Response evaluation in myeloma patients using integrated ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/magnetic resonance imaging (PET/MRI): The REVAMP study

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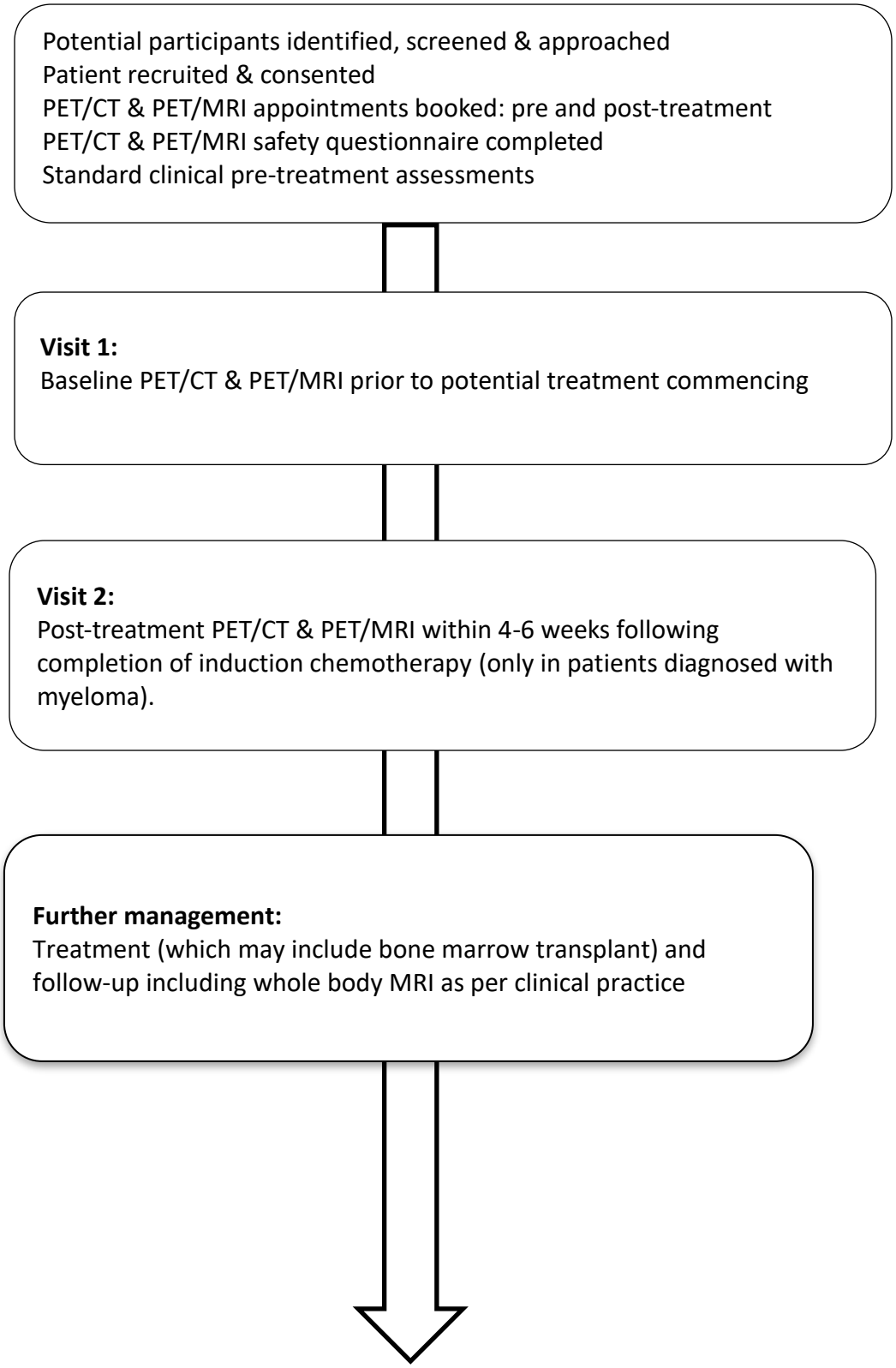
1. Abbreviations:

Abbreviation	Definition
ADC	Apparent diffusion coefficient
ARSAC	Administration of Radioactive Substances Advisory Committee
CR	Complete Response
CRF	Case Report Form
DCE	Dynamic contrast enhanced
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
Gd	Gadolinium
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
rSI	Relative signal intensity
SOP	Standard Operating Procedure
SUV / SUL	Standardised Uptake Value / Standardised Uptake value normalised to lean body mass

2. Protocol synopsis

Title	Response evaluation in myeloma patients using integrated ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/magnetic resonance imaging (PET/MRI)
Short title	REVAMP
Start and End Dates of Study	Start Date: 01/10/16 End Date: 01/09/22
Study design	Non-randomised single centre exploratory study
Number of patients	20 patients with completed PET/MRI imaging at baseline and post therapy
Primary objectives **Secondary Objectives**	1: To compare diagnostic accuracy of integrated ^{18}F-FDG PET/MRI with ^{18}F-FDG PET/CT at baseline and post-induction chemotherapy (prior to potential bone marrow transplantion). 1: To develop, implement and assess software for lesional and global disease burden with integrated ^{18}F-FDG PET/MRI (and PET & MRI separately) 2: To assess the software repeatability for whole body and target lesional quantification 3:To correlate ADC50-900 & fat fraction with i)clinical biomarkers including serum paraprotein level, bone marrow aspirate & ii)18-F FDG PET SUL; 4: To correlate 18F FDG PET SUL with clinical biomarkers; 5: To assess the lesional & inter-lesional heterogeneity of quantitative parameters (FF, ADC) using statistical radiomic methods.
Imaging	Research: Integrated 18F-FDG PET/MRI at baseline and following completion of induction chemotherapy. Comparator: - 1: Clinical assessment and clinical biomarkers 2: ^{18}F-FDG PET/CT and WB-MRI alone
Endpoints	Response versus non-response to induction chemotherapy. Response versus non-response to transplantation. Time to relapse.
Inclusion criteria	Referrals to our institution with suspected or newly diagnosed myeloma who are suitable to undergo ^{18}F-FDG PET/MRI and who are being considered for bone marrow transplantation.
Exclusion criteria	1. Contraindications to contrast-enhanced MRI or FDG-PET/CT. 2. Other known primary malignancy. 3. Patients not being considered for systemic disease control treatment.

3. Trial Schema



4. Background and Rationale:

Response assessment - a clinical challenge:

Multiple myeloma (MM) is a debilitating disease characterised by monoclonal plasma cell proliferation, affecting 4,800 patients/year [Cancer Research UK, 2014]. 80% of patients have lytic bone lesions at diagnosis. In recent years studies have shown that advanced imaging techniques e.g. whole body MRI (WBMRI) and CT have sensitivity and specificity of > 80% in detection of focal lesions [Regelink et al, 2013] whilst skeletal survey (SS) has a high false negative rate of 30-70% [Baur-Melnyk, AJR 2008, Fruehwald, Invest Radiol 1988]. This growing body of evidence supporting advanced imaging techniques has prompted a change in the International Myeloma Working Group (IMWG) guidelines for imaging evaluation of MM patients [Dimopoulos, 2015]. The IMWG now advocates use of WBMR in patients with solitary plasmacytoma and in asymptomatic/smouldering myeloma (SM).

WBMRI is a highly sensitive non-ionising radiation technique, and incorporation of diffusion-weighted and DIXON sequences provide additional quantitative information: apparent diffusion coefficient (ADC50-900, mm2/s) and fat fraction (%). WBMRI may improve lesion detection, staging accuracy, treatment response assessment, and influence clinical management when used complementary to conventional clinical/biochemical review. The emergence of WBMRI in clinical practice has highlighted a need for better quantitative tools to assess and quantify whole body disease burden and treatment response. At present 18F-FDG PET is reserved for problem solving in individual cases; it remains unclear how it compares to WBMRI, the latter having the advantage of no ionising radiation, although PET/CT may be superior in early treatment response assessment [Spinnato et al, 2012]. There has been limited work to date evaluating the potential additive value of integrated ^{18}F-FDG PET in disease assessment in myeloma.

5. Hypotheses:

We hypothesise that: 1) combined PET/MRI will improve staging and response assessment of MM compared to PET/CT or WB-MRI alone, 2) lesion (SUV, ADC) or whole body quantitative imaging (including total tumour volume, ADC50-900, fat fraction) derived from an in-house multimodal software (FAST, KCL)) to assess MM tumour activity / burden can quantify disease at staging, & serial whole body metrics may improve treatment response assessment.

6. Aims:

6.1. Primary aims:

To compare diagnostic accuracy of PET/MRI tumour assessment with PET/CT and WB MRI alone in comparison with current reference standard (MDT review including clinical imaging and biomarkers, as assessed by consensus panel) in assessing staging and treatment response.

6.2. Secondary aims:

1: To develop, implement and assess software for lesional and global disease burden with integrated ^{18}F-FDG PET/MRI (and PET & MRI separately)
2: To assess the software repeatability for whole body and target lesional quantification
3)To correlate ADC50-900 & fat fraction with i) clinical biomarkers including serum paraprotein level, bone marrow aspirate & ii)18-F FDG PET SUL;
4) To correlate changes in 18F FDG PET SUV and MRI ADC, FF with clinical biomarkers;
5) To assess the baseline and treatment-related changes in lesional & inter-lesional heterogeneity of quantitative parameters (FF, ADC) using statistical radiomic methods.

7. Study Plans

7.1. Study design:
Prospective non-randomised feasibility and pilot study in suspected or newly diagnosed transplant eligible MM patients planned for treatment. All patients will undergo integrated 18F-FDG PET/MRI immediately after 18F-FDG PET/CT (clinical routine) at baseline and**,** where a diagnosis of myeloma is confirmed on bone marrow biopsy**,** following completion of induction chemotherapy. Up to 20 completed datasets will be acquired. Patients not subsequently confirmed as having myeloma (based on clinical parameters including bone marrow biopsy) will be withdrawn from the study and will not undergo follow-up PET/CT and PET/MRI. Data for patients not subsequently confirmed as having myeloma will be used for research purposes (assessment of diagnostic accuracy as per primary study objective) unless consent is withdrawn.

7.2. Participants:
Adults (>18 years) with a suspected or new diagnosis of myeloma.

7.3. Inclusions:
Patients with suspected or new diagnosis of myeloma due to systemic disease control treatment.

7.4. Exclusions:
Pregnant females.
Concomitant uncontrolled medical conditions.
ECOG performance status > 2. Estimated prognosis < 12 weeks.
Contraindications to contrast-enhanced MRI or FDG PET/CT including significant renal impairment (eGFR < 50).
patients not being considered for systemic disease control treatment.

7.5. Imaging:

^{18}F-FDG PET/CT (clinical routine) followed by research PET/MRI:

PET/CT: Following a 6hr fast, 400 MBq ^{18}F-FDG will be administered. At 90 +/-5 mins p.i. imaging (GE Discovery PET/CT) will commence from vertex-feet as per clinical practice.

Following completion the patient will be imaged on Siemens mMR 3T PET/MRI from vertex-feet. Free-breathing DW-MRI (b50, 900s/mm^2) sequences at the same bed positions will be obtained simultaneously to the PET acquisition. Corresponding T1 & T2 sequences will be acquired. A whole body contrast-enhanced MRI sequence will be obtained (*). Imaging will be repeated post-induction chemotherapy to assess response/non-response.

Quality assurance & control: Departmental processes & SOPs for scanner image acquisition QC will be followed. Additionally, phantom quantitation of ADC and SUV is performed as per normal departmental SOPs.

7.6. Follow up:

Patients will be reviewed in haematology outpatients as per institutional practice. Patients with suspected myeloma who are not confirmed to have myeloma subsequently with be withdrawn from the study. Routine clinical response assessment with other clinically appropriate tests for an individual patient as determined by the patient's haematologist as per institutional practice (including 100 day post bone marrow transplant bone marrow biopsy results where applicable). Follow-up imaging will include whole body MRI. Time to relapse will be assessed. The end of study definition is the patient's final clinic visit before discharge.

7.7. Image analysis:

Research PET/MRI imaging biomarkers

Target lesion(s): SUV_{max}, SUV_{mean}, SUL_{peak}, $ADC_{mean\ and\ min}$, $rSI_{normalised}$.

These will be quantified using standard manufacturer software (Siemens/Hermes) following segmentation, thresholding, & volume-of-interest analysis.

Exploratory whole body parameters: **WB-volume$_{MRI\ \&/or\ PET}$, WB-SUV_{mean}, WB-ADC_{mean}, WB-rSI_{mean}, WB fat fraction.**

Additional exploratory analysis will be performed using in-house developed software (FAST, KCL) to generate the above parameters. Inter-lesional heterogeneity will be assessed as the standard deviation (SD). The software will also enable intra-lesional heterogeneity to be quantified.

8.0 Statistical Analysis

Feasibility and Pilot study

This is an exploratory study and therefore no formal sample size calculation has been performed.

Data:
Each patient will have PET/CT and PET/MRI at baseline. Patients with confirmed myeloma diagnosis will have a clinical PET/CT and research PET/MR following completion of induction chemotherapy.

Parameters estimated from this exporatory study:
Diagnostic accuracy: Sensitivity, specificity, PPV, NPV, accuracy will be assessed for 18F-FDG PET alone, CT alone, MRI alone 18-F FDG PET/CT, 18F-FDG PET/MRI compared to consensus MDM review.
Comparisons: Between tumour volume metrics will be assessed using appropriate parametric and non-parametric tests and via Mann-Whitney test, (if non-parametric data)
Correlations: Between quantitative MRI & 18F-FDG PET & correlations between quantitative imaging parameters & clinical biomarkers will be assessed using Spearman correlation (if non parametric).
Repeatability: Software repeatability will be assessed using Bland-Altman statistics
Changes with treatment: Changes in tumour volume, ADC, fat fraction, SUV & heterogeneity will be assessed using Wilcoxon's signed rank test (if non-parametric data)

9. Summary of Procedures and Assessments

Procedure	Recruitment	Baseline	Post-treatment
Documentation			
PIS and consent signed	x		
PET/CT & PET/MRI safety questionnaire passed		x	x
Inclusion & exclusion criteria met	x	x	x
Routine Investigations			
PET/CT		x	x
Research Investigations			
PET/MRI (no additional tracer injection)		x	x

10. Data Collection:
Case Report Forms will be completed by the research team or designates.

11. Data monitoring:

Eligibility criteria will be reviewed by the data manager on potential recruitment of patients into the trial. Consent forms will be reviewed for accuracy, dates, signatures and completeness. The data stamp or version number of the patient information sheet and study protocol currently in use will form part of the normal eligibility criteria to ensure up to date study documentation are being used in the recruitment process. The data managers for completeness will check CRFs as data is entered into the database. Statistical data monitoring of the database will be performed at regular intervals to ensure completeness and accuracy of data.

12 Trial Monitoring:

Monitoring of the study will be according to ICH-GCP standards and within the framework of the GSTT Research and Development/Ethics monitoring policies. All patients will be registered on the day of consent or shortly afterwards.

No additional safety issues or adverse events are anticipated from PET/MRI scans. The overall monitoring of safety issues related to the trial will be performed by the trial management group.

13. Study Procedures:

13.1 Start date: Recruitment will only commence once the Chief Investigator has received written notification of ethical and R&D approval, and the study has been activated.

13.2. Patient Recruitment: Suitable patients will be invited to take part in the study. They will be given verbal and written information about the study, including a patient information sheet, and informed that their entry into the study is entirely voluntary. Study-specific procedures will only commence once the patient has signed informed consent.

13.3. Consent: Eligible patients will be identified and initially approached by the direct care team. Patients will be consented for use of their data including anonymised images and clinical data acquired as part of clinical care. Whilst the direct care team will initially discuss the project with the patient, further discussion and consent will be obtained by either the direct care team or the research team. The direct clinical care team and research team will both have access to patient data.

13.4. Subject withdrawal: Subjects may withdraw from the trial at any point. Data acquired up to that point will be used.

14. Adverse Events:

Serious Adverse Event Reporting: No adverse effects are expected from the PET/MRI scans. However, In line with the Trust's Generic Standard Operating Procedure for Adverse Events Reporting for Non-CTIMP Trials sponsored and hosted by GSTT any serious adverse events will be reported to the Chief Investigator and co-investigators and managed appropriately. The Chief Investigator has responsibility to notify the ethics committee.

15. Regulatory & Ethics Committee Approval:

15.1. Ethical Considerations: The Chief Investigator will ensure the study is carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments, or the laws and regulations of the country, whichever provides the greatest protection for the patient.
The trial protocol will be granted approval by the REC (Research Ethics Committee) and will only be open to recruitment after this has occurred. Subjects will only be allowed to enter the study when they have given written informed consent following a full explanation of the study and opportunity to read the information sheet (Appendix). The patient information sheet may be translated into other languages if necessary.
Subjects will be informed that they have the right to withdraw from the study at any stage without prejudice to their further treatment and care and without having to give a reason.
This study may be terminated at the request of the Chief Investigator or the Independent Ethics Committee if during the course of the study concerns about the safety of the proposed imaging emerge. The Chief Investigator will update the ethics committee of any new information relating to the trial treatment where appropriate.

15.2. Informed Consent: Written informed consent will be obtained from each patient in accordance with regulatory requirements, GCP and the Declaration of Helsinki (appendix 4). The subject will have the exact nature of the study explained to them (written and verbal), and the anticipated benefits and known side effects. They will be advised that they are free to withdraw from the study without obligation. The consent form will also request permission for personnel involved in the research to have access to the subject's medical records.
Both the person taking consent and the patient should personally sign and date the form. The original copy of the signed Consent Form will be retained by the Investigator in the Study File, a copy will be put in the subject's notes, and a copy will be given to the subject. Patients will be asked permission to inform their GP of participation within this trial and if they agree, a letter will be sent to their GP.

15.3. Patient Confidentiality: All trial staff will abide by the Data Protection Act 1998 and behave in accordance with the confidentiality code of practice and data protection policy and procedure.

15.4. Data Handling and Record Keeping: Data will be collected and maintained according to ICH-GCP standards. The data manager assigned to the study will enter

data from the CRFs into a trial-specific database. All source documents relating to individual research participants will be anonymised and maintained securely within the hospital (locked room). Personnel who have access to the database are legally bound by the confidentiality agreement in their contract of employment.

Source documents will be maintained for 5 years and will be available for inspection by authorised staff including the Chief Investigator, Study Coordinator, Clinical Trials Manager, Research Nurse and statistician. Source documents will be made available if requested for monitoring and audit purposes to the Ethics and Research and Development departments and for inspection by regulatory bodies.

15.5. Quality Control and Quality Assurance: The monitoring processes above will form the mainstay of quality control within the study. Laboratory tests are subject to internal validation and standardisation processes. Imaging will be co-reported by two consultant radiologists experienced in WBMR and FDG-PET. Established secure and confidential computed systems for recording data are in place. Investigators and study personnel will be made available for possible audits and inspections by the institutional review board or Ethics Committee and by the regulatory bodies. All source documentation and the site study file will be available for inspection.

16. Financing, Indemnity and Insurance:

KCL and NHS indemnity processes are in place. KCL has non-negligent harm insurance whilst GSTT is covered by the NHS Clinical Negligence Scheme.

17. Publication Policy:

The aim of the investigators is to author and publish the mature results of this study in peer reviewed journals. All presentations and publications require authorisation from the Chief Investigator.

18. References:

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3. Baur-Melnyk A., Buhmann S., Becker C. et al. Whole-Body MRI Versus Whole-Body MDCT for Staging of Multiple Myeloma. AJR 2008;190(4):1097-104.
4. Fruehwald F.X.J., Tscholakoff D., Schwaighofer B. et al. Magnetic resonance imaging of the lower vertebral column in patients with multiple myeloma. Invest Radiol 1988;23:193-199.

5. Dimopoulos M.A., Hillengass J., Usmani S. et al. Role of magnetic resonance imaging in the management of patients with multiple myeloma: a consensus statement. Journal of Clinical Oncology 2015; 6:657-664.
6. Spinnato P., Bazzocchi A., Brioli A., et al. Contrast enhanced MRI and 18F-FDG-PET in the assessment of multiple myeloma: a comparison of results in different phases of the disease. EJR 2012;81:4013-8.