Objective tumor response (OR) to treatment is conventionally assessed by measurement of change in tumor size. Response evaluation (the RECIST criteria) recognizes four categories: Progressive Disease, Stable Disease, Partial Response and Complete Response. Vigorous debate has challenged the adequacy of anatomic assessments alone, as it may take two or three months to detect tumour shrinkage. More seriously, OR produces many false positives (drug shrinks tumour but does not prolong survival) as well, no doubt, as false negatives. RECIST-OR is therefore suitable neither as a surrogate endpoint nor for early-phase PK-PD. There is clearly interest in supplementing anatomic assessment of tumor burden with functional/molecular imaging assessment.

3'-deoxy-3'-(18F)fluorothymidine (18F-FLT) was introduced as a PET proliferation imaging biomarker in 1998. 18F-FLT is monophosphorylated by thymidine kinase 1 (TK1), which leads to intracellular trapping. Since the concentration of TK1 is up-regulated during the S phase of the cell cycle, the uptake of 18F-FLT reflects tumor cell proliferation.

The gold standard method for quantification of 18F-FLT uptake is kinetic modeling, which requires blood sampling during the dynamic 18F-FLT-PET scan at several intervals to measure parent fraction of 18F-FLT, blood activity concentration and plasma-to-blood ratio. However, such a procedure is not feasible in daily clinical practice. Therefore, QuIC-ConCePT consortium investigated whether simplified quantitative methods can be used as an alternative to full kinetic modeling, to quantify changes in 18F-FLT uptake in 10 lung cancer patients undergoing tyrosine kinase inhibitor treatment\(^1\). The study concluded that standardized uptake value (SUV) and (tumor-to-blood ratio) TBR measures can be used as substitute parameters to assess changes in 18F-FLT uptake at the cost of a small underestimation in 18F-FLT uptake changes and the need for a blood sample and metabolite measurement respectively. The optimized 18F-FLT protocol was summarized as below:
1 Mandatory Scanner Entry Parameters

The following parameters should be entered into the scanner acquisition console prior to scan acquisition start for each patient and each visit:

♦ Patient weight
♦ Patient height
♦ Patient sex
♦ Injected activity and time (the injected activity = assayed dose – residual in the injection system)

2 Patient Preparation

♦ Measure patient height and weight before each 18F-FLT PET/CT examination
♦ Place IV device for injection of 18F-FLT
♦ A minimum fasting period of 4 hours before administration of 18F-FLT should be applied.

3 Injection of 18F-FLT

♦ 18F-FLT will be synthesized and prepared in accordance with USP compendia reference standards.
♦ Ensure synchronization of all clocks (dose calibrator, injection room, PET/CT). Clocks should be synchronized with the official local time within one minute.
♦ The procedure aims at an accurate and reproducible administration of 18F-FLT, minimizing or avoiding remaining activity in the administration system and thus ensuring that the exact net dose administered is known (within 3%).
The prescription of 18F-FLT activity should equal at least 4 MBq/kg with a maximum activity of 500MBq assuming an acquisition duration per bed position of 4 min for systems with < 30% overlap between beds and 2 min per bed position for systems with more than >30% overlap between beds. See tables below for more detailed minimal 18F-FLT activity recommendations.

For systems with <30% overlap between beds (typically Siemens and GE):

<table>
<thead>
<tr>
<th>Time/bed</th>
<th>Minimum Activity/kg</th>
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<tbody>
<tr>
<td>Min</td>
<td>MBq/kg</td>
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<tr>
<td>5</td>
<td>3.2</td>
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<td>4</td>
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<td>3.5</td>
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<td>3</td>
<td>5.3</td>
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</table>

For 3D systems with >30% overlap between beds (typically Philips):

<table>
<thead>
<tr>
<th>Time/bed</th>
<th>Minimum Activity/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>min</td>
<td>MBq/kg</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
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<tr>
<td>3.5</td>
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<td>2</td>
<td>4.0</td>
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</tbody>
</table>

We recommend to limit the maximum activity at 500MBq, for very obese patients the acquisition time per bed (min/bed) should be increased instead of giving more than 500MBq.
The 18F-FLT activity calibration time, the administered activity of 18F-FLT and the time of injection should be recorded.

In case of manual administration:

♦ Make sure that if there is a needle on the syringe it is free from 18F-FLT or measure its residual activity and record these data

In case of automated administration:

♦ Make sure that the automated system and procedures assures a net administered 18F-FLT activity within 3% accuracy (this must be ensured by manufacturer and verified by the user), i.e., the actual administered activity may not deviate more than 3% from the indicated by the reading of that devise or used dose calibrator. Follow instructions given by the manufacturer.

♦ It is preferred to administer 18F-FLT through a 3-way valve system attached to a venous cannula.

♦ After injection, the entire administration system should be flushed with at least 42 cc saline at 2.0 mL/s, to avoid remaining activity in the system.

♦ Remove administration line and syringe (but keep venous cannula for later blood sampling when applicable). Measure residual activity in syringe and administration line and record data

♦ The IV cannula can be removed:

♦ After the last blood sample has been taken (see later)

♦ (After the IV administration if no blood samples are taken)

4 Patient positioning, scan acquisition and reconstruction

♦ Ask the patient to use the bathroom immediately before the start of the PET study.
The patient must have arms up; anatomy coverage must include from the mid thighs to base of the skull. Scan in the same direction (e.g. feet first supine/head first supine (FFS/HFS)). If participants cannot tolerate this position for the duration of the PET/CT study, a different position may be chosen. However, arms should be positioned in the same way at the baseline and the follow-up studies.

Preferred scanning sequence: Scout, CT-AC, PET Emission Scan

CTAC should be performed with shallow breathing, no need to instruct the patient.

All scans of a patient should be performed on the same system

4.1 CT AC sequence

A low-dose CT scan will be acquired for attenuation correction and anatomical localization of findings.

Acquisition parameter for the low-dose CT scan for attenuation correction should be according to those recommended by your scanner's vendor.

CT AC acquisition and reconstruction FOV must be the same as for the emission scan (mid thighs to base of the skull) to ensure correct attenuation profile and complete anatomy coverage.

kV = vendor recommendation .

effective mAs = 30-80 mAs or vendor recommendation (patient dependent).

gantry rotation time ≤ 0.5 sec or vendor recommendation.

maximum reconstructed width = 3-5 mm without overlap or vendor recommendation.

standard reconstruction algorithm, reconstruction diameter = skin to skin.

The axial field of view of the CT scan for attenuation correction will range from mid thighs to base of the skull. Arm positioning will be the same as for the PET scan.
♦ No respiratory gating will be applied.

♦ No breathing instructions are needed and patients can breathe normally during the CT-AC acquisition.

### 4.2 PET sequences

♦ Scanning must begin 60 - 65 minutes after 18F-FLT injection for all scans, for all patients participating to this study.

♦ The start time of the follow up scans should be matched as closely as possible to that of the first scan (aim: same time interval as for baseline scan; maximum tolerated deviation ±5 min).

♦ Use of the same PET/CT system, acquisition, and reconstruction settings. Whole body FOV – same as the CT AC to ensure proper attenuation correction and complete anatomy coverage.

♦ The PET/CT scan will start at the mid thighs and extend to the base of the skull or superior to it for each visit of the same patient (e.g. FFS/HFS)

♦ The number of bed positions and the acquisition time per bed position will be scanner and patient specific (options are provided above and listed in table above).

**Acquisition and reconstruction parameters should be the same across all visits for the same patient.**

### 5 Venous blood samplings

♦ In case the site has access to and/or possesses a calibrated well counter, venous blood samples should be collected for assessment of whole blood activity concentrations.

♦ The 18F-FLT administration IV cannula may only be used to collect the samples when flushing of the administration lines was completed successfully (at least 40 ml of saline directly after administration of 18F-FLT and no clotting of the lines).
A venous blood sample must be collected shortly before and directly after the start of the 18F-FLT PET acquisition.

First collect about 3-5 ml blood or the amount needed to fully flush the IV line. This first sample should be disposed (not used to measure blood activity). Next collect a sample of typically 5 ml. Thereafter, flush the IV lines and cannula with 3-5 ml of heparin/saline solution.

Determine the exact amount of blood in your sample (net weight) which is required for accurate activity concentrations measurements. Adhere to local procedures for measuring blood sample activities and activity concentrations.

Record time of sample collection

Record the net weight of whole blood sample.

Use your well counter to determine the total activity and activity concentration of the venous blood samples. Record measurement times. In addition, specify to which time the samples are decay corrected for the recorded activities and activity concentrations. Preferably decay corrected to time of injection or to the time of sample measurement. In all cases this should be clearly specified.

In multi-center clinical trials, it is highly recommended to obtain FDG-PET/CT Accreditation through EARL (EANM Research Ltd.). More information can be obtained via EARL’s web site: [http://earl.eanm.org](http://earl.eanm.org)

For further information about the acquisition, please contact:

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