FDG-PET/CT versus conventional CT for response monitoring in metastatic breast cancer: A multicenter randomized clinical trial (MONITOR-RCT)

Sponsor: Odense University Hospital, J. B. Winsløws Vej 4, 5000 Odense, Denmark

Delegated sponsor and authorized person:

Malene Grubbe Hildebrandt, MD, PhD, Clinical professor,
Department of Nuclear Medicine, Odense University Hospital, Denmark

Involved countries and centers:
Denmark:

Region of Southern Denmark:
- Odense University Hospital, Odense, Denmark
- Hospital Lillebaelt, Vejle, Denmark
- Esbjerg Hospital, Esbjerg, Denmark
- Sønderborg Hospital, Sønderborg, Denmark

Central Denmark Region:
- Aarhus University Hospital, Aarhus, Denmark

North Jutland Region:
- Aalborg University Hospital, Aalborg, Denmark

Capital Region of Denmark:
- Rigshospitalet, Copenhagen, Denmark
- Herlev og Gentofte Hospital, Copenhagen, Denmark

Germany:
- Technical University of Munich, Munich, Germany

Italy:
- IRCCS Humanitas Research Hospital, Milan, Italy
- IRCCS Bologna University Hospital, Bologna, Italy

Declarations:

The clinical trial will comply with the protocol, current statutory legislation, the CTR regulation, and the principles of good clinical practice (GCP).

Time schedule:

Start of trial: 01.10.2024

Recruitment period: 12-18 months

Individual Follow-up-period: Between 36 and 54 months

End of trial / end of data collection: 01.04.2029

Completion of primary analyses: 01.07.2029

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1. List of abbreviations

FDG: Fludeoxyglucose (18F)

CE-CT: Contrast-enhanced CT

EMA: European Medicines Agency

MBC: Metastatic breast cancerPERCIST: PET Response Evaluation Criteria in Solid Tumors

RECIST: Response Evaluation Criteria in Solid Tumors

EANM: European Association of Nuclear Medicine

PROM: Patient-reported outcome measure

eGFR: estimated glomerular filtration rate

WOCBP: Women of childbearing potential

SmPC: Summary of Product Characteristic

PERCIST-MBC: MBC-adjusted version of PERCIST

CRF: Case Report File

C(M)R: Complete (metabolic) response

P(M)R: Partial (metabolic) response

S(M)D: Stable (metabolic) disease

P(M)D: Progressive (metabolic) disease

AE: Adverse event

SAE: Severe adverse event

SAR: Serious adverse related event

SUSAR: Suspected Unexpected Serious Adverse Reaction

GCP: Good clinical practice

GDPR: General Data Protection Regulation

PI: Principal Investigator

QoI: Quality of life

HRQoL: Health-related quality of life

2. Background information

2a) Study rationale

Investigational medicinal product

Fludeoxyglucose (18F)

The glucose analog —Fludeoxyglucose (18F)—FDG for PET/CT can be used to detect metabolic active malignant lesions from cancer and for monitoring response in cancer diseases, i.e., breast cancer. The isotope 18F emits radiation that is detected in the PET scanner. FDG-PET can be combined with diagnostic contrast-enhanced CT (CE-CT) with iodinated contrast administered intravenously. Throughout this protocol, the procedure referred to as FDG-PET/CT is in fact the combination of FDG-PET with a contrast-enhanced diagnostic CT scan.

The European Medicines Agency (EMA) has proposed therapeutic indications for FDG-PET/CT in breast cancer, which include staging locally advanced breast cancer and detecting recurrence. However, as of now, monitoring response in metastatic breast cancer (MBC) is not included. Evidence from several observational studies supports its use (see 2b), but this evidence requires validation through prospective randomized trials. It is worth noting that FDG-PET/CT has been approved for response monitoring in other types of cancers, such as malignant lymphoma and head-and-neck cancers, according to EMA's Core Summary of Product Characteristics for Fludeoxyglucose.

Auxillary medicinal products

Conduct of a diagnostic contrast-enhanced CT scan in the comparator group or of the CT-part of the PET/CT in the intervention group will require an injection of some solution as standard iodinated contrast. The choice of the solution varies from center to center. In addition, medical breast cancer-directed treatments, including standard and experimental treatments, will be applied to all patients. These medical treatments are not the treatments under study and do not influence the conduct of the study.

Rationale for comparison

FDG-PET/CT is increasingly used in cancer staging, and several studies have shown improved sensitivity of FDG-PET/CT compared with conventional imaging for diagnosing metastatic breast cancer (MBC). Consequently, it has to be expected that FDG-PET/CT can detect disease progression earlier than CT in patients treated for MBC, which a prospective study has corroborated.

We hypothesize that MBC patients monitored with FDG-PET/CT will start second-line therapies earlier due to earlier detection of disease progression. This has the potential to increase the beneficial effect of second-line therapies at the individual level and result in a delayed need for third-line therapies, prolonged overall survival, and improved quality of life compared with patients monitored with conventional CT. This hypothesis aligns with the results of a retrospective, observational study.

2b) Current knowledge

Extensive literature has shown the high accuracy of FDG-PET/CT for detecting distant metastases from primary and recurrent breast cancer in most molecular subtypes (1-3). Consequently, FDG-PET/CT has recently been introduced in European clinical guidelines for metastatic staging in breast cancer patients (4). Most molecular subtypes of breast cancer appear FDG-avid with higher FDG-uptake in tumours with more aggressive characteristics (Triple-negative breast cancer, high Ki67, and high-grade tumours) (5-7). Lobular carcinomas remain the most challenging type to diagnose since these tumours and corresponding metastatic lesions tend to have lower FDG uptake and a less typical dissemination pattern (6, 8).

Some observational studies have directly addressed the question of the value of FDG-PET/CT in monitoring MBC patients compared to CT and are briefly described below.

1) Riedl et al. (2017) reported on 65 MBC patients who had both FDG-PET/CT and CT before initiation of therapy (baseline scan) and 90 days afterwards. The prediction of outcome was compared between the modalities. They concluded that PET Response Evaluation Criteria in Solid Tumors (PERCIST) was superior to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in predicting progression-free and disease-specific survival (9).
2) Naghavi-Behzad et al. (2021) analyzed the clinical impact of CT or FDG-PET/CT for response monitoring. In 286 CT scans and 189 FDG-PET/CT scans, it was shown that FDG-PET/CT classified scans as a regressive disease more often than CT (46.0% vs 12.2%) and classified scans as stable disease less often than CT (31.2% vs 70.6%) (10).
3) Vogsen et al. (2021) performed a feasibility study of PERCIST for monitoring patients with MBC. In this study, the one-lesion SULpeak was used and along with the nadir scan, PERCIST one-lesion was found as a feasible tool to apply for monitoring response in MBC patients (11).
4) Vogsen et al. (2023) reported the results of a prospective study in 87 MBC patients monitored by CT scans every 3rd month and a median follow-up time of 16 months. PET/CT was applied in a blinded manner in addition to CT, which was used for routine clinical evaluation. The median time from detection of progression by FDG-PET/CT to detection by CT was six months. CT detected progression earlier than FDG-PET/CT only in one patient (12).
5) Naghavi-Behzad et al. (2022) reported the results of a retrospective analysis of all MBC patients diagnosed with MBC at Odense University Hospital between 2007 and 2018. During this time, the treating clinician made the monitoring modality choice and reflected mainly personal preferences. Consequently, the two groups monitored only with CT (n=144) or FDG-PET/CT, respectively (n=83), were comparable in their patient characteristics. The median survival was 44 months in the FDG-PET/CT group compared to 30 months in the CT group. A multivariable Cox regression analysis indicated an HR of 0.44 (95%CI: 0.29-0.68, p=0.001). The patients monitored with PET/CT had, on average, a larger time from detection of the first progression to detection of the second progression and received, on average fewer treatment lines (13).
6) Vogsen et al. (2023) analysed FDG-PET/CT compared with CT and found that tumour response was significantly associated with progression-free and disease-specific survival, while no association was found for tumour response on CT (14).

In summary, the existing clinical knowledge suggests that patients with MBC may benefit from being monitored by FDG-PET/CT instead of CT with respect to prolonged survival and reduced treatment burden. The reduced treatment burden may result in improved quality of life.

2c) Potential benefits and risks

FDG-PET/CT is a frequently used modality in daily clinical practice, with no reported toxicities following injection of FDG.

The use of FDG-PET/CT instead of CT for response monitoring implies an increase in radiation dose from 9 mSv to 13 mSv, which results in an increase in 4 mSv per scan, thus ranging from a minimum of 4 mSv (one scan) to 92 mSv (23 scans) with a long-term risk of secondary radiation-induced cancers (cf. Appendix 1).

The interventional arm examinations will last up to two hours, while conventional examinations in the CT arm last less than 30 min. The physical exposure (placement in a tube) is comparable across the two modalities.

Participation in the trial implies a minimal additional burden for the patients. The additional procedures are limited to being informed about the study, deciding on participation, signing the informed consent form, and filling out questionnaires at home every three months during the first year and every six months later. Questionnaires can be filled out electronically or on paper, depending on patient preferences.

2d) Interventions

Response monitoring based on FDG-PET/CT (intervention) will be compared with response monitoring based on CT (standard).

The FDG dose depends on the PET scanner system, but it is usually between 3-4 mBq per kilo bodyweight, following local guidelines adhering to the European Association of Nuclear Medicine (EANM) guidelines (15). The FDG dose will be registered for each scan. The exact FDG dose will be registered for each scan. FDG will be administered in nuclear medicine departments as a single intravenous injection, 45-75 minutes before the examination begins. The image acquisition takes 20-60 minutes.

The schedule for response monitoring scans will adhere to international clinical guidelines. As such, scans are expected to be performed every 8-16 weeks, depending on the type of systemic treatment given. Medical treatment will be given according to local guidelines or as part of experimental trials and is not considered an intervention in the study.

2e) Study population

The study population will consist of patients with newly diagnosed metastatic breast cancer initiating first-line treatment at one of the participating sites.

2f) Patient involvement

Two patient representatives with prior breast cancer and two with metastatic breast cancer are currently involved in designing the MONITOR-RCT study. They contribute to developing patient

information material, deciding on ethical issues, and communicating the project objectives and, later, the results to patients and citizens in layman terms.

2g) Relevance of the trial

Breast cancer is the most commonly diagnosed cancer in Europe, and it is widely anticipated that 30% of patients diagnosed with primary breast cancer will eventually develop MBC (16). Exact numbers for MBC patients are unavailable at the European level, but about 120,000 patients per year are suggested to reach this state. Due to in the improvement in survival rates among MBC patients, the number of patients living with MBC will increase in the future.

There has been substantial progress in the treatment of MBC patients over the last decades, allowing to select today from a variety of (individualized) treatment choices in the case of a need for a second or third-line therapy. However, MBC patients can only benefit from these advantages if the need for treatment is detected in good time. The current response monitoring with CT cannot be regarded as optimal in this situation, as it only allows the detection of morphological changes. Molecular imaging such as FDG-PET/CT can be a game changer, as it relies on changes in metabolic activity. Consequently, FDG-PET/CT can detect disease progression earlier than CT in patients treated for MBC, which a prospective study has corroborated (12).

The MONITOR-RCT is hence addressing a highly relevant question, and in case of demonstrating the expected benefit, it may substantially impact care in MBC patients. It is designed to target the population expected to benefit from FDG/PET-CT and to compare the interventions of interest.

3. Trial plan and trial design

3a) Study objectives

The primary objective of the MONITOR-RCT is to demonstrate that in patients with MBC, response monitoring based on FDG-PET/CT is superior to response monitoring based on CT with respect to overall survival. The objective will be based on applying standardized response evaluation criteria, using an appropriate adaptation of the PERCIST criteria for FDG-PET/CT and the RECIST1.1 criteria for CT.

Secondary objectives of the MONITOR-RCT are to demonstrate superiority with respect to the quality of life and exposure to oncologic treatment and to investigate the cost-effectiveness.

Consequently, the primary endpoint of the study is overall survival. Secondary endpoints are quality of life, exposure to oncologic treatment, and cost-effectiveness.

3b) Study design

The MONITOR-RCT study will be an international multicenter study. The design will be a parallel group comparative randomized trial comparing an experimental monitoring strategy based on FDG-PET/CT with a standard monitoring strategy based on CT.

A flowchart depicting the trial design is seen in Figure 1.

3c) Randomization

Randomization will be based on electronic randomization within a REDCap database. It will be stratified by site and and an prognostic index based on blocks with a randomized block length of 4 or 6. The prognostic index will be based on the same variables as used for adjustment in the primary analysis (cf. Section 8a). The prognostic index will describe the estimated 42-months-survival-probability when monitored by PET/CT and will be dichotomized at a threshold of 0.5.

Blinding of patients and health care professionals involved is not intended. However, data collection of quality-of-life questionnaires will be based on a centralized procedure, minimizing the risk of assessment bias.

3d) Details on intervention

Scan techniques

Imaging will be performed with the standard equipment of the Department of Radiology and the Department of Nuclear Medicine at each site, which will be in accordance with international and national guidelines of CT and FDG-PET/CT (15).

CT scans will be performed in diagnostic quality, using iodinated contrast (CE-CT). In cases of allergy to the iv contrast or compromised kidney function, diagnostic CT scans will be performed without iodinated contrast.

FDG-PET/CT scans will be performed with at least 4 hours faste before the FDG injection and serum glucose level (no correction) must be less than 200 mg/dL. Additionally, the estimated glomerular filtration rate (eGFR) needs to be a minimum of over 30 ml/min/m², while adhering to local guidelines. FDG is injected intravenously (iv) one hour before imaging, and patients must rest between the injection and the scan. The FDG dose depends on the PET scanner system, but it is usually between 3-4 MBq per kilo bodyweight, following local guidelines adhering to the EANM guidelines (15). CT scans as part of FDG-PET/CT will be performed in diagnostic quality, using iodinated contrast (CE-CT).

All CT and FDG-PET/CT scans for individual patients will be intentionally performed on the same type of scanner, with any deviations documented during the study. Each local site will establish and apply scan protocols that are comparable, though not identical, between hospital sites. Scan protocols will be regularly monitored, and any necessary updates will be registered.

Precautionary measures

The guidelines for FDG-PET/CT scans include several precautionary measures to ensure the safety of the patients. Consequently, various parameters will be considered, including the patient's latest chemotherapy, weight, height, blood sugar levels, eGFR, FDG dose, injection-scan time, fasting duration, scan type, acquisition protocol, reconstruction method, software version, and CT contrast. Additionally, we will adhere to local guidelines to determine an acceptable delay between the latest received treatment (including chemotherapy) and the scanning as one of the precautionary measures before conducting the scan.

Furthermore, as a precautionary measure, a pregnancy test is required for women of childbearing potential (WOCBP), defined as those who have not undergone surgical sterilization or who have not been postmenopausal for at least 12 consecutive months, if they have missed periods. The test

used for pregnancy confirmation will be a standard blood test, such as the serum beta-hCG test. It's important to note that according to the Summary of Product Characteristic (SmPC), no special recommendations are needed for patients regarding the use of contraceptives.

Each patient will receive a daily weight-adapted FDG-dose for each scan, and the dose will be registered for each scan for reference and analysis.

Similarly, the guidelines for CE-CT scans include several precautionary measures. Consequently, factors such as the patient's latest chemotherapy, eGFR, CT contrast usage, and any other relevant scans and results will be taken into account. Additionally, as a precautionary measure, pregnancy status will be assessed in accordance with local guidelines.

Number of response monitoring scans

At the level of a single patient, a maximum of one baseline scan and about 23 follow-up scans will be performed in MONITOR-RCT. Additional scans, i.e., bone scans or brain MRI, can be used at the discretion of the oncologists and will be an option in both the CT and FDG-PET/CT arm.

A baseline scan should be performed according to randomization, i.e., CE-CT in Arm A and FDG-PET with diagnostic contrast-enhanced CT in Arm B. In case a corresponding scan already exists, a new baseline scan can be omitted. However, the time between the baseline scan and treatment initiation may not exceed 28 days (Table 1).

Assessment of treatment response

The assessment of treatment response will be locally performed by specialists in radiology or nuclear medicine at each patient-recruiting center using standard response evaluation criteria for both modalities. In the CT arm, a radiologist will prepare a report which directly refers to RECIST 1.1. (17) or allows the oncologists to apply RECIST 1.1. In the FDG-PET/CT, a nuclear medicine physician will prepare a report which directly refers to an MBC-adjusted version of PERCIST (PERCIST-MBC) (18). The diagnostic CT part of the FDG-PET/CT will be visually assessed and reported by a radiologist.

In cases of equivocal findings, we seek confirmation by consulting with another specialist. This typically involves reaching a consensus on the report or conducting a review of the initial evaluation before communicating the findings to the oncologists. This process applies to both types of scans.

In both groups, radiologists or nuclear medicine specialists will report incidental/unsolicited findings considered relevant for clinical reporting. This process will ensure that all relevant findings are communicated to the treating oncologists, who will then take care of any issues from the imaging reports. Additionally, participants will be notified directly if there is certainty or a high probability of a serious illness that can be treated, prevented, or alleviated. This decision is made by the treating oncologists – as it is already today clinical practice. This direct communication ensures that participants are promptly informed about relevant health information concerning their well-being. This information on incidental findings and their related consequences is integral to the implementation of FDG-PET/CT and is part of the overall study outcomes, such as quality-of-life and cost-effectiveness analyses.

Deviations from the intended modality

Monitoring by a specific modality means the intention to consider this modality as the first choice at any scan visit. However, if there are temporary clinical indications against this modality (e.g. entering pharmaceutical clinical studies requiring a specific modality for response monitoring), an

alternative modality should be used. Corresponding modality-specific guidelines should be followed.

In cases of a new incidence of allergy to FDG during the study, patients in the FDG-PET arm will be monitored using CT.

In case of a patient becoming pregnant during the study, monitoring will proceed according to local standards.

In case it is clinically indicated that monitoring is no longer necessary, monitoring should be stopped.

In all these cases, the patient will remain in the study.

3e) Study procedures

The informed consent for the trial will be obtained according to applicable national legislation.

Quality of life questionnaires

Quality of life questionnaires will be completed at home every three months during the first year and every six months later. Depending on patient preferences, these questionnaires can be filled out electronically or on paper. The sponsor will contact the patient directly. In the case of using paper forms, the patient will send back the questionnaire directly by ordinary mail to the sponsor (at the sponsor's cost).

Only at baseline, the patients will be offered to fill out the questionnaire at the clinic, either on paper or a tablet. In case of using a paper form, the local site will send the form to the sponsor.

In case of missing questionnaires, the sponsor will automatically send reminders to the patient either electronically or per ordinary mail in accordance with the preference chosen by the patient. In case of lacking response in spite of a reminder, the local investigator will be informed and local staff will remind the patients at their next visit or directly by telephone or SMS.

Information from the questionnaires will only be used for research purposes, not for daily clinical management.

Two questionnaires will be used:

- EQ-5D-5L
- FACT-B

In addition, patients can report complaints related to the conduct of scans in a final open question at the end of the questionnaires.

All questionnaires will be available in English, Danish, German, and Italian.

Variables collected

A list of all variables collected as part of the study is seen in Table 3. It also informs about how the data is collected.

In addition, data on healthcare utilization and costs will be extracted from national registries at the end of the trial period.

Data Registration

Data will be collected in a secure and central REDCap database. All sites will be able to use the REDCap database for data entry. The local investigator will manage the extraction of data from the hospital records.

If patients do not show up for a follow-up scan or oncology visit, the the patient and/or relatives will be contacted to check the reason and to plan another day for the scan/visit. These follow-up/reminders will be performed in accordance with applicable national requirements.

At the end of the data collection phase, patients with unclear living status will be checked by contact with local authorities/local registries.

3f) Authorizations

Fludeoxyglucose (18F) follows the specifications set by the European Pharmacopeia and is an authorized medicinal compound (Marketing Authorization). Fludeoxyglucose (18F) is produced according to the standards laid out in the EU-GMP legislation for sterile and radioactive compounds. The production facilities are controlled via inspections from the Danish Medicines Agency; approximately every 2 years. Fludeoxyglucose (18F) can be distributed to other hospital facilities following the EU-GDP legislation.

3g) Groups and subgroups

Participating patients should have newly diagnosed metastatic breast cancer and be considered eligible for initiating first-line medicinal treatment and subsequent regular response monitoring.

This is the patient population for whom a benefit from FDG-PET/CT-based response monitoring is expected. They are very similar to the criteria defining the populations investigated in Vogsen et al. (2023) and Naghavi-Behzad et al. (2022) (12, 13).

3h) Duration of participation and trial periods

In MONITOR-RCT, patients will be followed for a maximum of 4 years and 6 months, encompassing a maximum of about 23 monitoring scans for each patient following the initial baseline scan. Recruitment is planned to begin uniformly across centers between October and December 2024. The recruitment period will last between 12 and 18 months, aiming to enroll a total sample size of 420 patients. The last follow-up assessment will be conducted no later than April 1, 2029.

3i) End-of-trial

Data collection will cease latest April 1st, 2029, with statistical reporting completed by July 1st, 2029 and the main publication finalized by October, 1st 2029. The trial will end together with the end of data collection.

This plan is based on the assumptions that recruitment can be finished within 18 months after start of the trial. In this case the intended follow up times between 36 and 54 months will be sufficient for evaluation of the primary endpoint according to the sample size considerations in Section 8b). In case of delays in the recruitment phase, the trial period will be extended to ensure an average follow-up time of 45 months.

3j) Stopping of trial

The coordinating investigators can stop the trial if external evidence or feedback from the local investigators indicates potential harm to patients or in case of practical issues such as insufficient inclusion of patients.

3k) Randomization code

The randomization code will be stored in the REDCap database. Code breaking is not relevant in MONITOR-RCT.

3l) Case Report Files (CRFs)

Data to be extracted from the hospital records (cf. Table 3) will be directly typed into the central REDCap data base.

Questionnaires filled out by the patient electronically at home or on a tablet at the first visit will directly be stored in the central REDCap data base. Questionnaires filled out by the patient on paper will be sent to the sponsor and typed into the data base by the sponsor.

All variables collected by the local investigator at randomization, at the Department of Radiology, or the Department of Nuclear Medicine (cf. Table 3),will be directly typed into the central REDCap data base.

Paper CRFs will be used to collect data on deaths and reasons for stopping before end-of-study. They will be typed into the REDCap data base by the local investigator.

3m) Embedding of MONITOR RCT in the Horizon Europe project "PREMIO COLLAB"

The MONITOR-RCT will be part of the PREMIO COLLAB project funded by the European Commision as part of the HORIZON-MISS-2023-CANCER-01 call. It constitutes one of ten work packages. The MONITOR-RCT will interact with the other work packages in various forms:

1. All participating patients in MONITOR RCT will be offered participation in a research cohort, aiming at including at least 100 patients. Participants of this cohort will be asked for blood samples at each scan visit. These will be used to analyze the value of ctDNA analysis and deeper genome sequencing for early detection of non-response and identification of treatment targets (WP8). In addition, a low-dose CT will be performed in these patients and evaluated with respect to the ability of non-response detection (WP7).
2. Participating patients (and their family members) will be offered to participate in a one-point survey. The survey aims to investigate family health in the diagnostic period, covering aspects such as family social and emotional health processes, family healthy lifestyle, family health resources, and family external social supports. In addition, patients will be asked about their experience with being monitored (WP4).
3. The FDG-PET/CT scans, data on the clinical evaluation, and clinical outcomes will be used to develop next-generation response criteria (WP6).
4. The CT and FDG-PET/CT scans and the result of the evaluation of the RECIST and PERCIST-MBC response evaluation criteria will be used to develop tools for improved

image analysis (WP2), for automatic reporting generation and writing, for early detection of non-reponse, and for assessment of heterogeneity (WP7).

5. To ensure ethical and legal requirements for human subjects in research, an ethical work package (WP9) is established to support and better understand patients' and carers' diagnostic needs as health needs, with the goal of developing guidelines for ethical decision-making for diagnostic imaging in cancer care in the context of monitoring.

For all these activities, we will seek approval separately.

4. Selection of trial subjects and criteria for inclusion and exclusion

4a) Inclusion criteria

Criteria for inclusion will be:

1) Women and men aged ≥18 years
2) Diagnosis of distant relapsed MBC (biopsy-verified) or de novo breast cancer. In patients with distant relapsed MBC, biopsy verification from a distant metastasis is required. In patients with de novo MBC, biopsy verification of primary tumor and diagnostic imaging with distant metastasis with a typical pattern of MBC is required.
3) Considered eligible for first-line systemic treatment
4) Considered eligible for continuous treatment monitoring by scans.
5) Signed informed consent
6) Participants must have the ability to read and understand the following languages based on their country of participation: in Denmark, patients must be able to read and understand Danish; in Italy, they must be able to read and understand Italian or English; and in Germany, they must be able to read and understand German or English.

In case of patients for whom it is necessary to start first-line systemic treatment while still waiting for the evaluation of the biopsy, it is allowed to include the patients, as long as the other criteria are fulfilled and the biopsy is made or planned. In case verification by biopsy fails, the patients will leave the trial (cf. 4c). We expect that up to 3% of the patients included will start first-line systemic treatment prior to evaluation of the biopsy.

4b) Exclusion criteria

Criteria for exclusion will be:

1) Pregnant or lactating women
2) Ongoing oncological treatment for another cancer
3) Exclusively brain metastasis
4) Allergy to FDG

The following arguments justify the exclusion criteria: Any radiation exposure should be avoided in pregnant women. Oncological treatment for another cancer type is associated with a high risk of dying for reasons the intervention cannot influence. For patients with exclusively cerebral metastases, a diagnostic modality (typically magnetic resonance imaging) other than those currently under study will be indicated.

Pregnancy status and lactation status will be assessed based on a self-reporting by the patient as part of the performing all scans. Necessary precautions will be implemented in adherence to local

guidelines to ensure patient safety regarding pregnancy. A more detailed assessment will be performed at each scan (cf. Section “Scan techniques”).

Other criteria of interest

Allergy to iodinated CT contrast will not be an exclusion criterion, but patients will be monitored using diagnostic CT without iv contrast or will obtain corresponding premedication (both groups).

Diminished renal function, typically characterized by an eGFR below 30 mL/min, will not serve as an exclusion criterion, but patients will be monitored using diagnostic CT without iv contrast (both groups). Patients can enter oncological treatment trials while being monitored in this study.

Scans would typically not be clinically indicated for patients who are unable to consent to study participation or for patients with a short expected lifetime.

4c) Leaving the trial

Patients can stop participating in the trial at any time point without explanation. The local investigators can withdraw patients from the trial if further participation constitutes a risk for the patient. Participants may be withdrawn if they exhibit serious anxiety or reluctance towards being monitored or completing questionnaires that remind them of the situation.

Patients who are withdrawn or withdraw themselves will be offered to continue monitoring at the participating center according to local standards. The statistical analyses will include the data collected from these patients until withdrawal.

Patients, who have been included while still waiting for the evaluation of the biopsy, will leave the trial in case of failure of verification. The data of these patients will not be included in any analysis.

4d) Inclusion of subjects who are incapable of giving informed consent

Informed written consent will be required from all participating patients.

4e) Exclusion of gender or age groups explanation

There are no restrictions on age and gender except for restricting the participation to adults. MBC is extremely rare below the age of 18.

As MBC is rare in males, we expect only a few males to be recruited. As the oncology department typically handles MBC in males, we do not expect males to be underrepresented.

5. Treatment of trial subjects

5a) Interventions

The intervention of interest is the use of FDG-PET/CT for response monitoring compared with CT for response monitoring. The use of CT as a monitoring modality represents the usual care in patients with MBC.

FDG-PET/CT scans will be evaluated using the PERCIST-MBC criteria, whereas the CT scan will be evaluated using the RECIST 1.1 criteria (17, 18). Both criteria aim at classifying the patient as

having complete (metabolic) response (CR/CMR), partial (metabolic) response (PR/PMR), stable (metabolic) disease (SD/SMD), or progressive (metabolic) disease (PD).

PERCIST-MBC is an adaptation of PERCIST (18, 24) for monitoring patients with MBC. PERCIST-MBC is defined based on data from the MESTAR study and previous studies (11, 12). It introduces the nadir scan for comparison in cases where the disease has regressed compared with the baseline scan. PERCIST-MBC constrains, in particular, the criteria for progression by detecting new lesions and aims to cover a broader group of MBC patients, hence covering also the patients with initially low metabolic disease.

Clinical decision-making: For patients in the intervention group, clinical decision-making will be supported by FDG-PET/CT and PERCIST-MBC, while the conventional group will be supported by the CE-CT and RECIST 1.1. The decision-making will be in both groups following the current standard according to the local practice and following international guidelines. The decision-making may include a request for further imaging procedures. Parameters such as toxicity profile and the patient's general condition will also influence treatment decisions. Major components of patient management and the main reasons for treatment decisions will be registered throughout the study.

Scan procedure and interpretation: All patients will have baseline scans performed before treatment and according to the randomization group. Treatment and follow-up scans will be approximated at regular intervals of 9-12 weeks or according to local guidelines. The choice of the diagnostic modality does not influence the monitoring intervals or time points.

Contrast-enhanced CT of at least the thorax and abdomen will be performed using diagnostic scan quality. Pelvic CT may be added based on clinical need. The scan reports will be made by specialists in radiology with an assessment according to the RECIST 1.1 criteria (17). FDG-PET/CT will follow standard guidelines from the European Association of Nuclear Medicine and the PERCIST guidelines (15, 18). The CT performed along with the PET scan will also be of diagnostic quality and will have contrast enhancement. The scans will be assessed by specialists in nuclear medicine according to the suggested PERCIST-MBC criteria.

According to RECIST 1.1 and PERCIST, disease measurability will be evaluated at the baseline scan in each study group. In cases of no measurable disease according to the respective criteria applied, the patient's scans will be assessed qualitatively with a parallel response categorization. This categorization slightly differs from the one used in the case of measurable disease, but it still allows for the distinction of progressive disease from all other states.

CT and FDG-PET/CT scans will be viewed based on the existing standard software. Viewing of FDG-PET/CT scans will be further supported by software developed as part of the establishment of the PERCIST-MBC criteria. Application of the criteria remains a task for radiologists or nuclear medicine specialists.

5b) Treatment definition in terms of active substance

Not applicable.

5c) Concomitant treatment/medication

Not applicable.

5d) Adherence

The data from each scan visit will be collected from the PI or a research technician at each participating site. The oncologist will refer patients to response monitoring scans according to randomization.

Batch number, accounts, and disposal of FDG will performed as part of daily standard in the Departments of Nuclear Medicine.

5e) Labelling and unblinding of investigational medical product

Not applicable.

5f) Compliance monitoring

The modality used initially at each scan visit, and all subsequently used modalities will be documented.

The weight-adjusted FDG dose will be registered for each scan.

5g) Subsequent treatment

There is no need for additional care for patients who leave/terminate the trial. They will be offered continuous response monitoring at the local site if indicated.

6. Evaluation of effect

6a) Outcome variables

The primary endpoint “Overall survival” will be addressed based on the primary outcome variable “Time from randomization until death”.

The secondary endpoint “Quality of life” will be addressed by two outcome variables. The first is the overall summary score of the FACT-B, the second the complaints related to the conduct of scans reported by the patients.

The secondary endpoint “Exposure to oncologic treatment” will be addressed by the following outcome variables describing different aspects of oncological treatment:

1) Experience of progression
2) Start of a new treatment line because of progression
3) Time to first progression
4) Time from first to second progression
5) Time from second to third progression
6) Experiencing other diagnostic procedures
7) Hospitalization

The secondary endpoint “Cost-effectiveness” will be adressed based on relating the outcome variable “Overall survival” to the outcome variable “Costs”.

These outcome variables correspond to the expected benefits described above.

6b) Measurements, registration, analysis

Measurement

Information on exposure to diagnostic procedures and treatment will be extracted from the hospital records at baseline and regularly during follow-up.

Assessement of Quality of life and survival is described in Section 3e).

Information on healthcare utilization and/or cost will be extracted from national registries.

Definition of efficacy parameters

Patients cannot immediately benefit from using FDG-PET/CT for response monitoring. They can only benefit after detecting their first progression from the earlier start of efficient second-line therapy. According to Vogsen et al. (12) (2023), the median time until detection of the first progression is about 15 months in this population. It also has to be expected that the benefit increases with increasing survival time due to the opportunity to benefit from the adequate time to start a third-line therapy. This is corroborated by the results of Naghavi-Behzad et al. (13) (2022), reporting a hazard ratio of 0.75 after 24 months, 0.4 after 36 months, and 0.2 after 60 months.

Due to the expected non-proportionality of the hazard ratio, the effect on survival will not be assessed by a hazard ratio. Instead, the effect of survival will directly be quantified by differences in survival probabilities at 36, 42, and 48 months.

The quality of life data collected will be used to compute the instrument-specific summary scores. Efficacy parameters are the expected quality of life difference between the two intervention groups for each score.

The data on management and treatment will be used to assess the difference between the two intervention groups with respect to the following parameters:

1) Risk of experiencing a progression
2) Risk of starting a new treatment line because of progression
3) Time to first progression
4) Time from first to second progression
5) Time from second to third progression
6) Risk of experiencing other diagnostic procedures
7) Risk of hospitalization

The healthcare utilization and cost data will be used to compute the incremental cost-effectiveness ratio, which relaties the difference in survival to the difference in costs.

7. Safety evaluation

7a) Safety evaluation

Definitions

- *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.

- *Adverse reaction (AR)*
  Any response to a medicinal product which is noxious and unintended.
- *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.
- *Serious adverse reaction (SAR)*
  An SAE in which 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.
  Causality assessment given by the investigator must not be downgraded by the sponsor.
  A planned hospitalization will not be considered an SAE.
- *Suspected unexpected serious adverse reaction (SUSAR)*
  A serious adverse reaction where the nature, severity or outcome is not consistent with the reference safety information and is therefore considered unexpected based on the reference safety information.

Reference safety information (RSI)

Section 4.8 in *Guideline on core SmPC and package leaflet for fludeoxyglucose (18F)* EMA/CHMP/448228/2012 https://www.ema.europa.eu/en/core-summary-product-characteristics-smpc-package-leaflet-fludeoxyglucose-18f-scientific-guideline (current version 19 July 2012)

Any change in RSI will only be done when the Annual Safety Report (ASR) is prepared unless new safety information makes it necessary. In that case, a Substantial Modification will be submitted for CTIS.

Risk adaption

With reference to

- Article 41 of regulation (EU) No 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use
- *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
- *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*, Version 1.0, October 2023

and risk assessment

- IMP is authorized and used for diagnostic purposes according to authorization
- The intervention is comparable to standard treatment
- IMP is used and well-known in all centers and SmPC will be followed by all investigators
- Population is comparable to the population mentioned in SmPC, e.g. recurrence of breast cancer and monitoring of other malignancies
- FDG dose will be weight-adjusted according to authorization

- No unknown adverse reactions are expected

the trial is evaluated as a low-risk trial, and the approach is adjusted according to this risk assessment and references mentioned above.

7b) Measuring, recording and analysing the safety parameters

Patients will automatically be observed after each FDG injection for at least one hour as part of the clinical routine, as the patients are waiting 60 minutes for the scan subsequent to FDG injection.

As no AEs or ARs are expected, only SUSARs will be registered. However, the investigator always has the option to report any event to the sponsor via email if deemed relevant.

7c) Reporting of adverse events

SUSAR

Only SUSARs will be reported to the sponsor. The investigator must assess the expectedness of the event and report it to the sponsor by the investigator through the eCRF within 24 hours.

With assistance from The GCP Unit at Odense University Hospital, the sponsor will report SUSARs in the EudraVigilance database within 7 days for fatal or life-threatening SUSARs and within 15 days for other SUSARs.

Annual Safety Report (ASR)

The sponsor will report the annual safety report, including a list of all investigator reported events and SUSARs, for the entire trial to CTIS. The ASR will describe the risk-adapted approaches as provided in the protocol and include an assessment of whether the benefit-risk balance is changed or unchanged.

The first ASR will be reported no later than 60 days after the first approval of the trial in a member state. Subsequently, ASR will be reported annually.

All investigators will receive a copy of the ASR, and if there are any changes in the risk-benefit balance or the RSI, this will be specified in the communication with investigators.

7d) Notifications about adverse events

When the investigator has completed the SUSAR report in the eCRF, the sponsor will automatically be informed about the SUSAR by e-mail. This procedure is incorporated into the eCRF system (REDCap) and validated.

7e) Arrangements for avoiding and treating complications

Complications are not expected, and hence, no special arrangements are made. See section 7f)

7f) Monitoring in case of adverse events/adverse reactions

If a study participant reports any adverse events or reactions, the investigator will offer additional consultations on a case-by-case basis according to local procedures. Within these consultations, a decision will be made with respect to future scan applications.

The duration and type of follow-up will be determined by the severity and nature of the adverse event, ensuring appropriate monitoring and management of patient safety throughout the trial period according to local procedures.

8. Statistics

8a) Statistics

The difference in survival will be visualized by model-based Kaplan-Meier-curves. These model-based Kaplan-Meier-estimate will also be used to compute the difference in survival rates at 36, 42, and 48 months together with 95% confidence intervals. The statistical significance of the difference in survival will be assessed using a statistical test procedure not relying on the assumption of proportional hazards.

The model-based approach will be used to adjust for variables which are expected to be of strong prognostic value in the rather heterogenous populations of MBC patients.

The analysis of the longitudinal quality of life scores will take into account the expected systematic difference in exposure time between the two groups due to the expected difference in survival and a potential general decline over time. Consequently, a model-based approach will be used.

Differences in the risk of progression, in the risk of starting a new treatment line because of progression, in the risk of experiencing diagnostic procedures, and the risk of hospitalization will be assessed by a Poisson regression with the risk time as offset. The first two analyses will be adjusted for the same variables as in the analysis for survival.

Time until progression and time between progressions will be analyzed by a Cox model with adjustment for the same variables as in the analysis for survival.

Patients complaints related to the conduct of scans will be categorized and the frequencies reported for each arm.

Cost-effective analyses will be based on computing an incremental cost effectiveness ratio (ICER). Effectiveness will be assessed by the gain in quality adjusted life years (QUAL) based on the data from the EQ-5D-5L and survival. Costs will be assessedby two different approaches: A) Difference in costs related to the scans and subsequent oncological treatment. B) Difference in cost of using of health care as documented in registry data.

A detailed statistical analysis plan will be finalized prior to recruiting the first patient. The plan will included specifications of the models and test procedures used. In particular the plan will include the following details:

- The selection of variables with a strong prognostic value.
- The prognostic index used for stratification in randomization.
- The model specifications to be used for computing model-based Kaplan-Meier-curves and subsequent inference.
- A choice of a powerful statistical test procedure based on simulation studies similar to those reported by Klingmüller et al (2023). [Florian Klinglmüller, Tobias Fellinger, Franz König, Tim Friede, Andrew C. Hooker, Harald Heinzl, Martina Mittlböck, Jonas Brugger, Maximilian Bardo, Cynthia Huber, Norbert Benda, Martin Posch, Robin Ristl (2023): A neutral

comparison of statistical methods for time-to-event analyses under non-proportional hazards. Preprint available at https://doi.org/10.48550/arXiv.2310.05622.]

- The model specifications to be used for a longitudinal analysis of the quality of life scores, including the handling of missing data.
- Planned sensitivity and subgroup analyses.

8b) Sample size considerations

Sample size considerations are based on using a direct comparison of the survival rates at 42 months. The statistical test finally used will be more powerful due to summarizing the information from all time points and adjustment for prognostic covariates.

In the study of Naghavi-Behzad et al. (13) (2022), the survival rate after 42 months was 34% in the CT group and 51% in the FDG-PET/CT group. Due to the introduction of new, more effective treatment lines in the last decade, we expect higher survival rates in this RCT. Sample size calculations are based on the assumption that true survival probabilities will be 39% and 56%, respectively. Under this assumption, we have to include overall 420 patients to reach a power of 87% (based on two-sided testing at the 5% level).

According to the timeline of the study, the minimal (planned) follow-up time of the patients will be 36 months, and the maximal follow-up time will be 54 months. In the above calculations, a uniform distribution of the follow-up time was assumed.

With respect to the primary outcome (survival), we do not expect drop outs, as we can rely also on national registries. Hence drop-outs are not accounted for in the sample size calculation.

8c) Significance level

A significance level of 5% (two-sided) will be applied.

8d) Termination of the trial and interim analyses

Interim analyses involving the outcomes of survival and quality of life are not planned.

The choice of treatment lines and diagnostic procedures will be continuously monitored to detect early potential differences between the participating centers with respect to the management and treatment of the patients. Such differences will be discussed with and across the participating centers.

8e) Handling of missing data

Missing data in the outcome variables are only to be expected with respect to the time-point-specific quality of life measurements. Details of the handling of these missing values will be described in the statistical analysis plan.

8f) Deviations from statistical analysis plan

Deviations from the statistical analysis plan will be reported in the final publications.

8g) Analysis population

All analyses will be based on all randomized patients. Sensitivtiy analyses may include the analysis of subpopulations.

9. Charter of DSMB/DMC

9a) Charter of DSMB/DMC

There are no plans to establish a Data Safety Monitoring Committee.

10. Source data

10a) Description of arrangements for monitoring the conduct of the clinical trial

Risk-based monitoring of MONITOR-RCT will be performed at the participating Danish centers by the GCP Unit at Odense University Hospital, while it will be performed locally in non-Danish centers.

10b) Statement of the sponsor

The sponsor of MONITOR-RCT confirms that the investigator and all institutions involved in the clinical trial will permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents.

11.Quality control and quality assurance

11a) a description of measures that will be implemented in case of data security breach in order to mitigate the possible adverse effects

MONITOR-RCT will be conducted following the study protocol, the declaration of Helsinki, and the principles of good clinical practice (ICH-GCP).

12. Ethical questions

12a) Summary and relevance

The study will be a parallel group comparative randomized trial comparing an experimental monitoring strategy based on FDG-PET/CT with a standard monitoring strategy based on CT. Participating patients should have newly diagnosed metastatic breast cancer and be considered eligible for initiating first-line medicinal treatment and subsequent regular response monitoring.

Current knowledge about the potential benefit of PET/CT comes from observational studies.Consequently, current evidence is only hypothesis generating and prospective, randomized trial studies such as the intended MONITOR-RCT are needed to corroborate these findings (cf. section 2b).

12b) Exposure to radiation

The radiation dose is an issue of consideration. The average radiation dose per patient per scan procedure is estimated, in conventional diagnostic CT, to be 9 mSv and in conventional 18F-FDG-PET/CT to an additional 4 mSv, respectively (see Appendix 1).

12c) Risks and benefits

The iodinated contrast agent of the CE-CT is applied both in the standard and interventional group. Iodinatied contrast is known to cause the following AEs and ARs in a substantial number of patients: allergic reactions, warmth, flushing, metallic taste, vomiting, and nausea. With a risk-adjusted approach, we avoid registration of these known AEs and ARs.

Taking into account the potential long-term benefit of patients with MBC (section 2b) and the potential direct benefit of patients randomized to monitoring with FDG-PET/CT, there is a fair balance between benefits and risks.

Patients will be fully informed about the potential benefits and risks of FDG-PET/CT. This includes understanding that while FDG-PET/CT may provide more accurate detection of metastases and potentially lead to improved survival and reduced treatment burden, it also exposes them to additional radiation and a higher detection rate of incidental findings.

12d) Informed consent procedure

Patients potentially eligible for the trial (based on inclusion criteria 1-4) will be identified by the oncologists and related clinical/research staff at the participating sites prior to a regular patient visit. A qualified medical doctor, who may be the Principal Investigator (PI) or another doctor at the Department of Oncology or Gynecology involved in the project with a written agreement from the PI, will check further in- and exclusion criteria and provide the information during oral information sessions at initial visit (Visit 1 in Table 1, providing a detailed description of the inclusion period), ensuring privacy. Additionally, participants receive handout information material and a link in case they consider giving or denying the consent electronically. Subsequently, participants are given a minimum of 24 hours to review the reading material at home and make decisions privately. Following this period, a responsible research technician/assistant will contact those patients who have not expressed their decision electronically via phone or video to inquire about their decision. In case the patient wishes to discuss her or his decision, the technician/assistant will inform qualified medical personnel at the Department of Oncology or Nuclear Medicine about this wish. After a phone or video contact between the qualified medical personnel and the patient, the research technician/assistant will repeat the inquiry, except if the patient has, in between, expressed her or his decision electronically or has denied participation during the contact with the qualified medical personnel.

If, in the inquiry by the research technician/assistant, the patient expresses the wish to participate, the patient is asked to sign the consent form which will be provided in English and the local language immediately and to confirm this signing verbally or show the signature in case of a video call.

If consent has been confirmed electronically or as part of the contact with the research technician/assistant, the patient will be randomized. Based on the result of the randomization, the

potential need for a baseline scan is determined. In case of this need, a corresponding visit (Visit 2) is arranged prior to the treatment initiation visit (Visit 3). The patient is informed by the research technician/assistant about the results of the randomization and the arrangements for a potential baseline scan, which would take place in Department of Radiology or Nuclear Medicine. This information is conveyed both verbally during the phone or video call and in written form. At the first in-person visit after the patient has consented via the phone or video call, a responsible research technician/assistant verifies the written informed consent.

Included patients can withdraw from the trial at any time point during the study as described in section 4c)

All participating centers will have handout information and the informed consent form in English, Danish, German, and Italian.

12e) Data protection

The study will adhere to the General Data Protection Regulation (GDPR) [EU] 2016/679 and the Declaration of Helsinki.

Data will be stored and managed securely as described in section 3k)

12f) Additional ethics

No data will be registered before signed informed consent, except for an anonymous registration of reasons for exclusion or non-participation.

13. Handling and archiving data.

13a) Rules on the protection of personal data.

All data from the different sources will be stored in a REDCap database maintained by the Open Patient Data Explorative Network (OPEN) and stored securely according to GDPR, the Danish data protection law, and the health law.

The database and the REDCap software are fully GCP compliant, and all input and modifications are logged.

A master data set with pseudonymized data will be created for the statistical analyses.

The REDCap database and the trial master file will be archived for 25 years.

The trial staff will ensure that the subjects' anonymity is maintained and that their data is fully protected. All data and documents will be stored in a secure REDCap database hosted by the Region of Southern Denmark. User privileges are utilized within the software, and access to the database is controlled by the coordinating investigator. All connections are fully encrypted and protected by multi-factor authentication. The system maintains a built-in audit trail that logs all user activity and pages viewed by every user, including contextual information (e.g., the project or record being accessed). The system in use is GCP-compliant and complies with the EU General Data Protection Regulation 2016/679.

In case of a data security breach, the sponsor will be immediately notified. The sponsor will promptly analyze the case and notify the relevant regulatory bodies, including the Danish Data Protection Agency and the Data Protection Officer of the Region of Southern Denmark, as necessary.

13b) Ensuring confidentiality

Data extraction from the medical records will be performed by authorized staff at the participating centers and typed directly into the REDCap database or imported. Collection of questionnaire data will be organized centrally by the Sponsor. Electronic collection of questionnaire data will be performed directly within REDCap.

14. Compensation trial participants, investigator and funding.

The MONITOR-RCT is fully financed by grants from the Danish Cancer Society (€282,000) and the Region of Southern Denmark (€242,000), and Horizon Europe Grant from the European Commission (€3,307,000), with a total fixed amount of €3,831,000. The financial agreement between the sponsor and participating sites encompasses the coverage of agreed costs related to various aspects of the trial, including setup, patient recruitment, scans, and data collection and imaging analysis. This compensation will be in accordance with fair market value and will comply with all applicable laws and regulations.

14a) Insurance and Compensation in Denmark and Bologna (Italy)

Patients under study are financially covered by the public insurance program for all patients. If A patient experienceS unpredictable adverse events or other damages caused by the study, the patient has the right to complain and ask for compensation according to the patient insurance system in Denmark and Bologna (Italy).

14b) Insurance and Compensation in Germany and Milan (Italy)

Patients participating in the study in Germany and Milan (Italy) will be covered by the sponsor for all costs related to the study, including the scans, as these are not covered by the national insurance system. Additionally, the sponsor will provide necessary insurance coverage for patients in case of unpredictable adverse events or damages caused by the study. Patients will have the right to seek compensation through the sponsor's insurance system in Germany and Milan (Italy) if needed.

15. Guidelines for publication.

15a) Publication strategy

The MONITOR-RCT results are intended for publication in peer-reviewed scientific journals. The sponsor is responsible for ensuring corresponding submissions.

A writing committee will be selected 3 months prior to the end of the data collection. Each participating site is invited to suggest between one and three members. In addition, all other scientists who have made an intellectual contribution to the planning or conduct of the RCT will be offered participation. The writing committee will select a subgroup to prepare a first draft of the main publication. This draft will then be discussed with the writing committee.

A second publication to be prepared by the writing committee will be a report about the practical experience of implementing and conducting this study in order to encourage other researchers to conduct RCTs on diagnostic modalities.

As soon as possible and no later than one year after the trial has ended, the summary of the results will be submitted to the CTIS portal.

16. Summary and appendices.

16a) Synopsis

A synopsis has been uploaded to CTIS.

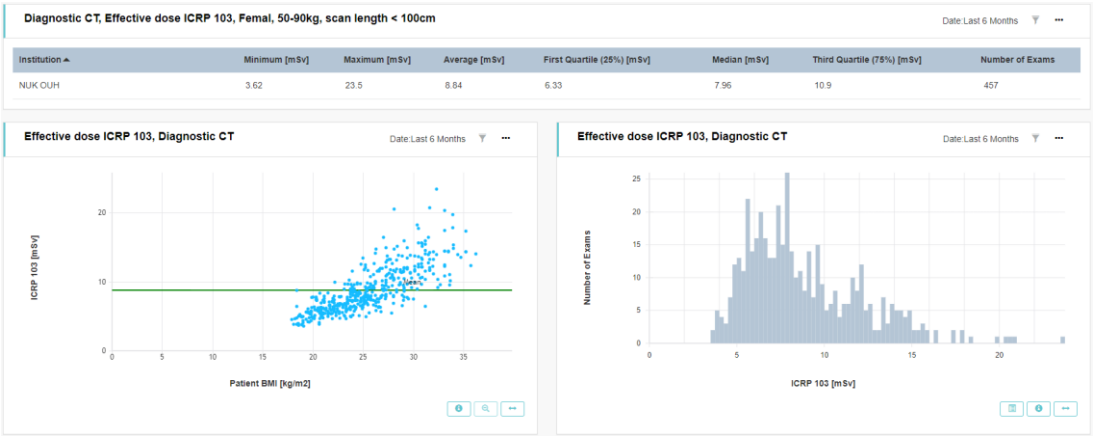
16b) Appendix 1: Estimated effective dose of MONITOR project patients

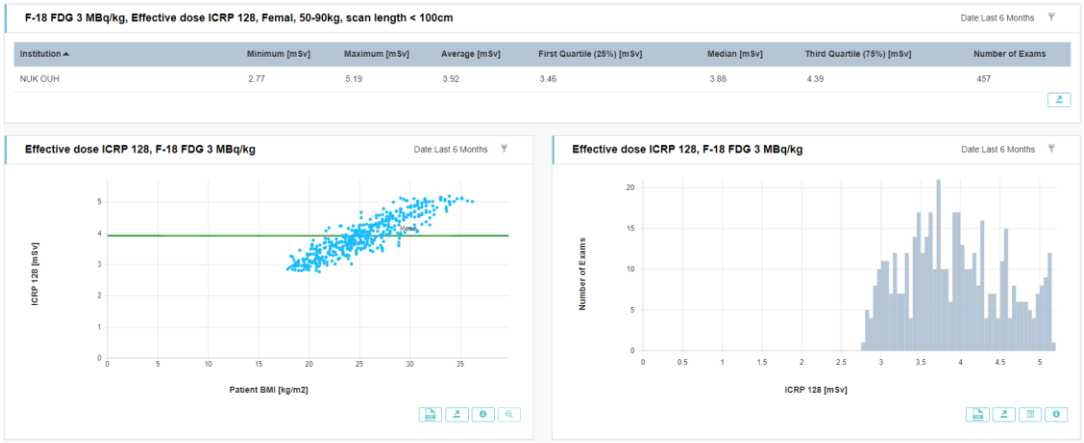
In order to estimate the effective dose given to the MONITOR project patients, effective doses from 457 PET/CT scans from representative patients were collected. The representative patients were chosen as adult non-pregnant females, weighing between 50 to 90 kg, with a scan length not longer than 100 cm.All 457 patient scans were performed within the last 6 months at the Department of Nuclear Medicine at Odense University Hospital. The CT scans were standard diagnostic CT scans.

In our protocol, we have meticulously calculated the average radiation dose per patient per scan procedure for Fludeoxyglucose (18F) PET/CT based on our specific dosing regimen. Utilizing a dose of 3 MBq/kg, we have estimated the average radiation dose to be 4 mSv for patients with an average weight of 70 kg. Even for patients with higher weights, our protocol specifies a maximal dose of 300 MBq, resulting in lower radiation doses compared to those mentioned in the SmPC. In the two tables below, the effective patient doses are plotted, for the diagnostic CT (following ICRP 103) and from the 18F-FDG-PET (following ICRP 128), respectively, the mean effective patient dose for the two modalities are:

$$Mean\ effective\ patient\ dose\ from\ diagnostic\ CT = 8.84\ mSv \approx 9\ mSv$$

$$Mean\ effective\ patient\ dose\ from\ ^{18}F - FDG - PET = 3.92\ mSv \approx 4\ mSv$$





16c) Appendix 2: Arrangements for tracing, storing, destroying and returning ***the investigational medicinal product in accordance with Article 51 of the regulation.***

The MONITOR-RCT protocol meticulously addresses the tracing, storing, destroying, and returning processes for the investigational medicinal product, Fludeoxyglucose (18F), in adherence with regulatory standards and safety guidelines. Regarding storage, it will be ensured to maintain Fludeoxyglucose (18F) below 25°C, as per national regulations governing radioactive materials. Each unit of the product is delivered in either a 30 ml or 15 ml glass container, meticulously sealed with silicone elastomer or chlorobutyl rubber stoppers, and further safeguarded within a 35 mm thick lead container during transportation. These measures ensure the product's stability and integrity throughout handling and transit.

Special precautions are outlined for handling and disposal to mitigate risks associated with radioactive materials. Only authorized personnel in designated clinical settings are permitted to handle Fludeoxyglucose (18F), and preparation must adhere to stringent radiation safety and pharmaceutical quality requirements. Aseptic precautions are emphasized to prevent contamination and ensure patient safety during administration.

Additionally, comprehensive measures are in place to address the risks posed by external radiation exposure or contamination from spills, such as urine or vomiting. Adherence to national regulations for radiation protection is mandatory to mitigate these risks effectively.

Furthermore, disposal procedures are strictly governed by local regulations to ensure the safe and proper handling of any unused product or waste material. This includes adherence to specific guidelines for the disposal of radioactive waste, emphasizing our commitment to safety and regulatory compliance throughout all stages of the clinical trial process. It should be noted that our protocol ensures thorough monitoring of materials from receipt, manufacturing, dispensing, and the product's journey to customers/consumers, allowing for recall if necessary due to quality issues.

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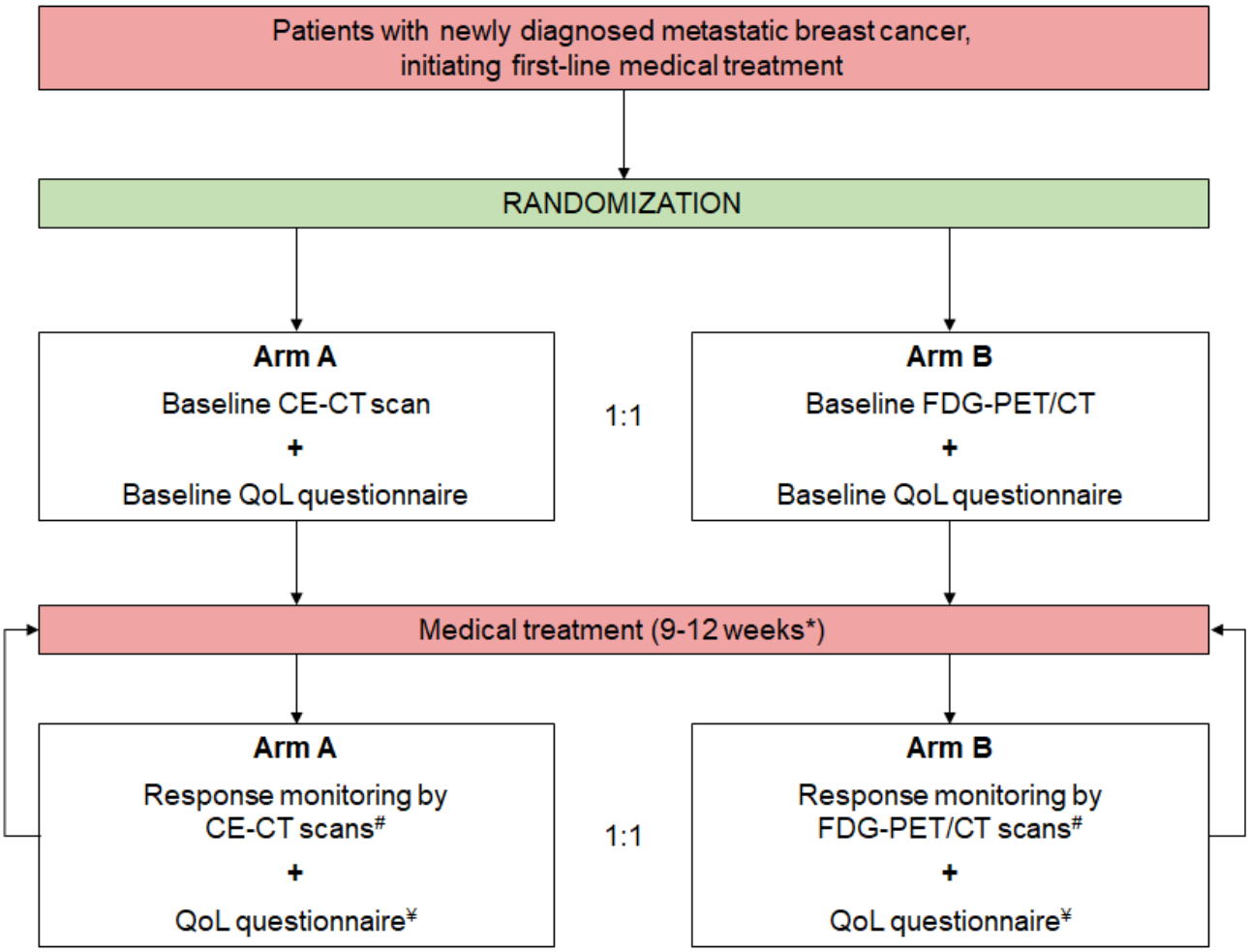
18. Figures and Tables.

Figure 1: Patient flowchart for MONITOR-RCT.



Abbreviations: CE-CT, contrast-enhanced CT; FDG-PET/CT, 2-deoxy-2-[18F]-fluoro-D-glucose positron emission tomografi CT; QoL, quality of life

* scan intervals depend on the choice of treatment, ie, the interval for endocrine therapy will be 12 weeks and for chemotherapy 9 weeks
# a maximum of 21 scans during the study period
¥ completed at home every three months during the first year and every six months later

Table 1: Timeline and data collection for the inclusion period for MONITOR-RCT

Task	Before visit 1	Visit 1	Between visit 1 and 2/3	Visit 2	Visit 3	Where	Who
Identification of potential candidates for MONITOR protocol	X					Department of Oncology	Oncologists of the Department
Information on diagnosis and treatment options		X				Department of Oncology	Qualified medical doctor (Oncologist)
Information on MONITOR project		X				Department of Oncology	Qualified medical doctor (Oncologist)
Reading information material on medical treatment and on the MONITOR project			X			At home	The patient and relatives
Finishing informed consent process[$]			X			At home	The patient and relatives Qualified medical doctor (Oncologist)
Randomization			X			At home	Oncologist/Study coordinator/ Research staff
Baseline scan (Only in patients with no scan within 28 days of randomization)				X		Department of Nuclear Medicine or Radiology	Study coordinator/ Research staff/ Radiology/Nuclear medicine staff
Treatment initiation					X	Department of Oncology	Oncology nurse
Baseline quality of life questionnaire*					X	Department of Oncology	Oncology nurse/ Study coordinator

Black: standard tasks
Red: study-related tasks
[$] In case of no consent, relevant clinical scans will be arranged
*Quality of life questionnaires can be filled out on paper or tablet

Table 2: Timeline and data collection for the response monitoring period for MONITOR- RCT

	Quality of life assessment	**Follow-up scan visits**	**Follow-up oncology visits**
When	Every 3rd month in year 1. Every 6th month afterwards.	Every 9.-12. weeks*	Every 9.-12. weeks*
What	Quality of life questionnaire#	Scan	Scan result
Where	At home	Department of Nuclear Medicine ¤ Department of Radiology ¤	Department of Oncology
Who	Patient and relatives	Research technical staff / Scan technicians	Oncology doctor
Details	Quality of life questionnaires are filled out electronically or on paper by the patients.	Conduct of scan	1) Information on the scan result and planning of further treatment 2) Referral for the next follow-up scan ¤ 3) Documentation of final scan interpretation and treatment change.
Data collection	Quality of life questionnaire	Information on 1) FDG-PET/CT scan (patient weight, blood glucose, FDG dose, injection-to-scan time, reconstruction, CT contrast) 2) CE-CT scan (CT contrast) 3) Information on potential SUSARs adverse events since the last visit within 1 hour after injection of FDG in the current scan ¥	

Black: standard tasks
Red: study-related tasks
* scan intervals depend on the choice of systemic treatment,
¤ according to randomization
quality of life questionnaires can be filled out on paper
¥ For patients followed with FDG-PET/CT

Table 3: List of variables for MONITOR-RCT¤

Baseline characteristics	**Randomization**	**CT**	**FDG-PET/CT**	**QoL**	**Patient management**	**End-of-study**
Extracted from hospital records	Local investigator	Department of Radiology	Department of Nuclear Medicine	Patient	Extracted from patient records	Local investigator
Age Performance status De novo or recurrent MBC ER status HER2 status Histological type Location of confirmatory biopsy Burden of disease	Date CT FDG-PET/CT QoL Inclusion- and exclusion criteria Reasons for non-participation Patient contact preferences Patient contact information	Latest chemotherapy eGFR CT contrast Other scans and results Response (RECIST 1.1) Measurability Reasons for progression Assessment system	Latest chemotherapy Weight Height Blood sugar eGFR FDG-dose Injection-scan time Faste time Scan type Acquisition protocol Reconstruction method Version of software CT contrast Adverse events Other scans Response (PERCIST-MBC) Measurability Reasons for progression Assessment system	EQ-5D-5L A subset of EORTC QLQ-C30 EORTC QLQ-BR42 FACT-B Patient complaints related to the conduct of scans	Type of treatment Reasons for changes Hospitalization Further diagnostics	Death Reasons for stopping before end-of-study

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth receptor 2; FDG-PET/CT, 2-deoxy-2-[18F]-fluoro-D-glucose positron emission tomografi CT; RECIST, response evaluation criteria in solid tumors; PERCIST, PET response evauation criteria in solid tumors; MBC, metastatic breast cancer; QoL, quality of life; QALY, quality adjusted life year; eGFR, estimated glomerular filtration rate
¤: Interview data and patient questionnaire after first scan and after 6 months are not listed here.