaction/adverse events.
The risk of side effects or adverse events when using [^{68}Ga]Ga-FAPI-46 is expected to be low based on previous studies. During the first 24 hours after administration, adverse events (AE), serious adverse events (SAE) will be reported in the eCRF and assessed as potential adverse reactions (AR). There are no expected AR or serious adverse reactions (SAR) to the administration of [^{68}Ga]Ga-FAPI-46.
The half-life of the radioactive probe [^{68}Ga] (bound to the FAPI compound) is 68 min, and it is estimated that a majority of the compound is non-measureable within 3xhalf-life of the compound. Preclinical studies have also shown that a majority of the FAPI compound bound is excreted within the first 24 hours (41, 44). Therefore, it is believed that potential side effects of the tracer will be evident within the first 24 hours after administration.

The following definitions on AE, SAE, AR, SAR and suspected unexpected serious adverse reactions (SUSARS) as well as reporting standards are based on the "Detailed guidance on the collection, verification and presentation of adverse even/reaction arising from clinical trials on medicinal products for human use", stated by the European Commission.

An AE is defined as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment". The PI is responsible for carrying out causality assessment of AEs and will update the protocol accordingly.
An AR is defined as "all untoward and unintended responses to an investigational medicinal product related

to any dose administered".
An SAE is defined: "any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect". SAEs of investigational medicinal product ([^{68}Ga]Ga-FAPI-46) must be reported within 24 hours by the investigators to the PI/sponsor.
SAR is defined as the above-mentioned AR, however with the addition of "serious" which covers the following: "… results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect". SARs are divided into the expected and unexpected SARs, where the unexpected adverse reaction is defined as: "an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)"(45).
As there are no expected serious adverse reactions to the administration of [^{68}Ga]Ga-FAPI-46, all SARs will be considered SUSARs .
SUSARS will be reported by the sponsor immediately to the regulatory authorities via EudraVigilance as soon as possible and no longer than 15 days. If the SUSARS result in death or is life threatening, the sponsor will report the incident within seven days after being made aware of the case. Within eight days after this reporting, the sponsor needs to send all relevant information in a follow-up report. The reporting of SUSARS will be done in accordance with the current reporting practice. Any report must be accompanied by comments on any consequences for the trial.
Throughout the duration of the trial, the sponsor will annually report a list of occurred suspected serious adverse reactions, and a report on the subject's safety via CTIS. All adverse reactions and events will be collected in a final report and send to CTIS within 1 year after the end of the trial.

The reference safety information (RSI) that will be used to asses AR and AE, will be the IMPD and Investigator's Brochure for the tracer [^{68}Ga]Ga-FAPI-46.

The RSI of the comparator [^{18}F]FDG is the product resume (appendix 1). Side effects related to the comparator product [^{18}F]FDG is exempted from reporting of AE, AR, SAE and SAR but not SUSARs due to the low risk profile (risk adapted adverse event management, please refer to appendix 2). [^{18}F]FDG is an authorised medicinal product, with low risk of adverse reactions (please refer to the product resume, appendix 1, section 4.8). [^{18}F]FDG is used for an approved indication in which the intervention is normal clinical practice. As such, the risk profile is believed to be low. However, investigators are allowed to report any SAEs immediately at their own discretion.
Registration of the events not exempted from reporting will be assessed within the first 24 hours after administration of [^{18}F]FDG. This will be done by evaluating the patients' electronic medical record.

All investigator reported events will be registered in the annual safety report. The annual safety report will describe the rules of registration and reporting of adverse events as given in this protocol.

8. Collection of biological material

One 4 ml serum blood samples will be taken before each scan. Thus, two serum blood samples will be taken during the trial. In total we will collect 8 ml of blood.
The blood samples will be transferred to the Department of Clinical Biochemistry Research Section Rigshospitalet as soon as possible after the sample has been taken. Trained personnel at this department will carry out the initial preparations of blood samples. Blood samples will clot for a minimum of 30 minutes at room temperature. Then, the sample will be centrifuge at 2000g for 10 minutes at +4°C or room temperature and no longer than 1 hour after sampling. The samples will then be transferred to 2 x 2ml cryo-tubes. The sample will be stored for 30 min in the storage box at -20°C or below for up to two weeks. For long term storage, the samples will be moved to a -80°C freezer. The blood samples will be pseudonymized with a project number.
The sample biobank will be stored at the Department of Clinical Biochemistry Research Section Rigshospitalet until collected by Nordic Bioscience. A list of the collected and stored blood samples will be available at the Department of Clinical Biochemistry Research Section Rigshospitalet. When all the blood samples have been collected (total of 40 samples), the samples will be transferred to Nordic bioscience.
A list of the transferred blood samples will be available in the TMF.
The samples will be analyzed by Nordic bioscience, using an in house competitive ELISA. Additionally, Nordic Bioscience will measure other tumor fibrosis biomarkers e.g., PRO-C3 (type III collagen formation). This to get the full picture of the tumor fibrotic responses associated with FAP-expression in cancer patients. A mean of 50 uL sample would be used for the assessment of each of the protein fingerprint markers including quality control assessments. Serum samples are run in duplicates. Around 50 uL will be used for the assessment of a single protein fingerprint markers including re-running samples with a CV% above the limit (20%).
After the analysis, all biological material will be destroyed.

The samples will primarily be stored at the Department of clinical biochemistry Research Section Rigshospitalet until all patients have been included and completed the study (maximum 2 years). The analysis of blood samples will be conducted at Nordic Bioscience. Here the material will be stored for up to 1 month. The unused biological material will be destroyed after analysis. Nordic Bioscience will retain a copy of the results from the measurements of the blood samples. The data will be pseudonymized. Nordic Bioscience will however not have access to the pseudonymization key. All results from the blood samples will be destroyed 10 years after the first date of measurement. The results can be used for scientific publications in collaboration with Sponsor/PI and after publication, the published data can be used for other purposes (e.g., patent application). A contract between Sponsor/PI of the study and Nordic Bioscience regarding these tasks will be made.

9. Data Management:

9.1 Respect for participants' physical and mental integrity and right to privacy:

The Danish health law, the Danish Data Protection Act and General Data Protection Regulation (GDPR) protect all participants in this trial (46). The trial will be reported to The Knowledge Centre of Data Protection Compliance at the Capital Region.

According to the Data Protection Act and Law Enforcement Directive, all data will be securely kept at the Dept. of Clinical Physiology and Nuclear Medicine, Rigshospitalet. A list revealing the identity of each participant will be kept locked-in at the Dept. of Clinical Physiology and Nuclear Medicine, Rigshospitalet on a local computer drive. These folders have restricted access, which only can be granted from the Centre of IT and Medical Technology (CIMT, Capital region), and the owner of the locked folders, which is an investigator. The eCRF will be stored in the database REDcap. Access to data in REDcap will be restricted to specified research workers. To gain access to REDcap, research workers need to be granted access by CIMT, Capital Region. A 2-step verification log-in is required to access REDcap. The owner of the eCRF (also called the project owner) will have the responsibility to grant access to the data set. The project owner of the eCRF will be an investigator.

Pseudonymized data will be stored in 25 years after trial finalization in accordance with the current legislation. At any given time the Good Clinical Practice (GCP)-unit, and representatives from the Danish Medical Research Ethics Committee, and the Danish Medicines Agency will be able to gain access to the source data in the patient medical record for monitoring and inspection. Research workers involved in the trial will also have access to the medical records for included participants. All data will be handled confidentially.

In the case of any data security breaches, the procedures and guidelines from the Capital Region and Rigshospitalet will be followed to mitigate possible adverse effects.

The participants must allow that pseudonymous scan-pictures can be used for publicly available publications, teaching purposes, and extern evaluation. The scan pictures will not include information that will identify the patients (such as dates, social security number or birthday). The use of scans will comply with GDPR, the Danish Data Protection Act and the Clinical Trial Regulation, article 28, section 1 (d-e).

9.2 Information from and interpretation of the [^{68}Ga]Ga-FAPI-46 PET/CT scans:

The batch number, injected dose, time of injection, and patients' height and weight will be documented on the PET administration sheet during the [^{68}Ga]Ga-FAPI-46 PET/CT scan. This is a routine procedure for the scanning personnel at the Dept. of Clinical Physiology and Nuclear Medicine. The PET administration sheet will be regarded as source data and the information will be recorded on eCRF. The analysis of the [^{68}Ga]Ga-FAPI-46 PET/CT scan will be performed by specialists on routine computer programs and afterwards documented in the eCRF by a co-investigator.

9.3 Analysis of blood samples

The results from the FAP-activity blood sample will be recorded in a secure database according to standard operating procedure at Nordic Bioscience. This dataset will be regarded as source-data. The results from the analysis will be send to the PI/Sponsor or co-investigator using a secure mail-system and recorded in the eCRF.

9.4 Information from the clinical record:

The following information will be registered in the eCRF for each trial participant and regarded as source information from the participant's electronical medical record and utility programs connected to the electronical medical record:

Variable	Reasons for registration
Age, gender, BMI.	For publication, background variables are required to verify that the participants are representative of the investigated group.
Inclusion and exclusion criteria.	To be able to include/exclude participants of the trial. This data will be acquired before the patient has given written and informed consent. This include: disease history, medicine, allergies, tumor biopsy material and treatment decision.
Cancer diagnosis, classified by the TNM classification system, anatomical location, histological type of tumor, and analysis of receptor-expression. Previous and current medication for cancer diseases.	For publication, background variables are required to verify that the participants are representative of the investigated group.
Other diseases and medication.	Other known disease/malignancies may affect the interpretation of the [^{68}Ga]Ga-FAPI-46 PET scan.
Standard imaging ([^{18}F]FDG PET/CT).	Lot number/batch number, administered dose, time and date of injection, images as well as the description of the scan from the routine diagnostic examinations. This will be used for registration of the comparator product and to assess treatment response during the follow up period.
Follow-up data 6 months after the [^{68}Ga]Ga-FAPI-46 PET : scans, clinical records, histology, and pathology samples, blood samples.	Follow up data are necessary to be able to verify tracer-uptake on [^{68}Ga]Ga-FAPI-46 PET in normal tissue and malignant lesions and are necessary to be able to correlate tracer uptake in normal tissue and malignant lesions to potential adverse reaction (IrAE). This will also be done to be able to correlate blood sample results with treatment outcome.

The eCRF will be stored in REDCap.

9.5 Quality control and monitoring:

The GCP-unit of Copenhagen University Hospital will monitor the trial. Monitoring visits will be conducted before, during and at the end of the trial. The visits will ensure that the trial is conducted according to the protocol and to the GCP regulations.

10. Science and ethics

The trial will be conducted in accordance with the protocol and the laws and regulations of the Danish state as well as applicable regulations from the European Commission. In addition, the trial will be conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) regulations and the common principals of good clinical practice.

All eligible participants will receive the standard treatment and standard surveillance of their cancer, no matter their participation status. The patients will not be informed of the results from the [^{68}Ga]Ga-FAPI-46 PET/CT , and the results will not affect their individual treatment or surveillance. This is clearly stated in the

participant information. Participants, who wish to gain access to the results from the trial, are allowed to do so, when the trial is finished.

The potential risks of the trial are believed to be low. The increased radiation burden is approximately 4 times of the annual background radiation in Denmark (3mSv) for both scans. The life-time risk of untreatable cancer will increase with 0.06% compared to the rest of the population. Based on previous experience with the tracer [^{68}Ga]Ga-FAPI-46 the risk of experiencing side effects is low.

The radiation burden of the standard [^{18}F]FDG PET/CT is 12-15 mSv. The [^{18}F]FDG PET/CT is a standard evaluation scan, which is performed during treatment with ICT. As such, the scan will be done regardless of the inclusion in the trial. The risk of any adverse reactions to the [^{18}F]FDG is believed to be low (please refer to the product resume, section 4.8, appendix 1).

The [^{68}Ga]Ga-FAPI-46 PET/CT is believed to improve response evaluation of patients with malignant melanoma treated with ICT, early detection of side effects to ICT, and patient comfort during PET/CT scans. We believe that these potential benefits outweigh the potential risk of the trial.

10.1 Guidelines for participants' information and written consent

The recruitment arrangements are described in the document "Recruitment arrangements" in part II of the application dossier.

10.2 Written consent

All participants must sign a written consent form to be able to participate in the trial.

The participants must allow that pseudonymous scan-pictures can be used for publicly available publications, teaching purposes, and extern evaluation. The patients most also allow for the analysis of blood samples and storage in a biobank (please refer to section 8). This will be clearly stated in the written consent form.

The participant must also allow all researchers involved in the trial (sponsor, PI, co-investigators, delegated research personnel) to obtain information from his/her medical record necessary to conduct the research. Participants must also allow representatives from the Danish Medical Agency, the GCP-unit of Copenhagen University and the Danish Medical Research Ethics Committee to examine his/her medical record for quality assessment, quality control and security of the trial. All information will be handled confidentially.

The investigators are responsible for obtaining the written and oral consent from the participant before the participant undergo any trial-related procedures. All signed consent forms will be transferred and stored at the Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet in the TMF.

11. Publication of results

The trial will be registered at clinicaltrials.gov as well as CTIS. During the publications process, the Vancouver Recommendations will be followed. The results will be published on CTIS and in international English-speaking peer reviewed journals as open access. All results will be published including positive, negative, and inconclusive findings. As stated in the participant information, pseudonymized scan-pictures can be used in both papers and presentations. The order of authors on the primary publications will be a

co-investigator as first author, and last author will be either the sponsor or on of the advisors. Both preliminary and final results will potentially be presented at relevant international conferences.

12. Insurance

The trial will be conducted at Rigshospitalet and the sponsor (BMF) and PI will be employed by Rigshospitalet and the Capital Region. Thus, participants in the study are legally regarded as patients, and will be covered by the normal insurance of patients hospitalized at Rigshospitalet as well as the normal insurance for patients stated by the Danish Law (Den offentlige patienterstatningsordning).

13. Timeframe of the trial

The inclusion of patients is expected to start in the spring of 2025, and inclusion period is expected to last for 1 year. All patients have a follow-up period of 6 months. The trial will end 6 months after the last participant has completed their second [^{68}Ga]Ga-FAPI-46 PET/CT. Data will be stored for 25 years after the collected data has been processed.

14. Protocol Synopsis

[^{68}Ga]Ga-FAPI-46 PET/CT for Better and Faster imaging in cancer

Protocol: [^{68}Ga]Ga-FAPI PET/CT for response evaluation during immune checkpoint inhibitor therapy in malignant melanoma patients in immune checkpoint inhibitor therapy

EU trial number:

2023-509549-11-00

Rationale of the study:

Malignant melanoma is a highly aggressive cancer and is treatment resistant especially in advanced stages. The introduction of immunotherapy and especially immune checkpoint inhibitor therapy (ICT) have improved survival rates for malignant melanoma patients with advanced stages. Current standard imaging for treatment monitoring with [^{18}F]FDG PET/CT lacks specificity in discriminating between side effects from ICT (immune related adverse events, IrAEs) and progression of cancer. Clear discrimination is a necessity for clinicians to be able to quickly optimize and change treatment strategy. Fibroblast activating protein inhibitor (FAPI) is a specific enzyme inhibitor that binds to fibroblast activating protein (FAP) expressing cells. FAP is found on cancer associated fibroblasts (CAFs) that exist in the tumor supporting tissues in epithelial cancers. FAP is upregulated in 90% of epithelial neoplasms and malignant melanoma. FAPI radiolabeled with gallium-68 ([^{68}Ga]Ga-FAPI, synonym [^{68}Ga]FAPI) has proven potential as a radiopharmaceutical agent in PET imaging for detection of malignant primary tumors as well as distant metastases in different cancer types. Case reports have demonstrated promising results in using [^{68}Ga]FAPI PET to visualize malignant melanoma cancer lesions. In addition, the potential use of [^{68}Ga]FAPI in diagnosing IrAEs have also been demonstrated in case reports and one feasibility study.
Therefore, we propose a clinical phase II clinical trial to investigate the potential use of the tracer [^{68}Ga]FAPI for PET/CT-imaging in patients with advanced stage malignant melanoma referred for ICT.

The activity of the protein FAP may be measured in liquid biopsies/blood samples from cancer patients. Nordic bioscience has developed a method to measure specific molecules in serum blood samples, which reflects FAP activity, from now on called FAP activity biomarkers. Therefore, we want to explore the correlation between FAP activity biomarkers with the FAPI-uptake on [^{68}Ga]FAPI PET imaging of patients with malignant melanoma. These biomarkers could be a potential screening tool for selecting the right patients to receive a PET/CT scan and to provide a way to monitor the patients between PET/CT scans.

Study hypothesis:

- [^{68}Ga]Ga-FAPI PET/CT can improve response evaluation in patients suffering from advanced stage malignant melanoma treated with ICT and potentially serve as a biomarker.

Objectives and endpoints:

The aim of the study is to evaluate [^{68}Ga]FAPI PET/CT as a non-invasive diagnostic tool for response evaluation during ICT in patients with advanced stage malignant melanoma.

The primary endpoint will be to evaluate changes in FAPI-uptake in both primary tumor and metastases on [^{68}Ga]FAPI PET/CT during ICT. These findings will be compared to changes in [^{18}F]FDG-uptake on standard imaging. The secondary endpoints will be to evaluate changes in [^{68}Ga]FAPI-uptake in healthy tissue on [^{68}Ga]FAPI PET/CT during ICT. This assessment will also be compared to findings on standard imaging as well. Changes in FAPI-uptake will also be compared to any side effect (IrAE) that the patients may experience during ICT. The presence of IrAE will be determined by an expert in oncology, who is blinded from the project scans. The [^{68}Ga]FAPI PET/CT assessment (including evaluation of healthy tissue and malignant lesions) will be compared to the findings from a composed reference standard. This will consist of all available imaging, biopsy results, blood tests, and information on hospitalization and changes in patient management up to 6 months after the [^{68}Ga]FAPI PET/CT.

The exploratory endpoint will evaluate the correlation between [^{68}Ga]Ga-FAPI-uptake and the level of FAP-activity biomarkers in blood samples from included patients. In addition, we will correlate results from the biomarker analysis with treatment outcome of immunotherapy within 6 months of treatment using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Trial Design and trial population

The study is a phase II nonrandomized clinical trial evaluating [^{68}Ga]FAPI PET/CT for response evaluation during ICT in patients with advanced stage malignant melanoma with visible target lesions on [^{18}F]FDG PET/CT. The study will be regarded as a pilot study and include 20 patients.

The included participants will undergo two scans in addition to their standard imaging (diagnostic [^{18}F]FDG PET/CT). At baseline the patients will undergo a [^{68}Ga]FAPI PET/CT. This will be performed before initiation of ICT. A blood sample will be collected prior to injection of the tracer. After 12 weeks of treatment, the participant will undergo another [^{68}Ga]FAPI PET/CT and a second blood sample in addition to their standard imaging (diagnostic [^{18}F]FDG PET/CT). During the [^{68}Ga]FAPI PET/CT, participants will be observed for adverse events and reactions. In addition, the participants will be contacted 24 hours after the first scan to evaluate potential adverse events or reactions. Thus, participants will be included for two [^{68}Ga]FAPI PET/CT and two blood samples. The patients will also be followed for period of 6 months after the last scanning session using the patients' medical record.

Intervention

Participants will undergo two [^{68}Ga]FAPI PET/CT scans at the department of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital, Rigshospitalet. The first scan will be performed prior to initiation of ICT and the second scan will be performed after 12 weeks of ICT-treatment.

Upon arrival, the participant will be placed in a bed in a relaxed prone position. If the participant is female and fertile, and if the pregnancy test from the inclusion consultation is more than 48 hours old, we will perform another urinary pregnancy test. If the pregnancy test is negative, the patient can go through with the project scan.

The participant will then be injected with 1-2MBq/kg of [^{68}Ga]FAPI, with a minimum dose of 100 MBq and a maximum dose of 246 MBq. The patient will then rest for 30-40 min and then undergo a PET scan for 10-20 min. The PET scan will cover an area from vertex to mid-thighs. The patient will also undergo a low dose CT scan, which will be performed prior to the PET scan. After 12 weeks of ICT, patients will undergo the second

[^{68}Ga]FAPI PET/CT and the same procedure will be followed.
Prior to injection of the tracers in each scan session, a serum blood sample will be taken.

Patients will be observed during the scan session for any adverse events. After 24 hours, after the first [^{68}Ga]FAPI PET/CT , the patient will be contacted by co-investigators or delegated research personnel, who will check the patients' condition.

Safety and risks

No adverse reaction or events have been reported after injection with [^{68}Ga]FAPI in previous studies. More than 1000 patients have been scanned with this tracer without any other reporting of side effects. More information on the tracer [^{68}Ga]FAPI is found in the Investigational Medicinal Product Dossier (IMPD) and in the Investigator's Brochure (IB) attached in the application.

The potential risks of the trial are believed to be low. The increased radiation burden is 6 mSv for each of the [^{68}Ga]FAPI PET with low dose CT. This will increase life-time risk of untreatable cancer with 0.06% compared to the rest of the population.

The radiation burden of the standard [^{18}F]FDG PET/CT is 12-15 mSv. The [^{18}F]FDG PET/CT is a standard evaluation scan, which is performed during treatment with ICT. As such, the scan will be done regardless of the inclusion in the trial. The risk of any adverse reactions to the [^{18}F]FDG is believed to be low (please refer to the product resume, appendix 1).

Ethics and data protection

The trial will be conducted in accordance the Danish and European laws and regulations on clinical trials, as well as ICH-GCP regulations and the common principals of good clinical practice. The Danish health law, the Danish Data Protection Act, and General Data Protection Regulation (GDPR) protect all participants in this trial (40). The trial will be reported to The Knowledge Centre of Data Protection Compliance at the Capital Region. All eligible participants will receive the standard treatment and follow up care of their cancer, no matter their participation status.

The [^{68}Ga]FAPI PET/CT is believed to improve response evaluation of patients with malignant melanoma treated with ICT. We believe that these potential benefits outweigh the potential risk of the trial.

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16. Appendix

LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

20 March 2024

SUMMARY OF PRODUCT CHARACTERISTICS

for

Fluor-18-FDG, solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Fluor-18-FDG, solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 14.0 MBq/ml to 7,24 GBq/ml of Fludeoxyglucose ^{18}F) at the date and time of calibration. The activity pr. vial ranges from 400 MBq to 210 GBq at the date and time of calibration.
Fluorine (^{18}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

Excipients with known effetcs:
Sodium
Ethanol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless or slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Fludeoxyglucose (18F) is indicated for use with positron emission tomography (PET) in adults and paediatric population.

Oncology:
In patients undergoing oncologic diagnostic procedures describing function or diseases, where enhanced glucose influx of specific organs or tissues is the diagnostic target. The following indications are sufficiently documented (see also section 4.4).

Diagnosis:
- Characterisation of solitary pulmonary nodule.

- Detection of cancer of unknown origin revealed for example by cervical adenopathy, liver or bones metastases.
- Characterisation of a pancreatic, hepatic or pelvic mass.

Staging:
- Head and neck cancers including assistance in guiding biopsy.
- Primary lung cancer.
- Locally advanced breast cancer.
- Oesophageal cancer.
- Carcinoma of the pancreas.
- Colorectal cancer particularly in restaging recurrences.
- Malignant lymphoma.
- Cervix cancer.
- Ovarian cancer.
- Malignant melanoma, Breslow >1.5 mm or lymph node metastasis at first diagnosis.

Monitoring of therapeutic response:
- Malignant lymphoma.
- Head and neck cancers.

Detection in case of reasonable suspicion of recurrences:
- Glioma with high grade of malignancy (III or IV).
- Head and neck cancers.
- Thyroid cancer (non-medullary): patients with increased thyroglobulin serum levels and negative radioactive iodine whole body scintigraphy.
- Primary lung cancer.
- Breast cancer.
- Carcinoma of the pancreas.
- Colorectal cancer.
- Cervix cancer.
- Ovarian cancer.
- Malignant lymphoma.
- Malignant melanoma.

Cardiology:
In the cardiologic indication, the diagnostic target is viable myocardial tissue that takes-up glucose but is hypo-perfused, as it must be assessed beforehand using appropriate blood-flow imaging techniques.
- Evaluation of myocardial viability in patients with severe impaired left ventricular function who are candidates for revascularisation when conventional imaging modalities are not contributive.

Neurology:
In the neurologic indication the interictal glucose hypometabolism is the diagnostic target.
- Localisation of epileptogenic foci in the presurgical evaluation of partial temporal epilepsy.

Infectious or inflammatory diseases:
In infectious or inflammatory diseases, the diagnostic target is tissue or structures with an abnormal content of activated white blood cells.

In infectious or inflammatory diseases, the following indications are sufficiently documented:

Localisation of abnormal foci guiding the aetiologic diagnosis in case of fever of unknown origin

Diagnosis of infection in case of:
- Suspected chronic infection of bone and/or adjacent structures: osteomyelitis, spondilitis, diskitis or osteitis including when metallic implants are present.
- Diabetic patient with a foot suspicious of Charcot's neuroarthropathy, osteomyelitis and/ or soft tissue infection.
- Painful hip prosthesis.
- Vascular prosthesis.
- Fever in an AIDS patient.
- Detection of septic metastatic foci in case of bacteremia or endocarditis (see also section 4.4).

Detection of the extension of inflammation in case of:
- Sarcoidosis.
- Inflammatory bowel disease.
- Vasculitis involving the great vessels.

Therapy follow-up:
Unresectable alveolar echinococcosis, in search for active localisations of the parasite during medical treatment and after treatment discontinuation

4.2 Posology and method of administration

Posology

Adults and elderly population
The recommended activity for an adult weighing 70 kg is 100 to 400 MBq (This activity has to be adapted according to the body weight of the patient, the type of camera used and acquisition mode), administered by direct intravenous injection.

Renal and hepatic impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Extensive dose range and adjustment studies with this medicinal product in normal and special populations have not been performed.

The pharmacokinetics of fludeoxyglucose (18F) in renally impaired patients has not been characterised.

Paediatric population
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group. The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and adolescents may be calculated by

multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below.

$$A\ [MBq]_{Aministered} = \text{Baseline Activity X Multiple}$$

The baseline activity for 2D imaging is 25.9 MBq and for 3D imaging 14.0 MBq (recommended in children).

Weight [kg]	Multiple	**Weight [kg]**	Multiple	**Weight [gg]**	Multiple
3	1	22	5.29	42	9.14
4	1.14	24	5.71	44	9.57
6	1.71	26	6.14	46	10.00
8	2.14	28	6.43	48	10.29
10	2.71	30	6.86	50	10.71
12	3.14	32	7.29	52-54	11.29
14	3.57	34	7.72	56-58	12.00
16	4.00	36	8.00	60-62	12.71
18	4.43	38	8.43	64-66	13.43
20	4.86	40	8.86	68	14.00

Method of administration:
For intravenous use.

For multidose dose use.

The activity of fludeoxyglucose (^{18}F) has to be measured with an activimeter immediately prior to injection. The injection of fludeoxyglucose (^{18}F) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts
For instructions on dilution of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4

Image aquisition
The emission scans are usually started 45 to 60 minutes after the injection of fludeoxyglucose (^{18}F). Provided a sufficient activity remains for adequate counting statistics, fludeoxyglucose (^{18}F)-PET can also be performed up to two or three hours after administration, thus reducing background activity.

If required, repeated fludeoxyglucose (^{18}F) can be reiterated within a short period of time.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated if necessary.

To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Renal and hepatic impairment
Due to the major renal excretion of fludeoxyglucose (^{18}F) in patients with reduced kidney function, careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible. Activity should be adjusted if necessary.

Paediatric population
For information on the use in paediatric population, see sections 4.2 or 5.1.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation
Fluor-18-FDG should be given to sufficiently hydrated patients fasting for a minimum of 4 hours, in order to obtain a maximum target activity, since glucose uptake in the cells is limited ("saturation kinetics"). The amount of liquid should not be limited (beverages containing glucose must be avoided).

In order to obtain images of best quality and to reduce the radiation exposure of the bladder, patients should be encouraged to drink sufficient amounts and to empty their bladder prior to and after the PET examination.

Oncology and neurology and infectious diseases
In order to avoid hyperfixation of the tracer in muscle, it is advisable for patients to avoid all strenuous physical activity prior to the examination and to remain at rest between the injection and examination and during acquisition of images (patients should be comfortably lying down without reading or speaking). The cerebral glucose metabolism depends on the brain activity. Thus neurological examinations should be performed after a relaxation period in a darkened room and with low background noise.

A blood glucose test should be performed prior to administration since hyperglycaemia may result in a reduced sensitivity of Fluor-18-FDG, especially when glycaemia is greater than 8 mmol/l. Similarly, PET with fludeoxyglucose (^{18}F) should be avoided in subjects presenting uncontrolled diabetes.

Cardiology
Since glucose uptake in the myocardium is insulin-dependent, for a myocardial examination a glucose loading of 50 g approximately 1 hour prior to the administration of Fluor-18-FDG is recommended. Alternatively, especially for patients with diabetes mellitus, the blood sugar level can be adjusted by a combined infusion of insulin and glucose (Insulin-Glucose-Clamp) if needed.

Interpretation of the PET with fludeoxyglucose (^{18}F) images
In the exploration of inflammatory bowel diseases, diagnostic performance of fludeoxyglucose (^{18}F) has not been directly compared with that of scintigraphy using labelled white blood cells which may be indicated prior to fludeoxyglucose (^{18}F) PET or after fludeoxyglucose (^{18}F) PET when inconclusive.

Infectious and/or inflammatory diseases as well as regenerative processes after surgery can result in a significant uptake of fludeoxyglucose (^{18}F) and therefore lead to false positive results, when search for infectious or inflammatory lesions is not the aim of the fludeoxyglucose (^{18}F) PET In cases where fludeoxyglucose (^{18}F) accumulation can be caused by either cancer, infection or inflammation, additional diagnostic techniques for the determination of the causative pathologic alteration may be required to supplement the information obtained by PET with fludeoxyglucose (^{18}F). In some settings e.g. staging of myeloma, both malignant and infectious foci are searched for and may be distinguished with a good accuracy on topographic criteria e.g. uptake at extramedullary sites and/or bone and joint lesions would be atypical for multiple myeloma lesions and identified cases associated with infection. There are currently no other criteria to distinguish infection and inflammation by means of fludeoxyglucose (^{18}F) imaging.

Because of the high physiologic uptake of fludeoxyglucose (^{18}F) within brain, heart and kidneys, PET/CT with fludeoxyglucose (^{18}F) has not been evaluated for the detection of septic metastatic foci in these organs when the patient has been referred due to bacteraemia or endocarditis

False positive or false negative PET with fludeoxyglucose (^{18}F) results cannot be excluded after radiotherapy within the first 2-4 months. If the clinical indication is demanding an earlier diagnosis by PET with fludeoxyglucose (^{18}F), the reason for earlier PET with fludeoxyglucose (^{18}F) examination must be reasonably documented.

A delay of at least 4-6 weeks after the last administration of chemotherapy is optimal, in particular to avoid false negative results. If the clinical indication is demanding an earlier diagnosis by PET with fludeoxyglucose (^{18}F), the reason for earlier PET with fludeoxyglucose (^{18}F) examination must be reasonably documented. In case of chemotherapy regimen with cycles shorter than 4 weeks, the PET with fludeoxyglucose (^{18}F) examination should be done just before re-starting a new cycle.

In low-grade lymphoma, lower oesophagus cancer and suspicion of recurrent ovarian cancer, only positive predictive values have to be considered because of a limited sensitivity of PET with fludeoxyglucose (^{18}F).

Fludeoxyglucose (^{18}F) is not effective in detecting brain metastases.

The accuracy of fludeoxyglucose (^{18}F) PET imaging is better using PET/CT than PET cameras alone.
When a hybrid PET-CT scanner is used with or without administration CT contrast media, some artefacts may occur on the attenuation-corrected PET images.

After the procedure

Close contact with infants and pregnant women should be restricted during the initial 4 hours following the injection.

Specific warnings

Depending on the time when you administer the injection, the content of sodium given to the patient may in some cases be greater than 1 mmol (23 mg). This should be taken into account in patient on low sodium diet.

This medical product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

Precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

All medicinal products that modify blood glucose levels can affect the sensitivity of the examination (e.g. corticosteroids, valproate, carbamazepine, phenytoin, phenobarbital and catecholamines).

Under administration of colony-stimulating factors (CSFs), there is an increased uptake of fludeoxyglucose(^{18}F) in the bone marrow and the spleen for several days. This must be taken into account for the interpretation of PET imaging. Separating CSF therapy from PET imaging by an interval of at least 5 days may diminish this interference.

The administration of glucose and insulin influences the influx of fludeoxyglucose (^{18}F) into the cells. In the case of high blood glucose levels as well as low plasma insulin levels, the influx of fludeoxyglucose (^{18}F) into organs and tumours is reduced.

No formal studies on the interaction between fludeoxyglucose (^{18}F) and any contrast for computed tomography have been performed

4.6 Pregnancy and lactation

Pregnancy

Women of childbearing potential

When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

Pregnancy

Radionuclide procedures carried out on pregnant women also involve radiation dose to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by the mother and foetus.

Breast-feeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breastfeeding should be interrupted for 4 hours and the expressed feeds discarded.

Close contact with infants should be restricted during the initial 4 hours following injection.

Fertility
No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines
Not relevant

4.8 Undesirable effects
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 7.6 mSv when the maximal recommended activity of 400 MBq is administered these adverse reactions are expected to occur with a low probability.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Websted: www.meldenbivirkning.dk

4.9 Overdose
In the event of administration of a radiation overdose with fludeoxyglucose (^{18}F) the

absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, other diagnostic radiopharmaceuticals for tumour detection, ATC code V09IX04.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, Fludeoxyglucose (^{18}F) does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Distribution

Fludeoxyglucose (^{18}F) is a glucose analogue, which is accumulated in all cells using glucose as primary energy source. Fludeoxyglucose (^{18}F) is accumulated in tumours with a high glucose turnover. Following intravenous injection, the pharmacokinetic profile of Fludeoxyglucose (^{18}F) in the vascular compartment is biexponential. It has a distribution time of 1 minute and an elimination time of approximately 12 minutes.

In healthy subjects, fludeoxyglucose (^{18}F) is widely distributed throughout the body, particularly in the brain and heart, and to a lesser degree in the lungs and liver.

Organ uptake

The cellular uptake of Fludeoxyglucose (^{18}F) is performed by tissue-specific carrier systems, which are partly insulin-dependent and, thus, can be influenced by eating, nutritional condition and the existence of a diabetes mellitus. In patients with a diabetes mellitus a reduced uptake of Fludeoxyglucose (^{18}F) into the cells occurs due to a changed tissue distribution and glucose metabolism.

Fludeoxyglucose (^{18}F) is transported via the cell membrane in a similar fashion to glucose, but only undergoes the first step of glycolysis resulting in formation of Fludeoxyglucose (^{18}F) -6-phosphate, which remains trapped within the tumour cells and is not further metabolised. Since the following dephosphorylation by intracellular phosphatases is slow, Fludeoxyglucose (^{18}F) -6-phosphate is retained in the tissue over several hours (trapping mechanism).
Fludeoxyglucose (^{18}F) passes the blood-brain barrier. Approximately 7 % of the injected dose is accumulated in the brain within 80-100 minutes after injection. Epileptogenic foci exhibit a reduced glucose metabolism in the seizure free phases.
Approximately 3 % of the injected activity is taken-up by the myocardium within 40 minutes. The distribution of Fludeoxyglucose (^{18}F) in normal heart is mainly homogenous; however, regional differences of up to 15 % are described for the interventricular septum. During and after a reversible myocardial ischemia, an increased glucose uptake occurs into the myocardial cell. 0.3 % and 0.9 - 2.4 % of the injected activity are accumulated in pancreas and lung. Fludeoxyglucose (^{18}F) is also bound to a lesser extent to ocular muscle, pharynx and intestine. Binding to muscle may be seen following recent exertion and in the event of muscular effort during the examination

Elimination

Elimination of Fludeoxyglucose (^{18}F) is chiefly renal, with 20 % of activity being excreted in urine in the first 2 hours following injection. Binding to renal parenchyma is weak, but because of renal elimination of Fludeoxyglucose (^{18}F), the entire urinary system, particularly the bladder, exhibits marked activity.

5.3 Preclinical safety data

Toxicological studies with mice and rats have demonstrated that with a single intravenous injection of 0.0002 mg/kg no deaths were observed. Toxicity with repeated administration was not performed because of Fludeoxyglucose (^{18}F) is administered in a single dose. This medicinal product is not intended for regular or continuous administration.
Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Di-sodium hydrogen citrate 1.5 hydrate
Ethanol
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

10 hours.

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze.

Storage of radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

6.5 Nature and contents of the container

Two types of containers are used. Ph. Eur. Type I clear glass vials; 30 ml (only for internal use), and 10 ml vials, both sealed with a clear silicone rubber septum and aluminium crimp cap or Ph. Eur. Type I clear glass vials 10 ml sealed with a chlorobutyl rubber septum and aluminium crimp cap.

The activity corresponds to 400 MBq to 210 GBq at time of calibration and is placed in a lead container.

Multidose vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General Warning
Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organisation.

Radiopharmaceuticals should be prepared by the user in a manner that satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.
The solution may be diluted with sodium chloride 9 mg/ml (0.9 %) solution for injection.

The administration of radiopharmaceuticals creates risks for other people from external radiation or contamination from spills of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must be taken.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Cyklotron og Radiokemi, enhed 3982
Afdeling for Klinisk Fysiologi og Nuklear Medicin
Rigshospitalet
Blegdamsvej 9,
DK-2100 Copenhagen Ø

8. MARKETING AUTHORISATION NUMBER

DK R 14

9. DATE OF FIRST AUTHORISATION

28 May1999

10. DATE OF REVISION OF THE TEXT

20 March 2024

11. DOSIMETRY

The data listed below are from ICRP 106 Publication.

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	**15 yrs old**	**10 yrs old**	**5 yrs old**	**1 yr old**
Adrenal	0.012	0.016	0.024	0.039	0.071
Bladder	0.13	0.16	0.25	0.34	0.47
Bone surfaces	0.011	0.016	0.022	0.034	0.064
Brain	0.038	0.039	0.041	0.046	0.063
Breasts	0.0088	0.011	0.018	0.029	0.056
Gallbladder	0.013	0.016	0.024	0.037	0.070
Gastrointestinal tract					
Stomach	0.011	0.014	0.022	0.035	0.067
Small intestine	0.012	0.016	0.025	0.040	0.073
Colon	0.013	0.016	0.025	0.039	0.070
(ULI wall	0.012	0.015	0.024	0.038	0.070)
(LLI wall	0.014	0.017	0.027	0.041	0.070)
Heart	0.067	0.087	0.13	0.21	0.38
Kidneys	0.017	0.021	0.029	0.045	0.078
Liver	0.021	0.028	0.042	0.063	0.12
Lungs	0.020	0.029	0.041	0.062	0.12
Muscles	0.010	0.013	0.020	0.033	0.062
Oesophagus	0.012	0.015	0.022	0.035	0.066
Ovaries	0.014	0.018	0.027	0.043	0.076
Pancreas	0.013	0.016	0.026	0.040	0.076
Red marrow	0.011	0.014	0.021	0.032	0.059
Skin	0.0078	0.0096	0.015	0.026	0.066

Spleen	0.011	0.014	0.021	0.035	0.066
Testes	0.011	0.014	0.024	0.037	0.066
Thymus	0.012	0.015	0.022	0.035	0.066
Thyroid	0.010	0.013	0.021	0.034	0.065
Uterus	0.018	0.022	0.036	0.054	0.090
Remanining organs	0.012	0.015	0.024	0.038	0.064
Effective dose (mSv/MBq)	**0.019**	**0.024**	**0.037**	**0.056**	**0.095**

The effective dose resulting from the administration of a maximal recommended activity of 400 MBq of fludeoxyglucose (18F) for an adult weighing 70 kg is about 7.6 mSv.
For an administered activity of 400 MBq, the typical radiation doses delivered to the critical organs, bladder, heart and brain are: 52 mGy, 27 mGy and 15 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Method of preparation

The package must be checked before use and the activity measured using an activimeter.
The medicinal product may be diluted with sodium chloride 9 mg/mL solution for injection.
Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.
If the integrity of this vial is compromised, the product should not be used.

Quality control

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

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October 2024
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The Danish Medicines Agency's guidance on risk-based recording and reporting of adverse events in clinical trials on medicinal products under Regulation (EU) no. 536/2014

Table of contents

1. Introduction

The recording and reporting of adverse events is a critical process for safeguarding the safety of participants in a clinical trial and essential for ensuring the evidence and accuracy of a medicinal product's safety profile. However, it is acknowledged that the collection and reporting of adverse events can be resource-consuming for both the investigator and sponsor and therefore should be risk-adjusted based on the added value gained from collecting the adverse event data.

Detailed recording of adverse events is particularly important for medicinal products that are not yet authorised, and where the data on the medicinal product's safety profile are insufficient. In contrast, clinical trials involving well-established authorised medicinal products contribute less with new significant safety data.

Article 41(2) of the legislation on clinical trials with medicinal products, regulation (EU) No 536/2014 of 16 April 2014 (CTR)[1] allows adaptation of adverse event management[2] in relation to the individual protocol:

REGULATION (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use:

CHAPTER VII, Article 41(2):
"The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report to the sponsor all serious adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.
The investigator shall report serious adverse events to the sponsor without undue delay but not later than within 24 hours of obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the serious adverse event has an impact on the benefit-risk balance of the clinical trial."

In practice, this means that the clinical trial adverse event management can be adapted based on the trial's specific design and purpose. Risk adaptation of adverse event management must be solid justified within the protocol with patient safety and the integrity of trial data remaining as the top priorities.

This guidance describes the requirements and processes needed for implementing risk-adapted adverse event management.

In the case of clinical trials serving a regulatory purpose (e.g. an indication extension or marketing authorisation), reference is also made to the *ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials*[3].

[1] More information about the clinical trials regulation is provided on the website of the Danish Medicines Agency.
[2] The term 'adverse event management' will be used in this guidance document as a collective term for recording and reporting of adverse events.
[3] ICH guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials is available on the European Medicines Agency's website.

For general considerations on the risk assessment of clinical trials, please refer to the *Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (25 April 2017)*[4].

2. Requirements in relation to risk adaptation in adverse event management

Sponsors intending to apply any risk adaptation in adverse event management in clinical trials should pay attention to the following:

1. Any risk-adapted adverse event management must be justified in relation to the specific trial's purpose, design and risk assessment. The protocol must include a clear justification along with a detailed description of the risk-based approaches, including a description of the processes in place for adverse event management. Guidance on these areas is given in the following sections:
   - Process for assessing adverse events in a clinical trial (section 3)
   - Risk assessment of a clinical trial (section 4)
   - Risk-adapted adverse event management in a clinical trial (section 5)

2. The sponsor must establish whether the medicinal products included in a clinical trial are subject to stricter national reporting requirements and/or additional monitoring in the EU. Risk adaptation is usually not possible for authorised medicinal products subject to stricter reporting requirements or additional monitoring. In case of risk-adapted adverse event management, the sponsor must confirm in the protocol that the medicinal products in a clinical trial are not subject to stricter national reporting requirements in the concerned Member States involved in the clinical trial or additional monitoring in the EU. The medicinal products subject to stricter reporting requirements in Denmark is available in the list published by the Danish Medicines Agency. The list of medicines under additional monitoring in the EU is available on the European Medicines Agency's website.

3. Risk-adapted adverse event management may only be implemented in relation to the recording and reporting of adverse events and adverse reactions from investigator to sponsor. For information about the sponsor's reporting obligations, reference is made to the requirements of the CTR[5].

4. Clinical trials investigating diseases with high morbidity or mortality may have primary or secondary efficacy endpoints that fall under the definition of a suspected unexpected serious adverse reaction (SUSAR). In such trials, according to CTR Annex III, section 2.5 point (21), it may be justified to designate specific serious events as disease-related and exempt them from SUSAR obligations. This in order to avoid systematic unblinding and to maintain the integrity of the trial data. In such cases, a Data Safety Monitoring Board (DSMB) should be established to monitor unblinded data. If a DSMB is not established, it must be justified how continuous safety monitoring is ensured in some other way. It may also be justified to exempt the same serious events from immediate reporting by the investigator to the sponsor. However, this requires an alternative procedure to ensure that the DSMB has continuous access to complete safety data.

[4] Risk proportionate approaches in clinical trials - Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (25 April 2017) is available at EudraLex - Volume 10 - Clinical trials guidelines.
[5] The sponsor's obligations in relation to reporting to the authorities are provided in articles 42 and 43 of CTR 536/2014.

5. The annual safety report (ASR) must describe the risk-adapted approaches under which the ASR has been prepared. The sponsor is obligated to include all serious adverse reactions (SARs) and all suspected unexpected serious adverse reactions (SUSARs) in the ASR. If there are exemptions to immediate reporting of serious adverse events to the Sponsor, it is important to note that all registered serious adverse events must still be reported to the sponsor, in a timely manner, for the sponsor to include all the registered serious events in the ASR. The protocol must also state if a single safety report is submitted for all investigational medicinal products used in the clinical trial, see article 43(2) of the CTR.

6. Adverse events exempted from recording are not expected to be documented elsewhere. However, the investigator remains responsible for ensuring that the trial participants' medical records are continuously updated with clinically relevant information for healthcare professionals who are otherwise involved in the patients' present or future care and treatment. During GCP-inspections particular attention may be given to how medical records entries are handled.

The protocol template published by the Danish Medicines Agency can be used to prepare the protocol. The template describes the particulars to be included in the protocol for compliance with the CTR.

3. Process for assessing adverse events in a clinical trial

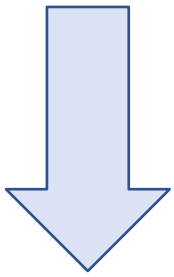
It is essential for the safety of trial participants and the data integrity, that the sponsor, investigator and other relevant staff understand and have received training in the processes for assessment, recording and reporting of adverse events. The processes for assessment of adverse events and the definitions of relevant terms must therefore be sufficiently described in the protocol.

The process for assessing whether it is a serious adverse event (SAE), a serious adverse reaction (SAR) or a suspected unexpected serious adverse reaction (SUSAR) is described below (Figure 1). You will find the full flow chart for assessment of all events in Appendix 1 and a description of relevant terms in Appendix 2.

These processes must be in place irrespective of whether risk-adapted recording and reporting of adverse events is implemented.

Figure 1. Assessment of serious adverse events and adverse reactions.

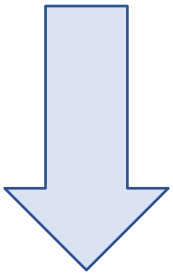
SAE (serious adverse event)	A serious adverse event (SAE) means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.



Causality assessment – is the serious adverse event related to the investigational medicinal product?
In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product (IMP) based on an analysis of available evidence.

See the reference provided in Appendix 2 for guidance on the causality assessment

SAR (serious adverse reaction)	A serious adverse reaction (SAR) is an SAE that is assessed to be related to the IMP, i.e. the treatment administered in the clinical trial.



Is the serious adverse reaction expected or unexpected?
The determination of whether an event is expected or unexpected is assessed based on the reference safety information (RSI).

Example: In the case of authorised medicinal products, the RSI is often section 4.8 of the summary of product characteristics (SmPC). Therefore, an adverse reaction appearing in the SmPC section 4.8 is expected, and an adverse reaction not appearing in section 4.8 of the SmPC is unexpected.

SUSAR (suspected unexpected serious adverse reaction)	A suspected **unexpected** serious adverse reaction means a serious adverse reaction, the nature, severity or outcome of which is not consistent with the RSI.
ASR (annual safety report)	Annual safety report: It is expected that any relevant safety information will be described in the annual safety report. The report is expected to include a list of SARs and SUSARs and an assessment of whether these events give rise to updating the protocol. Likewise, the annual safety report is expected to include an assessment of whether the benefit-risk balance is changed or unchanged, meaning if the trial may continue or if a protocol amendment is required for it to continue.

Annual safety reports must be prepared and reported for all trials

Once a year, the sponsor must summarise cumulative safety information in the annual safety report. Based on this report, the safety of the trial is evaluated, including if the benefit-risk balance has changed and whether, on the basis thereof, the trial may continue. The annual safety report ensures the continuous safety assessment and may therefore not be exempted despite any applied risk-adapted adverse events management.

The annual safety report must describe the risk-adapted approaches as provided in the clinical trial protocol, under which the report has been prepared.

4. Risk assessment of a clinical trial

The level needed for adverse event recording and reporting depends on the evidence base of the investigated medicinal product. As mentioned earlier, risk-adapted adverse event management must be justified on the basis of a trial-specific risk assessment.

A risk assessment means the identification of potential risks associated with the concerned trial, based on the safety of the participants, the investigational medicinal product and the trial design and methods. A number of different factors influence the extent to which the safety of the trial participants is affected in the trial, e.g. the status, type and safety profile of the medicinal product, the difference between intervention and normal clinical practice, and the complexity of the trial. The risk assessment and the associated risk categorisation of a trial are described below in Figure 2, points 1-4.

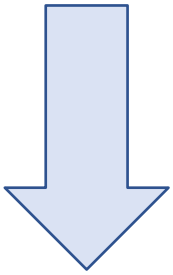
Figure 2. Risk assessment of a trial for the purpose of applying risk-adapted adverse event management.

1) Consider the RISK FACTORS likely to impact the safety of the trial participant

At least the following points must be considered and addressed in a risk assessment:

- Whether the medicinal product is authorised, including the total exposure of the medicine and whether the available safety data of the medicinal product provides sufficient grounds to implement risk-adapted adverse event management.
- The type of medicinal product/intervention (e.g. mechanistic characteristics, pharmaceutical form, route of administration).
- Indication, including the difference between intervention and normal clinical practice.
- Population, including age, gender and other patient characteristics.
- Dose and treatment regimen compared to the authorised dose and treatment regimen described in the product information, including the use of combination therapy or other medicines given concurrently, including an assessment of whether this may lead to serious or more frequent adverse reactions, new adverse reactions or new drug interactions.
- Complexity of the trial design.

See Appendix 3 for more considerations of risk factors likely to impact the safety of trial participants.



2) Assess the RISK LEVEL based on the difference between intervention and normal clinical practice

What is the risk posed to the patient compared to the standard treatment?
What are the risks, and how can they be handled?

INCREASED RISK FOR PATIENTS

"Low-risk" trial = **risk level 1**	**"Medium-risk"** trial = **risk level 2**	**"High-risk"** trial = **risk level 3**
➢ The investigational medicinal product(s) is/are authorised ➢ The intervention is comparable to standard treatment ➢ The intervention and the medicinal product's evidence base and safety profile are robust, also in relation to rare adverse reactions ➢ Expected new signals are minimal Application of risk-adapted adverse event management can generally be justified. See examples in Appendix 4.	➢ The investigational medicinal product(s) are authorised, but are used for an unapproved indication ➢ The intervention is not significantly different from the standard treatment, and the safety profile is expected to be comparable ➢ The safety profile of the medicinal product is robust Application of risk-adapted adverse event management can be justified if based on a trial-specific risk assessment. The risk assessment and justification should address the risk factors listed under point 1) of this figure. See examples in Appendix 4.	➢ Investigational medicinal product or indication is not authorised ➢ The intervention has not been studied before or is significantly different from the standard treatment ➢ The intervention and the safety profile of the medicinal product have not been sufficiently studied, and evidence on the efficacy and safety of the product is insufficient ➢ The investigational medicinal product is authorised but subject to stricter national reporting requirements or additional monitoring. See point 2 in section 2. Thorough adverse event management is needed to safeguard patient safety and to ensure the collection of data on the safety profile of the medicinal product. Full adverse event management is expected, unless adaptation can be justified on robust grounds based on a trial-specific risk assessment. See examples in Appendix 4.

3) Assess if risk-adapted adverse event management may be justified

Based on the above risk assessment, a risk-adapted approach to recording and reporting of adverse events may be possible if sufficiently justified.

Even so, borderline cases may exist, which means that an assessment of the individual protocol and trial design is needed to determine the required level of adverse event management. In borderline cases, variables like the duration of treatment, whether or not a life-threatening disease is involved, knowledge of the product's mechanistic effects, as well as non-clinical signals, along with data from the clinical development and the total exposure of the medicinal product, may determine which approach is justifiable. This must be seen in the context of the robustness of the safety profile, also in relation to rare adverse events.

If there are doubts about whether the evidence base of the product's safety is sufficiently known or whether the intervention may expose the patient to a risk, conservative/full adverse event management must be applied.

See section 5 on risk adaptation in the management of adverse events.

4) Dedicate a section in the protocol specifically to the justification of risk-adapted adverse event management

This justification must at least include the following:

- Risk assessment of the trial and justification of the level of risk chosen for the trial.
- Description of risk-adapted adverse event management, including reasons why certain SAEs are not be recorded or not immediate reported to the sponsor.
- Considerations about the risks associated with the chosen risk-adapted adverse event management:
  - For trial participants?
  - For data integrity?
- How risks in the trial can be prevented and/or reduced?

The extent of the justification depends on the level of risk associated with the trial.

5. Risk-adapted adverse event management in a clinical trial

In general, all adverse events must be recorded and all serious adverse events must be reported to the sponsor, unless the risk-adapted adverse event management is supported by the risk assessment documented in the protocol.

Authorised medicinal products have generated a sufficient evidence base for their use with respect to the populations and indications as described in the SmPC, and the safety of authorised medicinal products is monitored on an ongoing basis (see Appendix 5). In relation to clinical trials with authorised medicinal products, it may therefore be possible to adapt recording and reporting of adverse events proportionate to the risk level of the trial. Conversely, it can usually not be justified to reduce the recording and reporting of adverse events for trials with non-authorised medicinal products.

The protocol must always provide justification for any risk-adapted approach on the basis of a trial-specific risk assessment and if there is a risk of new, more serious or more frequent adverse reactions. Regardless of the selected approach, the investigator must always have the possibility of recording any event and reporting these to the sponsor if the investigator finds this relevant/necessary.

The possibility of applying a risk-adapted approach to the recording and reporting of adverse events and adverse reactions from investigator to sponsor is described below in Table 1 and Tabel 2. SUSARs must always be reported by the sponsor to the EudraVigilance database regardless of the risk-adaptation applied to adverse event management, as stipulated in the CTR[6]. Likewise, the sponsor is required to submit annual safety reports (ASRs) via CTIS[7].

Table 1. Risk-adapted adverse event management based on the level of risk associated with the trial

Risk level:	**Risk level 1 = "Low"**	**Risk level 2 = "Medium"**	**Risk level 3 = "High"**
Recording of adverse events			
Is risk-adaptation for **AE recording possible**?	YES – AE recording can be exempted	YES – AE recording can be exempted	NO[b)] – all AEs must be recorded
Is risk-adaptation for **SAE recording possible**?	YES – SAE recording can be exempted	YES[a)] – SAEs pursuant to a predefined list in the protocol can be exempted from recording	NO[b)] – all SAEs must be recorded
Is risk-adaptation for **SAR recording possible**?	YES – only suspected unexpected serious adverse reactions (SUSARs) must be recorded	YES[a)] – SARs pursuant to a predefined list in the protocol can be exempted from recording	NO[b)] – all SARs must be recorded
Reporting of serious adverse events from investigator to sponsor			
Is risk-adaptation for **SAE reporting to sponsor possible**?	YES – SAE reporting can be exempted	YES[a)] – immediate reporting of recorded SAEs can be exempted, but must be reported to the ASR	NO[b)] – all SAEs must be reported immediately to sponsor
Is risk-adaptation for **SAR reporting to sponsor possible**?	YES – only suspected unexpected serious adverse reactions (SUSARs) must be reported immediately to sponsor	NO[b)] – all recorded SARs must be reported immediately to sponsor	NO[b)] – all SARs must be reported immediately to sponsor
Sponsor's reporting obligations			
SUSAR reporting	SUSARs must always be reported by the sponsor to the EudraVigilance database.		
Annual safety report (ASR)	The ASR must always be submitted by the sponsor via CTIS. See also section 3.		

[a)] Must always be justified based on the trial-specific risk assessment

[b)] Generally not possible, unless robust justification provided

[6] Find more information about reporting to the EudraVigilance database on the website of the Danish Medicines Agency.

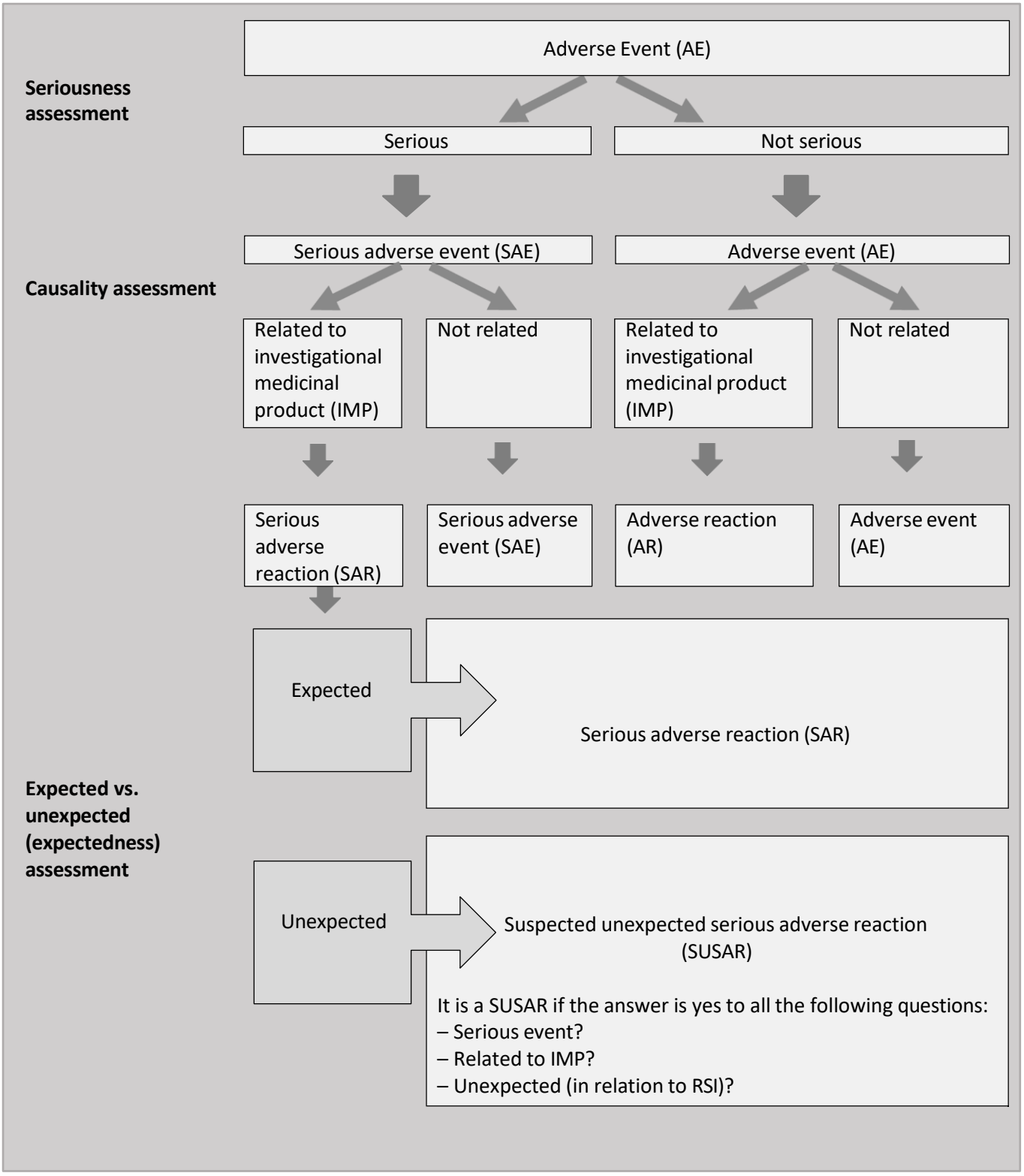
[7] Clinical Trials Information System (https://euclinicaltrials.eu/)

Tabel 2. Description of risk-adapted adverse event management.

Description of risk-adapted adverse event management based on the risk level	
Adverse event management at <u>risk level 1:</u>	The investigator must at least record adverse events satisfying all the following three criteria: 1) The adverse event must be serious (serious adverse event, SAE) 2) The adverse event must be suspected to be related to the investigational medicinal product (serious adverse reaction, SAR) 3) The adverse event must <u>not</u> appear in section 4.8 of the summary of product characteristics. In reality, it is the investigator who must assess expectedness when only suspected unexpected serious adverse reaction (SUSARs) are to be recorded. The investigator must report all recorded adverse reactions (subject to the above requirements) to the sponsor within 24 hours. The investigator must always have the possibility of recording and reporting any event to the sponsor if the investigator finds this relevant/necessary and this must be stated in the protocol.
Adverse event management at <u>risk level 2:</u>	In general, all SAEs must be recorded, but the sponsor may include in the protocol a predefined list of SAEs not to be recorded. This could be SAEs either associated with the investigational medicinal product or an underlying disease. SAEs in this category could be administrative/planned hospitalisation, exacerbation of underlying disease, or in the case of the treatment of intensive-care patients expected to have a critical disease course involving, for example, multiple organ failure. SAEs that are related to the investigational medicinal product (=SARs) and are listed in section 4.8 of the product information (known adverse reactions) may generally be exempted from recording. In case of that other SARs than expected (known adverse reactions, see 4.8 of the product information) will be exempted from recording, this must be further justified. Any SAEs and/or SARs exempted from the recording must always be clearly stated and justified in the protocol. The reporting of SAEs to the sponsor within 24 hours can be omitted, if predefined in the protocol and justified. However, all SAEs recorded and deemed related to the intervention (causal relationship) must be reported immediately to the sponsor. In other words, <u>all recorded SARs</u> must be reported to the sponsor within 24 hours. If SARs are exempted from immediate reporting due to the fact that they are recorded as part of the clinical trial's primary or secondary efficacy endpoints, continuous safety monitoring must be ensured through a DSMB. Please see point 4 in section 2. For SAEs exempted from immediate reporting, it is important to note that all SAEs recorded but not reported immediately, must still be reported to the sponsor no later than before preparation of the ASR, and the specific frequency of reporting must be stated and justified in the protocol. The investigator must always have the possibility of recording and reporting any event to the sponsor if the investigator finds this relevant/necessary and this must be stated in the protocol.
Adverse event management at <u>risk level 3:</u>	It is expected that all AEs/SAEs are recorded, and that all SAEs/SARs are reported to the sponsor within 24 hours. Risk-adaptation is in general not possible, unless the sponsor can provide a robust justification based on a trial-specific risk assessment.

6. Appendix

Appendix 1 – Assessment of events and adverse reactions in a clinical trial



Appendix 2 – Description of selected terms

Adverse event (AE):

Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Seriousness criteria:

The event is serious if at least one of the following criteria applies:

- *inpatient hospitalisation or prolongation of existing hospitalisation*
- *results in persistent or significant disability or incapacity*
- *results in a congenital anomaly or birth defect*
- *is life-threatening*
- *results in death*

Serious adverse event (SAE):

Any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

Causality assessment:

A causality assessment is used to assess if an event is related to investigational medicine/intervention or not. In determining whether an adverse event is an adverse reaction, consideration shall be given to whether there is a reasonable possibility of establishing a causal relationship between the event and the investigational medicinal product based on an analysis of available evidence.

In the absence of information on causality provided by the reporting investigator, the sponsor shall consult the reporting investigator and encourage him to express an opinion on this issue. The causality assessment given by the investigator shall not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor shall be provided with the report.

The WHO-UMC's method may be used to make the causality assessment:
https://www.who.int/docs/default-source/medicines/pharmacovigilance/whocausality-assessment.pdf

Serious adverse reaction (SAR):

Is an SAE in which the event is assessed to be related (see causality assessment) to the investigational medicine and/or intervention.

Suspected unexpected serious adverse reaction (SUSAR):

A serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information. Whether an incident is unexpected or expected is determined based on the reference safety information.

Reference safety information (RSI):

The determination of whether an event is expected or unexpected is assessed in relation to the reference safety information (RSI). Often, parts of the product information or parts of the Investigator's Brochure (IB) are used as RSI for the investigational medicinal product.

Example:
In the case of authorised medicinal products, the RSI is often a part of the summary of product characteristics (SmPC), i.e. an adverse reaction appearing in the SmPC, often section 4.8, is expected; an adverse reaction not appearing in the product information is unexpected.

Annual safety report (ASR):

Any relevant safety information is expected to be described in the annual safety report. A list of SARs and SUSARs is expected, including an assessment of whether these events give rise to updating the protocol.

The annual safety report must describe the risk-adapted approaches subject to which it has been prepared.

Likewise, the annual safety report is expected to include an assessment of whether the benefit-risk balance has changed or is unchanged, meaning if the trial may continue or if protocol amendments are required for it to continue.

It is possible to submit a single safety report on all investigational medicinal products used in a clinical trial, see article 43(2) of the CT regulation.

Appendix 3 – General considerations about risk factors and risk minimisation measures

The following may be considered in connection with the risk assessment (list is non-exhaustive):

- Does the trial population consist of healthy trial subjects or patients?

- Is the investigational medicinal product authorised, and is it used in compliance with what has been approved and described in the product information? If not, consider the following:
  - *Are there changes to the dosage regime/route of administration?*
  - *Are there changes to the population/indication?*
  - *How will these changes impact the safety of trial participants?*

- What are the known/expected risks, both in relation to the trial design and/or the investigational medicinal product?
  - *Have these risks been addressed in normal clinical practice?*
  - *If the adverse reaction profile of the investigational medicinal product is unknown, which risks are expected based on non-clinical data and/or based on the knowledge from other medicinal products containing the same active substance?*
  - *Is the duration of treatment supported by previous experience?*
  - *Is there a risk of dosing errors?*

- Are there any risks of interactions with other treatments given concurrently that could increase the risk to trial participants?

- Is there a need for further safety monitoring of the trial participant in addition to that provided in standard treatment? This could be additional laboratory tests, ECG, imaging, biopsy, more frequent visits to the doctor.

- Are further risk minimisation measures needed? The following may be considered:
  - *Restrictive inclusion and exclusion criteria, e.g. exclusion of persons with a particular risk due to secondary diseases, resulting from impaired kidney/lung/heart/liver function or the use of certain medicinal products.*
  - *Adjustment of treatment regimen and duration, including sufficient monitoring and facilities, rescue medicine and the presence of trained (emergency) staff when relevant.*
  - *Stopping criteria or (dose) modification of the investigational treatment, e.g. using a protocol-specified treatment algorithm or an independent Data Safety Monitoring Board (DSMB).*
  - *Focused recording of adverse events and adverse reactions, e.g. organ-specific events or events giving cause for specific concern; reporting to the sponsor and authorities must comply with the legislative requirements at all times.*
  - *Further safety monitoring, e.g. by way of experts in the disease, in its routine treatment and in the investigational medicinal product/study treatment; an independent DSMB for the assessment of new safety data and benefit-risk balance.*

Appendix 4 – Examples of clinical trials at the different risk levels

Examples "low-risk" trials (risk level 1):

- Low-intervention trials[8]
- Trials with authorised medicinal products involving an approved indication in which the intervention is normal clinical practice.
- Trials with authorised medicinal products involving a well-established off-label indication which is normal clinical practice and supported by published evidence.

Examples of "medium-risk" trials (risk level 2):

- Trials with authorised medicinal products involving an unapproved indication in which the studied indication/population/treatment DOES NOT differ significantly from the authorised indication or normal clinical practice, and where the safety profile is expected to be the same.
- PK/PD trials with data available from other authorised medicinal products in the same pharmacological class.

Examples of "high-risk" trials (risk level 3):

- Trials with non-authorised medicinal products or authorised medicinal products with limited knowledge about adverse reactions[9].
- Trials with authorised medicinal products involving an unapproved indication in which the studied indication differs significantly from the approved one, e.g. another disease area or a special population such as children for which the safety profile of the intervention has not been established despite the status of the medicinal product.
- Trials with combination treatment with two or more medicinal products, posing a risk of drug interactions and where it is not possible to break down the adverse event management on the individual medicinal products.
- Trials with modified medicinal products without a marketing authorisation, for example a new formulation/pharmaceutical form.
- Trials in which the medicinal product is used in combination with medical devices or other medicinal products with an expected synergistic effect (e.g. electroporation).

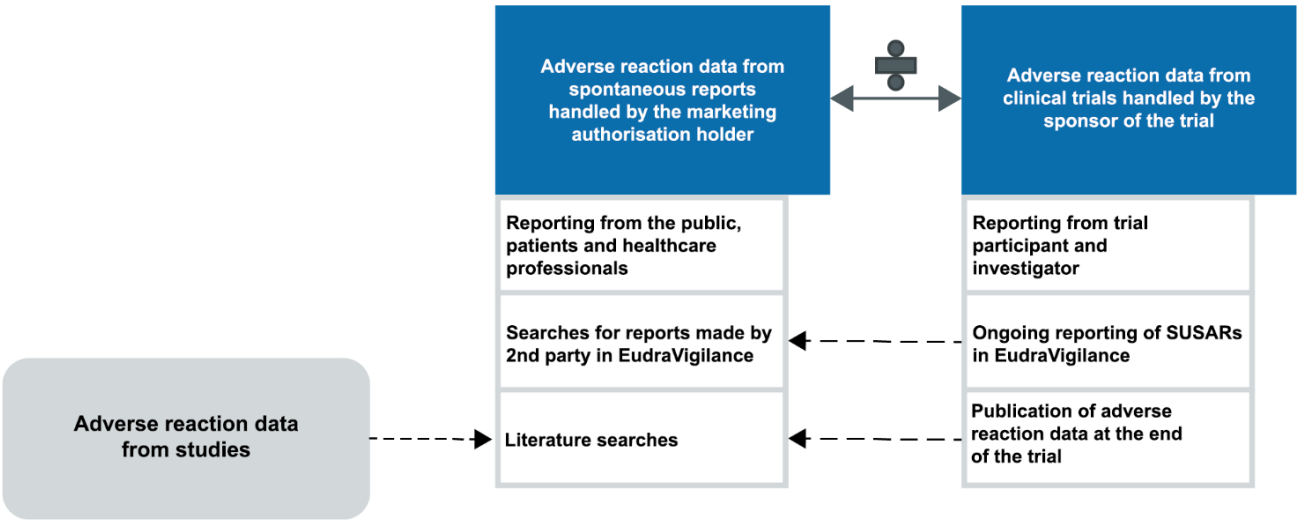
[8] Under article 2(3) of the CTR, a low-intervention clinical trial is a clinical trial which fulfils all the following conditions:
   a. the investigational medicinal products, excluding placebos, are authorised;
   b. according to the protocol of the clinical trial, i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
   c. the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

[9] Including authorised medicinal products subject to additional monitoring and stricter reporting requirements

Appendix 5 – Evidence generation and data sources for authorised medicinal products

Medicinal products used in clinical trials are categorised as investigational medicinal products whether or not they have a marketing authorisation. Consequently, adverse event data collected in a clinical trial are not automatically sent to the marketing authorisation holder. Instead, alternative mechanisms ensure that the marketing authorisation holder can gain a complete overview of emerging safety data. One such mechanism is the sponsor's ongoing reporting of SUSARs to EudraVigilance database which are searchable by the marketing authorisation holder. Another mechanism is the literature searches made by the marketing authorisation holder which aim to identify publications containing safety data related to the concerned medicinal product (Figure 3).

Figure 3 Safety data sources for authorised medicinal products



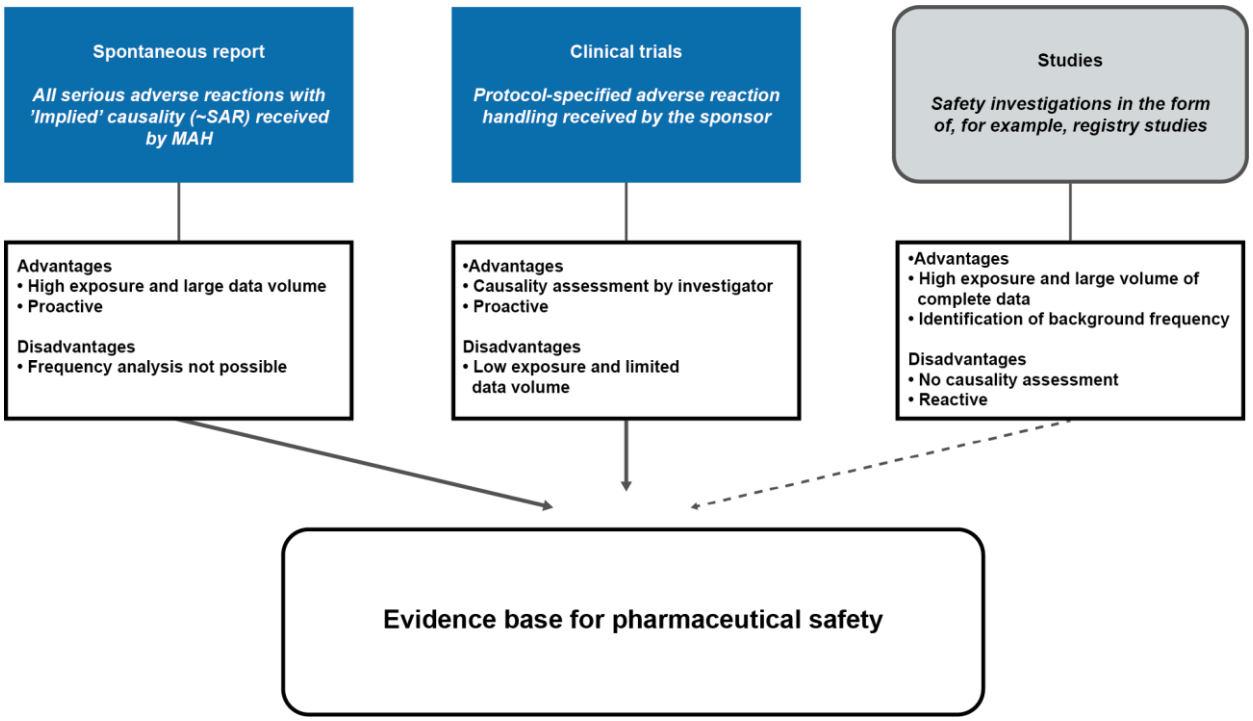
As illustrated in the figure above, literature searches will also identify adverse reaction data from other sources, such as registry-based studies. This reveals a complex array of data sources that collectively provide a comprehensive evidence base for the safety of the medicinal product.

Each source of adverse reaction data has its advantages and disadvantages concerning the quality of the evidence it provides, emphasising the importance of all data sources in enhancing the knowledge about pharmaceutical safety. Spontaneous reports related to authorised medicinal products generate a substantial volume of data. However, the lack of background frequencies is a significant disadvantage compared to controlled clinical trials, where frequency comparison is possible. While registry studies allow for such comparisons, they lack the medical causality assessment that are conducted for each recorded adverse event in a clinical trial (Figure 4).

Where the array of data sources is complex when it comes to authorised medicinal products, the sole source of evidence is clinical trials when it comes to non-authorised medicinal products. In this case, the safety profile has not been validated by means of a marketing authorisation application, and no post-marketing monitoring has begun. Hence, thorough adverse event management is essential, above all to safeguard the safety of patients and, secondly, to ensure a fit-for-purpose evidence for any future marketing authorisation application.

Exposure will be lowest in the development phase and will in most instances increase significantly once the product receives marketing authorisation. In the first two years following market placement in the EU, the medicinal product is subject to additional monitoring. The additional monitoring may be extended, reflecting the need for further evidence, and hence is important to consider when evaluating the product's exposure and evidence base for setting the necessary risk level of adverse event management.

Figure 4 Evidence base for safety data



7. Change log

Changes from version 1.0 to 2.0:

Version 2.0 includes the following updates:	• Section 2.2: New wording concerning additional monitoring list in the EU. • Section 2.4: Clarification and new wording concerning trials with high mortality and establishing DSMB. • Section 2.5: Clarification of which events must be included in ASR. • Editorial changes throughout the document, including changes to the layout.

Rigshospitalet

Patientforberedelse til PET-, PET/CT- og PET/MR-scanninger på Rigshospitalet			
Udgiver	Rigshospitalet		
Dokumenttype	Vejledning	Version	6
Forfattere	sektionsleder PET-scannersektion, overlæger PET-scannersektion	Gældende fra	12-12-2024
Fagligt ansvarlig	Annika Loft Jakobsen	Næste revision	12-12-2027
Ændringer	Dokument flyttet til Rigshospitalet og publiceret til alle. Ingen ændringer i indhold.		

Genvej til indhold

Formål

- Beskrive henvisende afdelings ansvar ifm. patientforberedelser til PET-, PET/CT- og PET/MR-scanning ved Afdeling for Klinisk Fysiologi & Nuklearmedicin, Rigshospitalet
- Beskrive kontraindikationer for PET-, PET/CT og PET/MR-scanning

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Målgrupper og anvendelsesområde

Vejledningen gælder for personale på kliniske afdelinger, der henviser patienter til PET-scanning, PET/CT-scanning eller PET/MR-scanning ved Afdeling for Klinisk Fysiologi & Nuklearmedicin, Rigshospitalet.

Tilbage til top

Definitioner

PET = Positron Emissions Tomografi

CT = Computed Tomography

MR = Magnetisk Resonans

Tilbage til top

Fremgangsmåde

Henvisning til undersøgelse

- Henvisning sendes via RIS til Afdeling for Klinisk Fysiologi, Nuklearmedicin og PET.
- Henvisende læge udfylder og underskriver MR-kontrolskema
- CT-skema udfyldes og underskrives
- Henvisende læge skal forud for henvisningen sikre sig patientens samtykke til at få undersøgelsen foretaget.

- Alle henvisninger visiteres på Afdeling for Klinisk Fysiologi & Nuklearmedicin, inden undersøgelsen bookes.
- Der udføres PET- og PET/CT-scanninger i afsnit 3982, 3985 og 4011 på Blegdamsvej og i afsnit ØB 2.sal på Rigshospitalet Glostrup.
- Der udføres PET/MR-scanninger i afsnit 3982 på Blegdamsvej.

Indikationer, kontraindikationer og relative kontraindikationer til PET, PET/CT og PET/MR

- **Indikation**
  - Mangfoldige, er angivet i forberedelsesskemaerne ved hver undersøgelse.

- **Kontraindikation**
  - Relativ ved gravide og ammende.
  - Metalgenstande i patienten, der IKKE er MR-kompatible, er kontraindikation for MR-scanning. Anfør **type og operations-år** i MR-kontrolskema:.
    - Metalklips i hjernen
    - Pacemaker (bemærk, at der kan sidde metal tilbage, selvom pacemakeren er fjernet)
    - Stent
    - Indopererede hjælpemidler som fx øreimplantat og insulinpumpe
    - Kunstige lukkemuskler
    - Elektroniske stimulatorer
    - Metalsplinter i øjne/krop: Angiv splintens art.

- **Relative kontraindikationer**
  - Graviditet:
    - Der foretages sædvanligvis ikke undersøgelser med ioniserende stråling på gravide kvinder. I sjældne tilfælde kan det dog være indiceret, og i så fald bør undersøgelsen konfereres med vagthavende læge på Afdeling for Klinisk Fysiologi, Nuklearmedicin og PET, tlf. 5-1379,mhp. at planlægge en skanning med lille dosis sporstof og ultra lavdosis CT.
  - Stort abdominalomfang:
    - Da PET/MR-scannerens åbning er forholdsvis lille (60 cm), kan patienter med meget stort abdominalomfang ikke være i scanneren. Lejet i scanneren har også en maksimal bæreevne. Mål patientens livvidde og kontakt PET-bagvagt på tlf. 5-1379, hvis der er tvivl om, hvorvidt patienten kan være i scanneren.
  - Motorisk uro og/eller manglende evne til at kooperere til undersøgelsen:
    - Hvis patienten ikke kan ligge helt stille under undersøgelsen, kan scanningen blive præget så meget

af uro, at den ikke kan tolkes. *Sedering kan være en mulighed*.

- Fysisk tilstand:

        - Ved fx smerter, rygproblemer eller gangproblemer må det overvejes om patienten kan ligge helt fladt på lejet i længere tid (>30min) under scanning. Hvis ikke dette er muligt, kan PET/MR-scanning vanskeligt gennemføres, og der anbefales separat PET/CT- og MR-scanning.
    - Klaustrofobi:
        - PET/MR-scanning frarådes til hjerne-demens-undersøgelser ved klaustrofobi, og separat PET/CT og MR skanning anbefales. Ellers skal tages stilling til evt beroligende medicin.
        - Da PET/MR-scannerens åbning er forholdsvis lille (60 cm) kan det for personer med svær klaustrofobi være svært at gennemføre undersøgelsen. Personalet i afdelingen har mulighed for at give patienten beroligende medicin forud for undersøgelsen
        - Da PET/CT-scannerens åbning er forholdsvis stor, vil de fleste, der blot lider af lettere klaustrofobi, kunne medvirke til en scanning. Personalet i afdelingen har mulighed for at give patienten beroligende medicin forud for undersøgelsen.

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Forberedelse til undersøgelser - generelt

Henvisende afdeling skal før undersøgelsen vurdere patienten med henblik på...:

- **Ledsagende plejepersonale.** Hvis patienten har brug for observation og pleje i undersøgelsesperioden, skal der være ledsagende personale med fra den henvisende afdeling. Personalet skal være uddannet i og i stand til at yde den pleje og/eller behandling patienten har behov for, herunder at kunne behandle forventelige komplikationer.
- **Svar på plasma-kreatinin.** Hvis der i forberedelsesskemaet er krav om ny plasma-kreatinin, påhviler det henvisende afdeling at sikre rettidig blodprøvetagning, og at svaret er tilgængeligt, inden PET/CT- eller PET/MR-scanningen skal foretages. Plasma-kreatinin svar anvendes i forbindelse med injektion af kontrast.
- **Smertepalliering.** Hvis patienten er plaget af smerter, er det henvisende afdelings ansvar, at denne er smertepallieret før scanningen. Det er vigtigt for resultatet af undersøgelsen, at patienten kan ligge stille i scanneren.
- **Tolk.** Hvis patienten ikke kan forstå nok dansk til at kooperere ved undersøgelsen, påhviler det henvisende afdeling af sørge for tolkning.
- **Påklædning.** Patienten skal være iført tøj uden metalknapper/lynlås mv. eller smykker svarende til det område, der skal scannes. Send gerne patientens strømper og sko med, da patienten skal ud at gå på gulvet.
- **Injektion på sengeafdelingen.** Patienter på intensive afsnit eller i isolation kan evt. få foretaget injektionen af det radioaktive lægemiddel på sengeafdelingen og transporteres til scanning til aftalt tidspunkt. Kontakt PET-bagvagt tlf.; 5-1379 for at planlægge forløbet.
- **Transport.** Det er henvisende afdelings ansvar at bestille transport til undersøgelsen. Afdeling for Klinisk Fysiologi, Nuklearmedicin og PET bestiller returtransport.

Ved tvivlsspørgsmål kan vagthavende læge på Afdeling for Klinisk Fysiologi & Nuklearmedicin kontaktes:

- PET-bagvagt tlf.: 5-1379.
- Drejer det sig om PET-hjerneundersøgelser, kontakt PET–hjerne-bagvagt tlf.: 5-7254
- Drejer det sig om PET-hjerteundersøgelser, kontakt KF–bagvagt tlf.: 5-1674

Forløbet af undersøgelsen

Patienten får injektion af et radioaktivt lægemiddel i en vene og hviler inden scanningen. Hviletiden varierer fra 5-60 minutter. Patienten placeres på et leje, og den kropsdel, som skal undersøges, placeres i scannerens åbning. Ved scanning af hele kroppen kører lejet ind gennem scanneren. Scanningen opsamler data, hvorefter vi kan rekonstruere serier af billeder.

Det kan tage lidt tid at blive placeret rigtigt i scanneren før undersøgelsens start.

PET eller PET/CT-scanningen tager 15-45 minutter og giver ingen smerter eller anden form for ubehag.

Ved PET/MR-scanning påspændes sædvanligvis antenner (coils) på det område, der skal skannes.

PET/MR-scanning tager op til 1 time. Da PET/MR-scanneren larmer meget, får patienten høreværn på, og patient og scannerpersonale kommunikerer via et samtaleanlæg.

Kontrast til CT eller MR: Intravenøs kontrast gives ved indsprøjtning i en vene. Kontrasten er uskadelig for kroppen og giver generelt ikke ubehag, dog eventuelt lette, forbigående bivirkninger i form af varme- og vandladningsfornemmelse samt metalsmag i munden.

Drikkekontrast gives til visse undersøgelser

Det er vigtigt, at patienten drikker rigeligt væske før og efter undersøgelsen. Dette medvirker til udskillelsen af det radioaktive lægemiddel og den intravenøse røntgenkontrast. Udskillelsen sker via urinen.

Hvis patienten skal have væske via sonde eller intravenøst, kontakt PET-bagvagt tlf. 5-1379.

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Patientforberedelser ved PET- og PET/CT-helkropsscanninger

^{18}F-FDG-PET-scanning el. ^{18}F-FDG-PET/CT-scanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**Forberedelse ved visitation til CT med kontrast**
Indikationer: En lang række cancersygdomme: Diagnostik, stadieinddeling, responsmonitorering, recidivpåvisning og planlægning af stråleterapi. Påvisning af infektionsfoci og aktivitet i inflammatorisk sygdom.	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand. Glukosedrop og parenteral ernæring skal være seponeret i 4 timer før undersøgelsen. Patienten bør undgå fysisk anstrengelse på undersøgelsesdagen	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand Tage vanlige dosis insulin, før faste. Ekstra insulin må ikke tages i fasteperioden. Bruger patienten insulinpumpe, fortsættes med basalinsulin under faste. **Pausere 48** timer med medicin, der indeholder Metformin, idet Metformin påvirker optagelsen af FDG i tarmen.	Plasma-kreatinin eller GFR-værdi skal inden undersøgelsen være.: Ambulante patienter: Under 3 måneder gammel Indlagte patienter: Under 7 dage gammel Akutte patienter: Under 24 timer gammel

^{68}Ga-DOTATOC-PET/CT-scanning el. ^{64}Cu-DOTATATE-PET/CT-scanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**Forberedelse ved visitation til CT med kontrast**
Indikationer: Neuroendokrine tumorer (NET), påvisning og stadieinddeling Påvisning af fæokromocytom, neuroblastom, ganglioneurom og	Ingen	Ingen	Plasma-kreatinin eller GFR-værdi skal inden undersøgelsen af være.: Ambulante

paragangliom Led i udredning af medullært thyroideakarcinom Vurdering af kendte tumores egnethed for radionuklidbehandling Vurdering af progression/regression af ovennævnte tumorer			patienter: Under 3 måneder gammel Indlagte patienter: Under 7 dage gammel Akutte patienter: Under 24 timer gammel

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Patientforberedelse ved PET og PET/CT–hjernescanninger

^{18}F-FDG PET/CT-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
Indikationer: **Ikke-maligne sygdomme:** Epilepsi. Præoperativ vurdering mhp. lokalisering af focus. Neurodegenerativ sygdom, tidlig diagnose og udbredelse, differential- diagnostisk subklassifikation, moni-torering af sygdomsudvikling. Cerebrovaskulær sygdom. Inflammatoriske CNS-sygdomme: SLE, Sarkoidose, limbisk encephalitis. **Maligne sygdomme:** Primært CNS-lymfom	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand. Glukosedrop og parenteral ernæring skal være seponeret i 4 timer før undersøgelsen.	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand. Patienten skal tage sin sædvanlige dosis insulin før faste. Ekstra insulin må ikke tages i fasteperioden. Bruger patienten insulinpumpe, fortsættes med basalinsulin under faste.	Der benyttes ikke CT-kontrast ved denne undersøgelse

^{18}F-FET PET-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
Indikationer: Vurdering af en uafklaret proces i hjernen. Præoperativ afgrænsning af et mistænkt gliom Postoperativ afgrænsning af resttumorvæv fra gliom Vurdering af en tumors malignitetsgrad	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand. Der må i denne periode ikke gives parenteral ernæring, inkl. proteinholdig/aminosyreholdig ernæring.	**Faste 4 timer**. Hvis det ikke er muligt at faste 4 timer, må henvisende afdeling vurdere, hvilke forholdsregler omkring faste og diabetesmedicin der klinisk er muligt. Dog skal proteinholdig/aminosyreholdig ernæring i videst muligt omfang undgås	Der benyttes vanligvis ikke CT-kontrast ved denne undersøgelse. Hos patienter med pacemaker eller anden kontraindikation for MR, kan der udføres CT før og efter kontrast, hvis det præciseres i

Mistanke om malign degeneration Planlægning af hjernebiopsi mhp. optimering af den diagnostiske kvalitet Differentialdiagnosticering mellem recidivtumor og stråleføl ger. Monitorering af behandlingsrespons – tidlig identifikation af tumorrecidiv. Vurdering af cerebrale metastaser indtegning af hjernetumorer/metastaser ved stråleterapiplanlægning. *OBS: 18F-FET indeholder små mængder ethanol svarende til 1/8 genstand (<1,5 g) som kan give lette reaktioner hos patienter i Disulfiram- (Antabus) eller metronidazol-behandling. Kontakt vagthavende ved spørgsmål, tlf. 35457254.*			henvisningen.

^{18}F-FE-PE2I PET-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
<u>Indikationer</u> Patienter med klinisk usikker Parkinsonisme *OBS: 18F-FE-PE2I indeholder små mængder ethanol svarende til 1/8 genstand (<1,5 g) som kan give lette reaktioner hos patienter i Disulfiram- (Antabus) eller metronidazol-behandling. Kontakt vagthavende ved spørgsmål, tlf. 35457254.*	Ingen	Ingen	Der benyttes ikke CT-kontrast ved denne undersøgelse

^{11}C-PiB PET-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
<u>Indikationer:</u> Mistanke om tilstande med øget amyloidophobning i hjernen. *OBS: 11C-PiB indeholder små mængder ethanol svarende til 1/8 genstand (<1,5 g) som kan give*	Ingen	Ingen	Der benyttes ikke CT-kontrast ved denne undersøgelse

lette reaktioner hos patienter i Disulfiram- (Antabus) eller metronidazol-behandling. Kontakt vagthavende ved spørgsmål, tlf. 35457254.			

^{68}Ga-DOTATOC-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
Indikationer: Påvisning af aktivt meningeomvæv ved primærdiagnostisk, vurdering af resttumorvæv, mistanke om recidiv og stråleterapiplanlægning.	Ingen	Ingen	Der benyttes ikke CT-kontrast ved denne undersøgelse

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Patientforberedelser ved PET- og PET/CT-hjertescanninger

^{82}Rubidium PET/CT-hjertescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
Indikationer: Vurdere tilstedeværelsen af iskæmigivende koronararteriesygdom hos patienter med intermediær prætest sandsynlighed for iskæmisk hjerte-sygdom. Vurdere graden af iskæmi før stillingtagen til revaskularisering hos patienter med kendt koronararteriesygdom. Mistanke om stum iskæmi. Før større operativt indgreb (fx nyre-transplantation) hos patienter med betydelig øget risiko for koronarsyg-dom. Kontrol efter hjertetransplantation. Kvantificering af koronar flowreserve	Fra kl. 16 dagen inden undersøgelsen må patienten ikke indtage koffein i form af fx chokolade, kaffe, cola, te eller energidrik Forud for undersøgelsen pauseres med følgende medicin: **72 timer (4 dage):** Viagra, Cialis, Levitra **48 timer (2 dage):** Persantin, Asasantin **24 timer (1 dag):** Nuelin Retard, Teofylamin, Theo-dur, UniXan. **12 timer:** Cardopax, Fem-Mono Retard, Imdur, Isodur. **2 timer:** Discotrine-plaster, tages af senest to timer før.	Samme som for ikke-diabetespatienter	Der benyttes ikke CT-kontrast ved denne undersøgelse

^{18}F-FDG- PET/CT-hjertescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
Indikationer:	**Faste 4** timer forud for undersøgelsen. Patienten må	**Ikke-insulinkrævende diabetes:** Tage	Der benyttes ikke CT-kontrast ved

Hjerteinsufficiens og svær koronarsygdom, hvor revaskularisering overvejes for at forbedre hjertets pumpefunktion. CTO (Chronic Total Occlusion) i koronararterie, forud for PCI-behandling.	dog gerne drikke vand.	diabetesmedicin som vanligt. **Faste 4** timer forud for undersøgelsen. Patienten må dog gerne drikke vand. **Insulinkrævende diabetes:** Patienten må spise morgenmad og få sin insulin som vanligt. **Insulin via pumpe: Faste 4 timer** forud for undersøgelsen og forblive tilkoblet insulinpumpe med vanlig basisinsulin. Patienten må dog gerne drikke vand.	denne undersøgelse

Kombineret ^{82}Rubidium- og ^{18}F-FDG-PET-hjertescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**CT med kontrast**
Indikationer: Samme som for ^{82}Rubidium PET/CT–hjertescanning og ^{18}F-FDG- PET/CT – hjertescanning	Patienten skal forberedes til begge undersøgelser. Se "Forberedelse" i ovenstående skemaer: ^{82}Rubidium PET/CT–hjertescanning og ^{18}F-FDG-PET/CT – hjertescanning	Patienten skal forberedes til begge undersøgelser. Se "Forberedelse, diabetespatienter" i ovenstående skemaer: ^{82}Rubidium PET/CT–hjertescanning og ^{18}F-FDG-PET/CT – hjertescanning	Der benyttes ikke CT-kontrast ved denne undersøgelse

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Patientforberedelse ved PET/MR-scanninger

18F-FDG PET/MR-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**MR med kontrast**
Indikationer: **Ikke-maligne sygdomme:** Neurodegenerativ sygdom, tidlig diagnose og udbredelse, differential- diagnostisk subklassifikation, monitorering af sygdomsudvikling	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand.	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand. Patienten skal tage sin sædvanlige dosis insulin før faste. Ekstra insulin må ikke tages i fasteperioden. Bruger patienten insulinpumpe, fortsættes med basalinsulin under faste.	Der benyttes ikke MR-kontrast ved denne undersøgelse

18F-FET PET/MR-hjernescanning	**Forberedelse**	**Forberedelse, diabetespatienter**	**Forberedelse ved visitation til MR med**

			kontrast
Indikationer: Vurdering af en uafklaret proces i hjernen. Præoperativ afgrænsning af en mistænkt primær hjernetumor. Postoperativ afgrænsning af resttumorvæv fra primær hjernetumor. Vurdering af en tumors malignitetsgrad. Mistanke om malign degeneration. Planlægning af hjernebiopsi mhp. optimering af den diagnostiske kvalitet. Differentialdiagnosticering mellem recidivtumor og stråleфølger. Monitorering af behandlingsrespons – tidlig identifikation af tumorrecidiv. Vurdering af cerebrale metastaser *OBS. 18F-FET indeholder små mængder ethanol svarende til 1/8 genstand (<1,5 g) som kan give lette reaktioner hos patienter i Disulfiram- (Antabus) eller metronidazol-behandling. Kontakt vagthavende ved spørgsmål, tlf. 35457254.*	**Faste 4 timer** før undersøgelsen. Patienten må dog gerne drikke vand. Der må i denne periode ikke gives parenteral ernæring, inkl proteinholdig/aminosyreholdig ernæring.	**Faste 4 timer.** Hvis det ikke er muligt at faste 4 timer, må henvisende afdeling vurdere, hvilke forholdsregler omkring faste og diabetesmedicin der klinisk er muligt. Dog skal protein-/aminosyreholdig ernæring i videst muligt omfang undgås.	eGFR alternativt P-kreatinin skal foreligge inden scan- opstart hvis... • Patienten har nedsat nyrefunktion. • eGFR alternativt P-kreatinin må ikke være ældre end 30 dage. Hvis eGFR alternativ. P-kreatinin er ældre end 30 dage, måler scannerpersonalet på Klinisk fysiologi & Nuklearmedicin, eGFR alternativt P- kreatinin.

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Ansvar og organisering

Ansvar hos henvisende afdelingers personale: Se afsnit "Fremgangsmåde"

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Referencer, lovgivning og faglig evidens samt links hertil

- Lov nr. 23 af 15/01/2018 om ioniserende stråling og strålebeskyttelse (findes på Retsinformation.dk)
- Bekendtgørelse 669 af 01/07/2019 om ioniserende stråling og strålebeskyttelse §16, §61 (findes på Retsinformation.dk)

Link til patientvejledninger på Rigshospitalets hjemmeside:

- Patientvejledninger til PET-undersøgelser findes på Rigshospitalets hjemmeside: https://www.rigshospitalet.dk/afdelinger-og-klinikker/diagnostisk/klinisk-fysiologi-og-nuklearmedicin/patientinformation/undersoegelse-paa-afdelingen/Sider/default.aspx

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Bilag

Ikke relevant.

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Herlev og Gentofte Hospital

06.2.HEH.11.1.1.18F-FDG PET/CT generel			
Udgiver	Herlev og Gentofte Hospital > Nuklearmedicin		
Dokumenttype	Instruks	Version	9
Forfattere	Lene Skads Jeppson/LENJEP01/RegionHovedstaden, Nina Tietgen/NINTI/RegionHovedstaden	Gældende fra	07-05-2024
Fagligt ansvarlig	Helle W Hendel	Næste revision	09-10-2024
Ændringer	Ændringer til afsnittet 'Forberedelse' - ændret fra gammel til ny version		

Formål

Præcis anatomisk påvisning af foci med øget optagelse af glucoseanalogen fluordeoxyglucose (FDG).

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Målgrupper og anvendelsesområde

Sygeplejersker, bioanalytikere, radiografer og læger på Afdeling for Nuklearmedicin, som arbejder med PET/CT.

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Undersøgelsesprincip

^{18}F-Fluordeoxyglucose (^{18}F-FDG) er en radioaktivt mærket glukose analog, der anvendes som sporstof til at påvise celler med højt glukoseforbrug. Maligne og visse inflammatoriske celler har et højere stofskifte end normalt væv og øget optagelse af glukose og FDG. PET-skanning (positron emissions tomografi) kan man påvise FDG-fordelingen i kroppen og dermed identificere områder med tumorer, metastaser, infektioner og inflammation.
Ved samtidigt at udføre (diagnostisk) CT-skanning kan den præcise lokalisation af FDG-optagelsen lokaliseres, hvilket øger den diagnostiske sikkerhed (specificiteten). Omvendt kan patologiske forandringer på CT-skanningen verificeres eller afkræftes. I flere tilfælde kan PET og CT visualiserer patologiske forandringer uafhængigt af hinanden; f.eks. kan PET ikke visualisere små lungemetastaser, og CT er i mange tilfælde mindre sensitivt til diagnosticering af knoglemetastaser.
Der suppleres ofte med intravenøs røntgenkontrast En lav dosis CT-skanning (ldCT) udføres til attenuationskorrektion af PET-data og antomisk vejledning, hvis der ikke er brug for en diagnostisk CT skanning (f.eks. hvis patienten har en relativt ny CT-skanning)

VARIGHED:

2,5 – 3 timer (forberedelse, skanning, evt. ventetid)

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Indikationer

1. Onkologiske sygdomme mhp. primær diagnostik (ukendt primær tumor, c. occulta) og stadieinddeling samt som led i behandlingskontrol mhp. påvisning af restsygdom eller recidiv. Endvidere som led i planlægning af stråleterapi eller kirurgi, hvor det er afgørende præcist at kunne adskille vitalt tumorvæv fra ikke-vitalt væv.
2. Infektionsudredning (alternativ til leukocytskintigrafi særligt ved kronisk/længerevarende infektion).

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Kontraindikationer

Ingen kontraindikation for PET-skanning, ud over svær adipositas (se specifikt for skanneren), eller tilfælde hvor patienten pga. svær klaustrofobi ikke vil være i skanneren, hvor besigtigelse af skanneren og evt. angstdæmpende medicin ikke skønnes effektfuldt. Ang. iv-kontrast, se ” Iodholdig kontraststof, Forholdsregler ved intravaskulær indgift”.

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Graviditet og amning

I tilfælde af graviditet må den henvisende læge sammen med en speciallæge fra PET-CT gruppen vurdere, om det er afgørende for patienten at få udført undersøgelsen.

Normalt ingen ammepause. FDG udskilles **ikke** via mælken. For at mindske stråling fra mor (hjerne, hjerte, blære) til barn frarådes tæt kontakt de første 3-6 timer (3-5 halveringstider fra inj af tracer). Det anbefales at malke de første portioner mælk ud , så en anden kan give barnet mælken i en sutteflaske.

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Forberedelse

Alle patienter skal faste i minimum 4 timer forud for undersøgelsen (injektion af sporstof). Patienten opfordres dog til at drikke vand i fasteperioden.

Parenteral ernæring og/eller intravenøse væsker, som indeholder glucose (inkl GIK-drop), dextrose eller laktose, skal seponeres minimum 4 timer før FDG-injektionen.

Hård motion indtil 24 timer før undersøgelsen skal undgås.

For patienter, hvor der er klinisk mistanke om nedsat nyrefunktion eller har kendt nyresygdom, skal der foreligge eGFR der er mindre end 3 mdr gammel.
Hos alle patienter med akut sygdom/indlagte skal der foreligge eGFR som er mindre end 7 dage gammel.

Nedenfor beskrives hvordan patienter med diabetes skal forholde sig.

I tvivlstilfælde kontaktes udgående diabetesteam (38681309).

Patienter i behandling med Metformin og Metforminkombinationspræparater anbefales at pausere i 48 timer før undersøgelsen.

Type 2 patienter, som ikke får insulin:
Antidiabetika skal tages som vanligt, fraset Metformin og Metforminkombinationspræparater som ovenfor anført.
Faste 4 timer før tracer-injektion.

Insulinkrævende diabetespatienter (både type 2 og type 1):
Indtagelse af morgenmad og morgen-insulin (dette gælder både basalinsulin og bolusinsulin) mindst 4 timer før injektion af sporstof. Faste 4 timer før injektion af sporstof. Ingen insulin-injektioner i fasteperioden.

Insulinpumpepatienter (type 1 diabetes):
Faste 4 timer før injektion af sporstof. Ingen insulin-bolus i fasteperioden. Pumpen skal uændret afgive basalinsulin i fasteperioden.

Hos patienter med insulinkrævende diabetes (injektionsbehandling og insulinpumpebærere) og hvis blodsukker > 10 mmol/l, kan gives hurtigtvirkende insulin Novorapid efter sliding scale indtil 4 timer før injektion af sporstof. Skal patienten undersøges kl. 11, skal der således måles blodsukker ved 6-tiden for at kunne nå at administrere Novorapid..

Blodsukkermåling gentages efter tre timer. Måles der fortsat blodsukker > 10 mmol/l kontaktes Afdeling for Nuklearmedicin mhp. om undersøgelsen skal aflyses/rykkes.

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Definitioner

Ikke relevant.

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Fremgangsmåde

Apparatur:

Siemens Biograph mCT, Siemens Biograph mCT FLOW, samt Siemens Biograph Vision.

Udførsel:

Skanneren:
Der udføres daglig kvalitetskontrol hver morgen, se vejledning. Henvisningen gennemgås mhp. forberedelse af patienten (anxiolytika, e-GFR og i.v. adgang).

Hvileområde:
Patienten identificeres ved navn og cpr.nr. På arbejdsskemaet noteres vægt, højde, samt for kvinder i den fertile alder (13-55 år) mulig graviditet. I tvivlstilfælde udføres graviditetstest. Patienten skal bekræfte, at faste er overholdt og spørges om diabetes.

Hvis patienten er visiteret til i.v.-kontrast, udfyldes arbejdsarket ang. kontraindikationer (se: " Iodholdig kontraststof, Forholdsregler ved intravaskulær indgift").

Patienten placeres på sengeleje i afslappet rygstilling.

Angste patienter eller patienter med kendt tendens til muskelspændinger (f.eks. smertebetingede muskelspændinger) gives evt. tablet Diazepam 2 mg. per. os før injektion af 18F-FDG.

Der anlægges venflon i armvene:

- PET-CT med i.v. kontrast: venflon 18 G (grøn)
- PET eller PET-CT uden i.v. kontrast 22 G (blå)

På venflonen påsættes en membranprop (Luer Access Split-Septum)

Hos alle patienter måles glukoseværdien før skylning af NaCl 0,9 % eller som beskrevet nedenfor og altid før injektion af ^{18}F -FDG:

- Fra venflon eller ved hjælp af microlet lancetter udtages blod til glukosemåling på Contour next glukoseapparat.
- Resultatet noteres på arbejsskemaet.
- Hvis glukoseværdien er > 8 mmol/l drøftes situationen med PET-afsnittets vagthavende læge (tlf. 8 1675)
- I.v. adgangen skylles igennem med NaCl 0,9% i 10 ml sprøjte.

Når der er sikret fri passage, injiceres ^{18}F –FDG afhængig af patientvægten. 4MBq ^{18}F –FDG pr kg legemsvægt, minimum 150 MBq og maksimum 400 MBq via venflonen vha. Intego. For patienter med BMI ≥ 35 rådføres med PET-afsnittes vagthavende læge (tlf. 8 1675), om FDG-dosis skal øges til 4,5 MBq/kg, minimum 400 MBp, max 500 MBp (se vejledning).

Ved håndinjektion injiceres i trevejshane. Der skylles grundigt med NaCl 0,9% i begge studser. Klistermærke med sporstof, dosis, samt optrækstidspunkt sættes på arbejdsarket og injektionstidspunktet noteres herpå.

Der dokumenteres for injektion i QDOC. Ved håndinjektion indskrives dosis manuelt.

Patienten hviler herefter i ca. 45 minutter og lader derefter vandet.

- Alt uønsket metal fjernes fra patienten inden undersøgelsen
- Patientens cpr-nummer tjekkes på skærmen i skannerrummet
- Patienten instrueres i at ligge uden at bevæge sig under hele undersøgelsen
- Placér patienten centralt på lejet på ryggen med hoved hvilende i hoved-holderen. Brug evt. kiler til fiksation
- Der gives evt. knæpude og armene lejres over hovedet, evt. på pude
- Hvis patienten ikke kan have armene over hovedet, lægges armene ned langs siden og spændes fast med det brede bånd (husk at fjerne ur og ring)
- Ved manuel injektion fjernes trevejshane inden skanning

Den inderste lasers placering afhænger af protokollen. Der skannes i protokol 926, 927, 935-950, 960 eller 961. Se protokoloversigt.

PET/CT planlægning og optagelse: Se instrukserne for den pågældende skanner.

Undersøgelsen planlægges således, at PET-skanningen opstartes 60 minutter ± 5 minutter efter ^{18}F -FDG-injektion. Ved afsluttet undersøgelse dokumenteres i QDOC. For CT-skanningen indskrives kontraststof + dosis og evt. udfordringer/kontraindikationer. For PET-skanningen noteres evt. forsinkelser/generelle udfordringer med hele skanningen.

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Fejlkilder

- Kontaminering
- Artefakter: Metal i kroppen (porta kath., plomber i tænder, proteser og andre stråleabsorberende genstande)
- Dårlig lejring af patienten
- Uro hos patienten i hvile-perioden
- Uro hos patienten under optagelsen (bevægelsesartefakter)
- Hård fysisk aktivitet 24 timer inden injektion
- Højt insulinniveau, trods normalt blodsukker
- Forsinket eller forlænget delay time (dvs. optagelsen er startet for tidligt/for sent)

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Lægemidler, aktivitetsmængde og stråledosis

Stråledosis til patienten skal søges at holdes så lav som muligt, under hensynstagen til opnåelse af brugbare billeder.

Røntgendosis: Stråledosis ved helkropsskanning ~ 11,7 mSv, thorax/abdomen ~ 10 mSv.

Ved "lavdosis-CT 50mA" er stråledosis ca. 2,8 mSv.

Effektiv dosis (^{18}F -FDG): 8 mSv (±10 %) ved standard dosis på 370 MBq ^{18}F -FDG

LÆGEMIDDEL/DOSIS:

PET-tracer:
18F- Fluordeoxyglucose (FDG).

4 MBq (±10 %) ^{18}F–FDG pr kg legemsvægt, minimum 150 MBq og maksimum 400 MBq

Patienter med BMI > 35, som tidligere har været skannet på standarddosis (4 MBq/kg), gives 500 MBq 18F-FDG mhp. optimering af billedkvaliteten, hvis standarddosis har givet forringet billedkvalitet (konference med vagthavende læge)

iv-kontrast:
Omnipaque 350 mgI/ml, indgives efter vægt (se display på kontrastsprøjte)

Muskelafslapning/sedering/angstdæmpning:
Tbl. Diazepam 2 mg p.o.

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Fortolkning og svar

Der afgives skriftligt svar i RIS.

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Ansvar og organisering

Overbioanalytikeren har ansvaret for at indholdet i denne instruks er korrekt og fyldestgørende. Den enkelte medarbejder har ansvaret for at kende og følge denne vejledning.

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Formularer

Ikke relevant.

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Referencer, lovgivning og faglig evidens samt links hertil

LOV nr. 23 af 15/01/2018
BEK 669 af 01/07/2019
BEK 670 af 01/07/2019
BEK 671 af 01/07/2019

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Bilag

Ikke relevant.

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