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Development of machine learning support for reading whole body diffusion weighted magnetic resonance imaging (WB-MRI) in myeloma for the detection and quantification of the extent of disease before and after treatment (MALIMAR): protocol for a cross-sectional diagnostic test accuracy study

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Manuscripts

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3 1 Development of machine learning support for reading whole body diffusion weighted magnetic
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5 2 resonance imaging (WB-MRI) in myeloma for the detection and quantification of the extent of
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7 3 disease before and after treatment (MALIMAR): protocol for a cross-sectional diagnostic test
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9 4 accuracy study
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14

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1
2
3 24 **Abbreviations:**
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5

6 25 **ADC:** Apparent Diffusion Coefficient
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9 26 **BMI:** Body Mass Index
10

11
12 27 **BRC:** Biomedical Research Centre
13

14
15 28 **CCR:** Committee for Clinical Research
16

17
18 29 **CPMS:** Central Portfolio Management System
19

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21 30 **CRF:** Case Report Form
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24 31 **CRN:** Clinical Research Network
25

26
27 32 **CRUK:** Cancer Research UK
28

29
30 33 **CT:** Computerised Tomography
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33 34 **CTIMP:** Clinical Trial of Investigational Medicinal Product
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35
36 35 **DWI:** Diffusion Weighted Imaging
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38
39 36 **EME:** Efficacy and Mechanism Evaluation
40

41
42 37 **F-FDG:** F-Fluorodeoxyglucose
43

44
45 38 **HRA:** Health Research Authority
46

47
48 39 **HV:** Healthy Volunteer
49

50
51 40 **ICHT:** Imperial College Healthcare Trust
52

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54 41 **ICR:** The Institute of Cancer Research
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57 42 **IRAS:** Integrated Research Application System
58

59
60 43 **ML:** Machine Learning

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3 44 **MM:** Multiple Myeloma
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6 45 **MRC:** Medical Research Council
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9 46 **MRI:** Magnetic Resonance Imaging
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12 47 **MS:** Microsoft
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15 48 **NHS:** National Health Service
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18 49 **NICE:** National Institute of Clinical Excellence
19

20
21 50 **NIHR:** National Institute of Health Research
22

23
24 51 **PET:** Positron Emission Tomography
25

26
27 52 **PPI:** Patient and Public Involvement
28

29
30 53 **QA:** Quality Assurance
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33 54 **REC:** Research Ethics Committee
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36 55 **sFLC:** serum Free Light Chain
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39 56 **TMG:** Trial Management Group
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42 57 **TSC:** Trial Steering Committee
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44
45 58 **WB-DW-MRI:** Whole Body Diffusion Weighted Magnetic Resonance Imaging
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47
48 59 **UKRI:** UK Research and Innovation
49

50
51 60 **Acknowledgements:**

52
53 61 We acknowledge NHS funding to the NIHR Biomedical Research Centre at The Royal Marsden and

54
55 62 Institute of Cancer Research and the NIHR Royal Marsden Clinical Research Facility.
56

57
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59
60 64 CRUK Imperial Centre and the Imaging Research Office at ICHT.

1
2
3 65 We acknowledge the support of the CRUK funded National Cancer Imaging Translational Accelerator
4
5 66 award (Institute of Cancer Research and Imperial College London).
6
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8
9 **67 Availability of data and materials:**

10
11 68 Not applicable.
12
13

14 **69 Ethics approval and consent to participate:**

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16
17 70 The Royal Marsden NHS Foundation Trust is the study sponsor and responsible for initiating and
18
19 71 managing the study, for oversight of the conduct of the study including submission of financial
20
21 72 returns to NIHR, for reporting trial progress in line with NIHR EME requirements, for submitting and
22
23 73 co-ordinating amendments to the trial protocol and for oversight of closure and archiving of all trial
24
25 74 materials. All publications must have the consent of the NIHR. The study protocol was reviewed by
26
27 75 the Royal Marsden NHS Foundation Trust and Institute of Cancer Research Combined Committee for
28
29 76 Clinical Research (CCR) and underwent proportionate review by the South Central – Oxford C
30
31 77 Research Ethics Committee in November 2017 (IRAS Project ID: 233501) and the Health Research
32
33 78 Authority. The study was also approved for CPMS Portfolio adoption (CPMS ID: 36766). This research
34
35 79 will be carried out in accordance with the Declaration of Helsinki (1996). The study will be conducted
36
37 80 in accordance with the conditions of ethical approval. Participation is limited to Healthy Volunteers
38
39 81 only. Before participation all participants will be provided with a Healthy Volunteer Participation
40
41 82 Sheet and will give written informed consent.
42
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46

47 **83 Consent for publication:**

48
49 84 Not applicable.
50
51

52 **85 Protocol version: 3.0 31/01/2019**

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2
3 **87 Abstract:**
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5

6 **88 Introduction:** Whole-body MRI (WB-MRI) is recommended by NICE as the first-line imaging tool for
7
8 **89** diagnosis of multiple myeloma. Reporting WB-MRI scans requires expertise to interpret and can be
9
10 **90** challenging for radiologists who need to meet rapid turn-around requirements. Automated
11
12 **91** computational tools based on machine learning (ML) could assist the radiologist in terms of
13
14 **92** sensitivity and reading speed and would facilitate improved accuracy, productivity and cost-
15
16 **93** effectiveness. The MALIMAR study aims to develop and validate a ML algorithm to increase the
17
18 **94** diagnostic accuracy and reading speed of radiological interpretation of WB-MRI compared to
19
20 **95** standard methods.
21
22
23

24 **96 Methods and analysis:** This phase II/III imaging trial will perform retrospective analysis of previously
25
26 **97** obtained clinical radiology MRI scans and scans from healthy volunteers obtained prospectively to
27
28 **98** implement training and validation of a machine learning algorithm. The study will comprise three
29
30 **99** project phases using approximately 633 scans to 1) train the ML algorithm to identify active disease;
31
32 **100** 2) clinically validate the ML algorithm; and 3) determine change in disease status following
33
34 **101** treatment via a quantification of burden of disease in myeloma patients. Phase 1 will primarily train
35
36 **102** the ML algorithm to detect active myeloma against an expert assessment ('reference standard').
37
38 **103** Phase 2 will utilise the ML output in the setting of radiology reader study to assess the difference in
39
40 **104** sensitivity when using ML-assisted reading or human-alone reading. Phase 3 will assess the
41
42 **105** agreement between experienced readers (with and without ML) and the reference standard in
43
44 **106** scoring both overall burden of disease before and after treatment, and response.
45
46
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49

50 **107 Ethics and dissemination:** MALIMAR has ethical approval from South Central – Oxford C Research
51
52 **108** Ethics Committee (REC Reference: 17/SC/0630). MALIMAR is funded by National Institute for
53
54 **109** Healthcare Research Efficacy and Mechanism Evaluation funding (NIHR EME Project ID: 16/68/34).
55
56 **110** Findings will be made available through peer-reviewed publications and conference dissemination.
57
58
59

60 **111 Trial registration:** The study was registered at clinicaltrials.gov (NCT03574454) on 2 July 2018.

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3 112 **Strengths and limitations of this study:**
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- 6 113 • This cross-sectional diagnostic test accuracy study will be the first of its kind to provide
7
8 114 evidence of whether a machine learning algorithm can deliver outputs to significantly
9
10 115 enhance the radiology reading process for the benefit of myeloma patients.
11
12
13 116 • The MALIMAR study will explore whether specific processes can be automated to augment
14
15 117 the ML process which could include the development of an automated segmentation tool to
16
17 118 depict bony anatomy and volume of disease and negate the need for manual outlining.
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19
20 119 • This study will provide ML outputs that can be tested across the NHS in live real-time clinical
21
22 120 settings.
23
24 121 • This study will acquire and characterise what is possibly the largest set of myeloma WB-MRI
25
26 122 scans in the UK; however, data will be acquired over a long period of time meaning scan
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28 123 quality could vary.
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31 124 • Replicating clinical reporting in a retrospective study setting can be difficult to achieve,
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33 125 particularly for analysis of reading time.
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126 Introduction

127 There is strong evidence in the existing literature for the use of whole-body MRI (WB-MRI) in the
128 management of patients with multiple myeloma. In 2016, the National Institute of Clinical
129 Excellence (NICE) made the recommendation of using WB-MRI as the first line imaging tool for
130 diagnosis, based on the literature(1). A consensus from the International Myeloma Working Group
131 agreed that identification of focal lesions more than 5mm on MRI should now be used as an
132 indication to treat (2,3). Evidence suggests that diffusion weighted (DW) WB-MRI (WB-DW-MRI) is
133 the most sensitive MR technique for detecting marrow disease (4–8) and superior to FDG-PET/CT for
134 the detection of small sites of disease and diffuse infiltration (9,10). Therefore, WB-MRI is
135 increasingly being adopted at centres worldwide for patients with myeloma. Treatment of high-risk
136 patients is known to improve overall survival (11), therefore improved diagnostic accuracy is likely to
137 translate into improved patient selection for treatment and prolonged survival.

138 Despite the acknowledged benefits of WB-MRI for patients with myeloma, with publication of the
139 NICE guidance, one of the major concerns is how these complex scans can be reported by a
140 radiology workforce in crisis. Specificity of disease detection in the marrow is improved by viewing
141 source DW images alongside quantitative Apparent Diffusion Coefficient (ADC) maps. This allows
142 differentiation of active sites of disease with restricted diffusion from treated sites of disease and
143 vertebral haemangiomas which conversely return a very high ADC (12). Dixon images are also
144 integral to image interpretation and morphological imaging is also necessary to identify mechanical
145 complications of myeloma bone disease. Therefore, diagnostic accuracy is dependent on viewing
146 multiple imaging sequences (7) and typically over 1200 image slices per WB-MRI scan in order to
147 achieve whole body coverage. Consequently, reading time for the scans may be significant. At least
148 9% of UK radiology posts are unfilled (13) and in 2015 clinical radiology was placed on the national
149 shortage occupation list. The time-consuming process of reporting WB-MRI scans is a concern for
150 radiologists who need to provide rapid turn-around with a high productivity to support the NHS.

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2
3 151 Automated computational tools based on machine learning (ML) could support reporting of these
4
5 152 large datasets and facilitate translation of this valuable imaging technique into the NHS, not only in
6
7 153 detecting active disease but also in identifying response to treatment. Ideally, a ML algorithm would
8
9
10 154 automatically detect and highlight suspicious regions and could reduce reading time. An accurate
11
12 155 and automatic detection of pathology may also increase diagnostic accuracy.

13
14
15 156 The possibility of using computer-assisted ML techniques has been considered in aiding
16
17 157 interpretation of complex imaging datasets (14–16). Current work in the EME NIHR funded MALIBO
18
19 158 study (17,18)(13/122/01) has demonstrated fully automatic multi-organ segmentation using WB-
20
21 159 MRI in healthy volunteers (HV) and ML detection of primary colorectal cancer and metastatic
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23
24 160 lesions.

161 **Aim**

25
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30 162 The aim of the MALIMAR study is to develop and validate a Machine Learning (ML) algorithm to
31
32 163 improve the sensitivity of radiologists to detect the presence and extent of active myeloma before
33
34 164 and after treatment, with high reproducibility and reduced reading time (WB-MRI with ML, the
35
36 165 intervention) when compared with the standard of care radiology read (WB-MRI without ML
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38 166 support, the comparator).

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43 44 168 **Methods and analysis**

45 46 47 169 **Study design**

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50 170 The study is based on a cross-sectional diagnostic test accuracy design and will comprise three
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52 171 distinct project phases as summarised in Figure 1.
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3 172 • In **Phase 1** the ML algorithm will be trained using both HV and myeloma patient scans to
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5 173 recognise active myeloma deposits as distinct from cases with no active disease, classifying
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7 174 disease as ‘focal’, ‘diffuse’ or ‘inactive’.
8
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10 175 • In **Phase 2** the ML algorithm will be validated using a second unseen dataset against a
11
12 176 reference standard (i.e. ground truth) to assess how accurately radiologists classify disease
13
14 177 using scans with the ML algorithm and compared to readings without ML. Diagnostic
15
16 178 accuracy on a per patient and per region (using 16 pre-defined anatomical sites – Table 1)
17
18 179 basis and reading time will be measured.
19
20
21 180 • In **Phase 3**, further development of the ML algorithm to quantify disease burden will be
22
23 181 undertaken using datasets from phase 1 and 2. This quantification output will be tested in
24
25 182 the phase 3 reader study in which readers will record disease burden and response between
26
27 183 paired baseline (new diagnosis or relapse prior to initiation of treatment) and single post
28
29 184 treatment WB-MRI scans, with or without ML support, and tested against the reference
30
31 185 standard.
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34

35 **Table 1: Comparison of MALIMAR anatomical regions between ground truth CRFs and reader CRFs**
36

Anatomical Regions	
Ground Truth CRFs (Phase 1 and 2)	Reader CRFs (Phase 2)
Skull	Skull
Scapula right	Ribs / clavicles / sternum / scapulae
Scapula left	Ribs / clavicles / sternum / scapulae
Clavicle right	Ribs / clavicles / sternum / scapulae
Clavicle left	Ribs / clavicles / sternum / scapulae
Sternum	Ribs / clavicles / sternum / scapulae
Spine upper	Cervical spine
Spine middle	Dorsal spine
Spine lower	Lumbar spine
Ribs right	Ribs / clavicles / sternum / scapulae

Ribs left	Ribs / clavicles / sternum / scapulae
Sacrum	Pelvis
Femur right	Long bones
Femur left	Long bones
Humerus right	Long bones
Humerus left	Long bones

187

188 Participants and Recruiting Centres

189 The study will be run at The Royal Marsden NHS Foundation Trust across two Royal Marsden
 190 Hospital (RMH) sites; Chelsea and Sutton, and Imperial College Healthcare Trust (ICHT). Patient and
 191 HV scans will make up the study population, and disease classification will be at both the scan and
 192 anatomical site level.

193 The scan population will comprise of; HV WB-MRI scans acquired from participants prospectively
 194 recruited from the Sponsor site only (RMH), with the option of the Imperial Site providing previously
 195 acquired HV scans; WB-MRI scans acquired as part of clinical care from patients being managed at
 196 RMH and ICHT; and WB-MRI scans previously acquired for a prospective research study in WB-MRI
 197 (iTMM study). All scans acquired for the study will be done so using clinical standard of care Trust
 198 protocols.

199 The inclusion/exclusion criteria for the HV and patient scans are detailed in Table 2 and the planned
 200 number of scans for each study phase is detailed in Table 3.

201 Table 2: Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Healthy volunteers	Written informed consent No contra-indication to MRI 40 years or above in age (attempts will be made to include similar age range as myeloma patients) No known significant illness No known metallic implant	Significant artifact on scan Corrupted scan data
Patients in	Patient with confirmed myeloma with WB-MRI scan	Corrupted WB-MRI scan

phase 1 & 2	<p>previously performed as part of clinical care.</p> <p>Sufficient imaging and clinical data for the expert reference panel to categorise the WB-MRI scan as:</p> <ol style="list-style-type: none"> 1. Previously treated inactive disease with no evidence of active disease based on expert reference panel 2. Active disease – focal 3. Active disease – diffuse 4. Active disease – extra-medullary 5. New active myeloma, no previous treatment <p>Patients may be included if the pattern of disease is a combination of focal, diffuse and/or extra-medullary.</p>	<p>data.</p> <p>Insufficient clinical data to allow the expert reference panel to categorise the scan.</p>
Patients in phase 3	<p>Training set: Phase 1 active disease cases and their post treatment scans from phase 2.</p> <p>Validation set: from iTIMM study.</p> <p>Written informed consent for iTIMM study</p> <p>All patients over the age of 18 with multiple myeloma planned for autograft.</p>	<p>Corrupted scan data.</p> <p>MRI incompatible metal implants</p> <p>Claustrophobia</p> <p>Diagnosis of other malignancy within 5 yrs</p>

202

203 **Table 3: Number of Healthy Volunteer (HV) and Multiple Myeloma (MM) scans in each category**
 204 **for each study phase.**

	HV**	MM inactive	MM active focal	MM active diffuse	MM new diagnosis	Total
Phase 1*	40	40	60	40	20	200
Phase 2	50	100	105	70	28	353
Phase 3 training***	0	(80 post treatment)	60	40	20	200
Phase 3 validation	0	60 patients in iTIMM study scanned at baseline and post treatment				120

205 *The number of scans in phase 1 may increase by 140-180 scans (100 subjects) if there is evidence
 206 of over-fitting in the development of the algorithm.

207 ** A total of 50 HV will be used, 40 in phase 1, which will be used again in phase 2, with the addition
 208 of 10 more HV.

209 ***Scans used in phase 3 training are scans that have been previously used in phase 1 and 2

210 Intervention and Reference Standard

211 *Intervention (including comparator)*

212 The comparator in this study is defined as WB-MRI scans read by experienced radiologists, as per

213 standard care (WB-MRI, the COMPARATOR). The intervention will use these standard methods with

214 the addition of machine learning (WB-MRI+ML, the INTERVENTION). The ML algorithm will be

215 developed during phase 1 of the study following data curation and scan allocation to phase 1 and 2.

216 DWI, ADC map and T1 weighted sequences (Dixon fat and water scans) will be used, reflecting the

217 radiological reading tools used by expert readers.

218 Radiologists or readers are defined as experienced based on their previous clinical radiology reading

219 skills and responsibilities, and their length of service in this role. Experienced readers will be required

220 to have completed at least 100 WB-MRI clinical scan reports.

221 *Reference standard*

222 There is no available histological reference standard for every site of bone marrow disease, as

223 trephine biopsy is usually restricted to a single site. The proposed reference standard thus

224 comprises the interpretation of an expert panel; a radiologist and a haematologist who are experts

225 in myeloma. They will have access to 1) WB-MR images; 2) bone marrow histopathology reports

226 (with quantitation); 3) serum paraproteins; 4) serum free light chain (sFLC), in order to categorise

227 per scan:

- 228 • Presence or absence of active disease
- 229 • The detailed disease distribution by anatomical site
- 230 • Quantitation of the burden of disease (using a validated MRI score (19,20) and sFLC)
- 231 including category of response to treatment .

232 Scan and site level data from these scans will be captured on Case Report Forms (CRFs) for all cases

233 in phases 1 and 2 and used as 'ground truth' in the classification of study output. Reference standard

234 for phase 3 will be obtained from the source (iTMM study).

235 **Objectives**

236 *Primary research objectives*

237 Phase 1: To develop a myeloma-specific ML algorithm to detect the presence of active disease on

238 WB-MRI+ML (with machine learning '+ML') with sufficient sensitivity.

1
2
3 239 Phase 2: To validate WB-MRI+ML against the comparator WB-MRI for sensitivity on a per-patient
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5 240 and per site basis.

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7
8 241 Phase 3: To develop and validate a ML algorithm to automatically quantify the burden of active
9
10 242 disease, before and after treatment.

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13 243 *Secondary research objectives (Phase 2 and 3 only)*

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15
16 244 For each of the following, our objective is to compare WB-MRI with and without ML support to the
17
18 245 reference standard for:

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20
21 246 1) Reading time

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23
24 247 2) Specificity

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26
27 248 3) Sensitivity of non-experienced readers

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29
30 249 4) Agreement of categorising disease as focal, diffuse and/or extramedullary.

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32
33 250 5) Agreement of categorising patients as responder or non-responder

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35
36 251 **Procedure**

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39 252 *Scan Acquisition – Healthy Volunteers*

40 253 Healthy Volunteers (HV) will be recruited to obtain data from normal bone marrow within the age
41
42 254 range typical of myeloma. Up to 50 HVs aged 40 years or above will be recruited using approved
43
44 255 advertisements at the Sponsor site and consented with the help of CRN resources (See
45
46 256 Supplementary S1a for consent form). The HV Information Sheet (Supplementary file S1b) will clearly
47
48 257 explain the MRI scanning procedure and the actions that will be taken in the event of incidental (i.e.
49
50 258 unexpected) findings. Contact details will be supplied on the HV Information Sheet to enable
51
52 259 volunteers to respond to the invitation or ask any questions. A total of 22 HV scans previously
53
54 260 acquired are also available for use from ICHT if needed.
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3 261 Participating HVs will undergo a single whole body MRI scan at RMH according to the trial specific
4
5 262 scanning protocol. HV scans will be acquired in the following sequences (T1, fat/water, Dixon, ADC,
6
7 263 etc) to mirror the clinical setting and on Siemens, Avanto and Aero (wide bore) MRI scanners
8
9
10 264 (Supplementary S2 details sequences). Subjects with a larger BMI will be scanned on the Siemens
11
12 265 Aero which has a larger bore diameter to optimise comfort.

15 266 *Scan Acquisition– Myeloma Patients*

16
17 267 Previously acquired patient scans will be identified by the investigators within the Sponsor's
18
19 268 myeloma clinical service (between 2011 and 2020), supplemented by scans from ICHT, until the
20
21 269 required sample size is reached. Scans will normally include the following sequences; T1, fat/water,
22
23 270 Dixon, ADC, etc, and on the following MRI machines; Siemens, Avanto and Aero MRI scanners
24
25
26 271 (Supplementary S2 for sequence details).

29 272 *Scan Classification and Allocation to Study Phase*

30
31 273 Patient scans will be categorised by the expert reference panel as showing inactive disease, active
32
33 274 focal, active diffuse (focal or diffuse) and new disease. HV scans will be classified as normal (i.e. non-
34
35 275 diseased). Scans will be allocated to Phase 1 or 2 as per Table 3. To minimise bias or 'over-learning',
36
37 276 no more than 5 scans from the same patient will be allocated to Phase 1. Phase 2 scans will not
38
39 277 include any patient scans that have been used in Phase 1 and thus comprise only those previously
40
41 278 unseen by the ML algorithm. A subset of scans from phase 1 and 2 will be used to further train the
42
43 279 algorithm at the start of Phase 3. Phase 3 validation scans have previously been acquired for the
44
45 280 iTTiM trial (NCT02403102) and include a unique series of paired scans, previously unseen by the ML
46
47 281 algorithm.

52 282 *Scan Curation (Quality Control) and Anatomical Segmentation*

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54
55 283 Eligible scans will be curated immediately prior to transfer to an online platform for secure storage
56
57 284 (ICR XNAT). This will ensure the ML algorithm is able to interpret all scans consistently. Curation
58
59 285 scripts will be written in python and ensure that scans exhibit consistent characteristics such as:

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2
3 286 correct sequential display of images, no missing slices, noting presence of unusual artifacts that
4
5 287 might interrupt ML reads and other factors which might compromise interpretation. Further details
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7
8 288 on the data curation will be published elsewhere.
9

10 289 Phase 1 scans will then be manually segmented into 16 bone regions (Table 1) using a boundary box
11
12 290 approach. These scans will be used to teach the ML algorithm to recognise active myeloma disease
13
14 291 (focal or diffuse) and precision metrics will be evaluated in order to achieve the optimal algorithm.
15
16 292 Initially, scans will be classified by the ML algorithm at scan level (i.e. patient level) only.
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20 293 *Testing of ML Algorithm – Radiology Reading Process*

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23 294 The ML algorithm will be tested by both experienced and inexperienced radiology readers.
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26 295 Phase 2 scans will be subjected to the ML algorithm which will provide an ML overlay on all scans
27
28 296 indicating areas of disease by means of a heat map. For each scan, a ‘standard’ and ‘machine
29
30 297 learning’ version will be available. The trial statistician will randomly allocate reads to each of the
31
32 298 (approximately 15 – 20) readers, using trial-specific algorithms written using Stata software
33
34 299 (StataCorp, Texas). The reads will be performed in two batches to incorporate a wash-out period.
35
36 300 Each batch will have 50% of cases with ML support and 50% without, to avoid reader training bias.
37
38 301 The reading process will be described in a Reader Manual and all readers will receive appropriate
39
40 302 training in viewing scans using the Biotronics 3D Web-based platform and completing a Read CRF
41
42 303 available via MS Forms (see supplementary file S3a). In the case of “inexperienced” readers, training
43
44 304 will comprise a review of the CRFs and the viewing software with a basic training on reporting
45
46 305 lexicon. A scribe will be provided to assist readers during the reading process and input data to the
47
48 306 CRF in each batch of reads. Following a 4-week wash out period, readers will be presented with the
49
50 307 second batch of reads with the opposite reading paradigm with regards to the ML support. The
51
52 308 same cases will be allocated to the same readers. A subset of approximately 50 scans will be read a
53
54 309 second time by a different reader as an interrater check.
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3 310 In Phase 3, scans from the iTIMM study, comprising paired baseline and follow-up post treatment
4
5 311 scans, will be used to test whether the ML algorithm is capable of distinguishing change in disease
6
7 312 status (i.e. disease burden) between the two time-points. Reads will again be randomly allocated to
8
9
10 313 the readers by the trial statistician. Readers will follow similar procedures to that outlined above
11
12 314 with one set of paired scans having the ML overlay and the other with no ML overlay (for CRF see
13
14 315 supplementary file S3b). A 4-week wash-out period will again apply between the two batches of
15
16 316 reads. A subset of approximately 20 scans will be read a second time by a different reader as an
17
18
19 317 interrater check.

21 318 *Data collection*

22
23
24 319 Reader responses will be captured using MS Forms with responses being transferred directly to an
25
26
27 320 excel spreadsheet. Examples of the CRFs to be used in both ML validation phases are given as
28
29 321 supplemental files (S3a, S3b). All readers will be provided with a manual describing CRF completion
30
31 322 (including a lexicon of disease definitions) and use of the software viewing tools and overlay of the
32
33 323 ML output heatmap and opportunity for live training using the online platform.

34 35 36 324 **Outcome measures**

37 38 39 325 *Phase 1 – ML Algorithm Training Phase*

40
41
42 326 Primary: Sensitivity for the detection of active myeloma on WB-MRI + ML detection tool against the
43
44 327 reference standard.

45
46
47 328 Secondary: 1. Specificity; 2. F1 score (a single measure of precision and recall).

48 49 50 329 *Phase 2 – ML Algorithm Clinical Testing Phase (Presence /Absence of active myeloma)*

51
52
53 330 Primary: Difference in sensitivity of WB-MRI +/- ML detection tool to diagnose the presence of
54
55 331 active myeloma on a per-patient basis, by experienced readers, assessed against the reference
56
57 332 standard.
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3 333 Secondary: For comparison of WB-MRI +/-ML: 1. Per-site sensitivity to diagnose active disease; 2.
4
5 334 Reading time; 3. Specificity; 4. Agreement with reference standard to categorise disease as focal,
6
7 335 diffuse and/or extramedullary; 5. Sensitivity of non-experienced readers for presence of active
8
9 336 disease.

10
11
12
13 337 *Phase 3 – ML Algorithm for quantification of disease burden with clinical testing*

14
15 338 Primary : agreement between experienced readers and the reference standard in scoring overall
16
17 339 burden of disease before and after treatment for response categorisation +/- ML quantification tool.

18
19
20
21 340 Secondary: For comparison of WB-MRI +/-ML: 1. Reading time; 2. Agreement of categorisation of
22
23 341 patients as responder or non-responder with the reference standard; 3. Agreement of non-
24
25 342 experienced readers for burden of disease and categorisation of response; 4. Estimated difference in
26
27 343 cost for radiology reading time for WB-MRI +/-ML.

28
29
30 344 Proposed tertiary: Verification of the team's previously published work regarding reverse
31
32 345 classification accuracy: predicting segmentation performance in the absence of a reference standard
33
34 346 (21).

35
36
37
38 347 **Sample size**

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40
41 348 *Phase 1:*

42
43
44 349 We will train the ML algorithm on a set of scans without and with active disease that will reflect the
45
46 350 categories of disease that may be encountered in clinical practice. The number of cases used for
47
48 351 training is arbitrarily chosen reflecting the knowledge that a large number of training datasets will
49
50 352 improve training accuracy, counterbalanced with the resources needed to curate and annotate a
51
52 353 large number of datasets.

53
54
55 354 *Phase 2:*

56
57
58 355 The study is powered on the primary outcome of sensitivity.
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3 356 In a meta-analysis, Wu et al have reported a pooled sensitivity of 88% and a pooled specificity of
4
5 357 86% (0.86 for WB-MRI with DW-MRI) (8). We anticipate that the addition of ML could increase this
6
7 358 by at least 7.5%, from 88% to 95.5%. There is no background data to indicate the expected
8
9 359 proportion of discordant pairs so we have estimated this as $(1-0.955)*0.88 + 0.955*(1-0.88)$, which is
10
11 360 equal to 0.154. To achieve 80% power using a two-sided alpha of 0.05 would require a total of 203
12
13 361 patients positive for myeloma using the gold standard.

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16
17 362 If it is assumed that the specificity will be unchanged using ML, a total number of cases with no
18
19 363 active disease of 150 (50 HV, 100 inactive treated myeloma), will give 80% power to show that the
20
21 364 difference is above a non-inferiority limit of 10%.

22 365 *Phase 3 training:*

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26
27 366 Approximately 200 cases that have at least two time points will be taken from phase 1 and 2, with
28
29 367 active disease present at least at one time point, and used for training and validation for burden of
30
31 368 disease; this will ensure efficient use of all data and segmentations.

32 369 *Phase 3 clinical testing:*

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36
37 370 This sample size is fixed at 60 patients, the full sample size of the iTIMM study, each of whom has a
38
39 371 baseline and one post treatment scan.

40 372 **Statistical Analysis**

41 373 *Phase 1 analysis*

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45
46 374 The ability to correctly localise and detect active disease will be evaluated by calculating sensitivity,
47
48 375 specificity and the F1 score (a single measure of precision (positive predictive value) and recall
49
50 376 (sensitivity)) for multiple algorithms and compared against the reference standard. Following TSC
51
52
53 377 approval, the optimal algorithm will move forward to phase 2.

54 378 *Phase 2 analysis*

1
2
3 379 In phase 2, the percentage of patients with active disease on WB-MRI +/- ML support who have
4
5 380 positive reference standard will be compared using McNemar's test with a two-sided alpha of 0.05.
6
7 381 Per patient and per site sensitivity and specificity with and without ML support will be reported with
8
9 382 95% confidence intervals. Reading time will be compared using Wilcoxon's test for paired data and
10
11 383 described using summary statistics.
12
13
14

15 384 The same analysis of sensitivity, specificity and reading time will be repeated for inexperienced
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17 385 readers.
18
19

20 386 Agreement between experienced and inexperienced readers will be measured in a subset of cases
21
22 387 with a Kappa coefficient, and overall proportion of concordant cases.
23
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25 388 All other endpoints will be summarised using descriptive statistics.
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27

28 389 Although the study is powered to detect superiority of the primary endpoint, if sensitivity is shown
29
30 390 to be non-inferior using ML and reading time is both clinically and statistically significantly lower
31
32 391 using ML, this would be considered as an indication to proceed. Non-inferiority in this context will be
33
34 392 defined as having any possible reduction in sensitivity with ML significantly higher than a lower limit
35
36 393 of -10% (using Tangos' test with one-sided alpha 0.05)
37
38
39

40 394 *Phase 3 analysis* 41 42

43 395 In phase 3, the difference between the experienced readers' disease score to the reference standard
44
45 396 disease score will be recorded and compared +/- ML support using Wilcoxon's test. Differences from
46
47 397 scores given by experienced readers and the reference standard will be described using Bland-
48
49 398 Altman plots for scores +/- ML support.
50
51

52 399 All other endpoints will be summarised using descriptive statistics.
53
54

55 400 A simple cost-effectiveness analysis may be performed depending on study findings, such as the
56
57 401 reading time.
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3 402 *Procedure(s) to account for missing or spurious data*

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6 403 If a scan is incomplete or the file is corrupted and not evaluable, it will be excluded from the dataset.

7
8 404 If a set of radiology reads is incomplete, a new trained reader will be identified to do the full

9
10 405 allocation of reads.

11
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13 406 *Timing and responsibility for analyses*

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15
16 407 Analyses will take place at both the end of phase 2 and then again at the end of phase 3, when all

17
18 408 readings have been completed.

19
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21 409 **Patient and public involvement (PPI)**

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23
24 410 A PPI representative was appointed from an established group at Myeloma UK. The individual gave

25
26 411 in-depth feedback on the study, particularly on the relevance to patient care and the use of

27
28 412 retrospective patient data and HV scans. Myeloma UK is fully supportive of the project and is willing

29
30 413 to assist with dissemination of important findings to the Myeloma UK community.

31
32
33
34 414 **Safety**

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36 415 As this study is recruiting healthy volunteers only, an a-priori agreement has been reached with the

37
38 416 Sponsor that safety reporting is not required. Sponsor procedures in respect of incidental (i.e.

39
40 417 unexpected) findings in healthy volunteers will be adhered to and results captured within the Trust's

41
42 418 Clinical Record.

43
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45 419 Monitoring against Source Data will not be required which is in line with the Sponsor's policy on

46
47 420 non-CTIMP trials.

48
49
50 421 **Trial funding, organisation and administration**

51
52 422 The study has been awarded funding by MRC NIHR EME (Efficacy and Mechanism Evaluation)

53
54 423 Awards Body (NIHR EME Project ID: 16/68/34). In addition, the Department of Radiology has agreed

55
56 424 to fund the cost of HV WB-MRI scans. The cost of recruitment and consenting of HVs will be

57
58 425 requested through the NHS Clinical Research Network. RMH is the study sponsor responsible for

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2
3 426 initiating and managing the study and the coordinating centre, including sign-off of the study
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5 427 protocol.

6
7
8 428 A Trial Management Group (TMG) meeting will be held regularly to ensure satisfactory progress of
9
10 429 the study. A Trial Steering Committee (TSC) will provide independent oversight for the study, review
11
12 430 the development of the ML algorithm, and advise the TMG where problems may arise. The TSC will
13
14 431 include a Patient Advocate.

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18 432

19 433 **Ethics and dissemination**

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21
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23 434 Ethical approval for MALIMAR was granted on 21/11/2017 (REC) and 21/12/2017 (HRA) Here, we
24
25 435 report version 3.0 of the protocol. All participating sites gained local approval prior to study
26
27 436 participation.

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29
30 437 Any protocol modifications will be submitted for approval to the REC, reflected in the online
31
32 438 registration and disseminated by e-mail to site principal investigators and trial coordinators. The
33
34 439 statistician will have access to the final linked trial dataset. There are no plans to provide public
35
36 440 access to the full protocol, participant-level data, or statistical code. The researchers aim to publish
37
38 441 results in a peer-reviewed journal and share via social media and conferences. Authorship will be
39
40 442 determined according to academic standards.

41 42 43 44 443 **Discussion**

45
46 444 This study aims to develop and validate a ML algorithm to augment the performance and efficiency
47
48 445 of the radiology reading process using WB-MRI. The results will show the impact of using the ML tool
49
50 446 and outcomes of the study will have implications for the application of ML with WB-MRI in myeloma
51
52 447 patients across the NHS. It is anticipated that feasibility analysis will follow the successful completion
53
54 448 of this study to pilot the implementation of the ML tool in a real-time prospective study prior to
55
56 449 future clinical setting.

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3 450 To avoid bias we ensure: 1) comparator and intervention tests are read by readers that are fully
4
5 451 blinded to the reference standard; 2) a mixture of cases with and without disease; 3) the reads will
6
7 452 be presented such that radiologists must read a mixture of cases without or with ML support during
8
9 453 each round of reading including a wash-out period. We will have unavoidable incorporation bias, as
10
11 454 the expert reference panel will use the MRI as part of the reference standard. The reference panel
12
13 455 will consist of a single person's opinion which is a limitation to our study. If resources had allowed,
14
15 456 the gold standard would have been to have two blinded opinions with a consensus panel in cases of
16
17 457 disagreement. Other limitations include varying scan quality as data is acquired over a 9-year period;
18
19 458 and replicating clinical reporting in a retrospective study setting can be challenging.
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21
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24 459 In conducting this study, we will have acquired possibly the largest set of characterised myeloma
25
26 460 patient MRI scans in the UK and we anticipate this will form the basis of a unique training resource in
27
28 461 the future.
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30

31 462 Machine learning techniques in WB-MRI scans of patients with myeloma is likely to be transferable
32
33 463 to other malignancies. In prostate and breast cancer, quantification of metastatic bone disease is an
34
35 464 unmet need as bone only disease is not uncommon and is currently classified as non-measurable by
36
37 465 RECIST 1.1 (22). The participating HVs will be consented to allow the anonymised datasets to be a
38
39 466 future resource for the wider research community.
40
41
42

43 467 **Study status**

44
45 468 The MALIMAR study opened on 26 April 2018 using protocol version 1.0 (30 Oct 2017). The study
46
47 469 was in phase II, using protocol version 3.0 (31 Jan 2019), at date of submission. Protocol
48
49 470 amendments are documented in Supplementary S4.
50

51 471

52 472 **Author contributions:**

53
54
55 473 AR, CM, TaB, BG, SW, TQ, ThB, SD, ML, MK and DK conceptualization and methodology; AR,
56
57 474 CM, TaB, ThB, MK, BG, TQ, XF and SW investigation; EA and AR resources; ThB and SD data
58
59 475 curation; LP and EG formal analysis; AR, DK and CM supervision; LP writing – original draft; AR,
60

1
2
3 476 CM, TaB, BG, LW and LP writing – review and editing; BG, TQ, XF and SW data visualisation; LW
4
5 477 project administration; EA and AR funding acquisition.
6
7

8 478 **Competing interests:**
9

10
11 479 AR receives honoraria for educational lecture at Garmisch International Symposium, has an unpaid
12
13 480 role on the European Society of Radiology Board of Directors and receives travel cost support where
14
15 481 necessary. BG receives grants from other entities; EU commission and UKRI London Medical Imaging
16
17 482 & Artificial Intelligence Centre for Value Based Healthcare, is a Scientific advisor for Kheiron Medical
18
19 483 Technologies (Jan 2018 – Sep 2021) and receives stock options as part of standard employment
20
21 484 packages from both Kheiron Medical Technologies and HeartFlow. EA has a patent pending for
22
23 485 Machine Learning in Alzheimer’s disease and has a role on the scientific advisory board for
24
25 486 Radiopharm Theranostics Limited. MK receives grants from both Myeloma UK and Celgene/BMS,
26
27 487 and consulting fees or payments from AbbVie, BMS/Celgene, Janssen, GSK, Karyopharm, Takeda and
28
29 488 Seagen. CM receives additional funding as a co-investigator on a radiology NIHR study and is part of
30
31 489 the joint venture Celescan with the Royal Marsden, The Institute of Cancer Research and Sopra
32
33 490 Steria. TB receives additional funding from CRUK grant funding (NCITA) and NIHR (HTA) and receives
34
35 491 honoraria from Bayer.
36
37
38
39

40
41 492 **Funding:**
42

43
44 493 This study (ID: 16/68/34) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an
45
46 494 MRC and NIHR partnership. In addition, the Department of Radiology has agreed to fund the cost of
47
48 495 healthy volunteer whole body MRI scans. The cost of recruitment and consenting of healthy
49
50 496 volunteers will be requested through the NHS Clinical Research Network. The views expressed in this
51
52 497 publication are those of the authors and not necessarily those of the MRC, NHS, the NIHR, or the
53
54 498 Department of Health and Social Care.
55
56

57
58 499 EG and LP’s posts are part funded by the National Institute for Health and Care Research (NIHR)
59
60 500 Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer

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3 501 Research, London. The views expressed are those of the author(s) and not necessarily those of the
4
5 502 NIHR or the Department of Health and Social Care.
6
7
8 503 SW is supported by the UKRI London Medical Imaging & Artificial Intelligence Centre for Value Based
9
10 504 Healthcare.

11
12
13 505 **Data sharing statement:**

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15
16 506 Anonymised data are available upon reasonable request as a resource for the wider research
17
18 507 community from Andrea Rockall (ORCID ID: 0000-0001-8270-5597), providing consent has been
19
20 508 granted from all participants.

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22
23 509 **References**

- 24
25 510 1. NICE. Myeloma: diagnosis and management NICE guideline [NG35]. 2016.
26
27 511 2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International
28 512 Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The lancet*
29 513 *oncology*. 2014;15(12):e538–48.
30
31 514 3. Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, et al. Role of
32 515 magnetic resonance imaging in the management of patients with multiple myeloma: a
33 516 consensus statement. 2015;
34
35 517 4. Pearce T, Philip S, Brown J, Koh DM, Burn PR. Bone metastases from prostate, breast and
36 518 multiple myeloma: differences in lesion conspicuity at short-tau inversion recovery and
37 519 diffusion-weighted MRI. *Br J Radiol*. 2012;85(1016):1102–6.
38
39 520 5. Squillaci E, Manenti G, di Stefano F, Miano R, Strigari L, Simonetti G. Diffusion-weighted MR
40 521 imaging in the evaluation of renal tumours. *Journal of Experimental and Clinical Cancer*
41 522 *Research*. 2004;23(1):39–46.
42
43 523 6. Dutoit JC, Vanderkerken MA, Anthonissen J, Dochy F, Verstraete KL. The diagnostic value of
44 524 SE MRI and DWI of the spine in patients with monoclonal gammopathy of undetermined
45 525 significance, smouldering myeloma and multiple myeloma. *Eur Radiol*. 2014;24(11):2754–65.
46
47 526 7. Messiou C, Hillengass J, Delorme S, Lecouvet FE, Moulopoulos LA, Collins DJ, et al. Guidelines
48 527 for acquisition, interpretation, and reporting of whole-body MRI in myeloma: myeloma
49 528 response assessment and diagnosis system (MY-RADS). *Radiology*. 2019;291(1):5–13.
50
51 529 8. Wu L, Gu H, Zheng J, Xu X, Lin L, Deng X, et al. Diagnostic value of whole-body magnetic
52 530 resonance imaging for bone metastases: a systematic review and meta-analysis. *Journal of*
53 531 *Magnetic Resonance Imaging*. 2011;34(1):128–35.
54
55 532 9. Messiou C, Porta N, Sharma B, Levine D, Koh DM, Boyd K, et al. Prospective evaluation of
56 533 whole-body MRI versus FDG PET/CT for lesion detection in participants with myeloma.
57 534 *Radiology: Imaging Cancer*. 2021;3(5).

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3 535 10. Pawlyn C, Fowkes L, Otero S, Jones JR, Boyd KD, Davies FE, et al. Whole-body diffusion-
4 536 weighted MRI: a new gold standard for assessing disease burden in patients with multiple
5 537 myeloma? *Leukemia*. 2016;30(6):1446–8.
- 7 538 11. Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, Corral LL, et al. Lenalidomide
8 539 plus Dexamethasone for High-Risk Smoldering Multiple Myeloma. *New England Journal of*
9 540 *Medicine*. 2013 Aug;369(5):438–47.
- 11 541 12. Padhani AR, Koh DM, Collins DJ. Whole-body diffusion-weighted MR imaging in cancer:
12 542 current status and research directions. *Radiology*. 2011;261(3):700–18.
- 14 543 13. Radiologists RC of. Clinical radiology UK workforce census 2015 report. The Royal College of
15 544 Radiologists London; 2016.
- 17 545 14. Juntu J, Sijbers J, de Backer S, Rajan J, van Dyck D. Machine learning study of several
18 546 classifiers trained with texture analysis features to differentiate benign from malignant
19 547 soft-tissue tumors in T1-MRI images. *Journal of Magnetic Resonance Imaging: An Official*
20 548 *Journal of the International Society for Magnetic Resonance in Medicine*. 2010;31(3):680–9.
- 22 549 15. Pauly O, Glocker B, Criminisi A, Mateus D, Möller AM, Nekolla S, et al. Fast multiple organ
23 550 detection and localization in whole-body MR Dixon sequences. In: *International Conference*
24 551 *on Medical Image Computing and Computer-Assisted Intervention*. Springer; 2011. p. 239–47.
- 26 552 16. Lavdas I, Rockall AG, Castelli F, Sandhu RS, Papadaki A, Honeyfield L, et al. Apparent diffusion
27 553 coefficient of normal abdominal organs and bone marrow from whole-body DWI at 1.5 T: the
28 554 effect of sex and age. *American Journal of Roentgenology*. 2015;205(2):242–50.
- 30 555 17. Lavdas I, Glocker B, Rueckert D, Taylor SA, Aboagye EO, Rockall AG. Machine learning in
31 556 whole-body MRI: experiences and challenges from an applied study using multicentre data.
32 557 *Clin Radiol*. 2019;74(5):346–56.
- 34 558 18. Lavdas I, Glocker B, Kamnitsas K, Rueckert D, Mair H, Sandhu A, et al. Fully automatic,
35 559 multiorgan segmentation in normal whole body magnetic resonance imaging (MRI), using
36 560 classification forests (CF s), convolutional neural networks (CNN s), and a multi-atlas (MA)
37 561 approach. *Med Phys*. 2017;44(10):5210–20.
- 39 562 19. Giles SL, Desouza NM, Collins DJ, Morgan VA, West S, Davies FE, et al. Assessing myeloma
40 563 bone disease with whole-body diffusion-weighted imaging: comparison with x-ray skeletal
41 564 survey by region and relationship with laboratory estimates of disease burden. *Clin Radiol*.
42 565 2015;70(6):614–21.
- 43 566 20. Giles SL, Messiou C, Collins DJ, Morgan VA, Simpkin CJ, West S, et al. Whole-body diffusion-
44 567 weighted MR imaging for assessment of treatment response in myeloma. *Radiology*.
45 568 2014;271(3):785–94.
- 47 569 21. Valindria V v, Lavdas I, Bai W, Kamnitsas K, Aboagye EO, Rockall AG, et al. Reverse
48 570 classification accuracy: predicting segmentation performance in the absence of ground truth.
49 571 *IEEE Trans Med Imaging*. 2017;36(8):1597–606.
- 51 572 22. Lecouvet FE, Talbot JN, Messiou C, Bourguet P, Liu Y, de Souza NM, et al. Monitoring the
52 573 response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear
53 574 medicine techniques: a review and position statement by the European Organisation for
54 575 Research and Treatment of Cancer imaging group. *Eur J Cancer*. 2014;50(15):2519–31.

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577 **Figure 1: MALIMAR Study Flow Diagram**

For peer review only

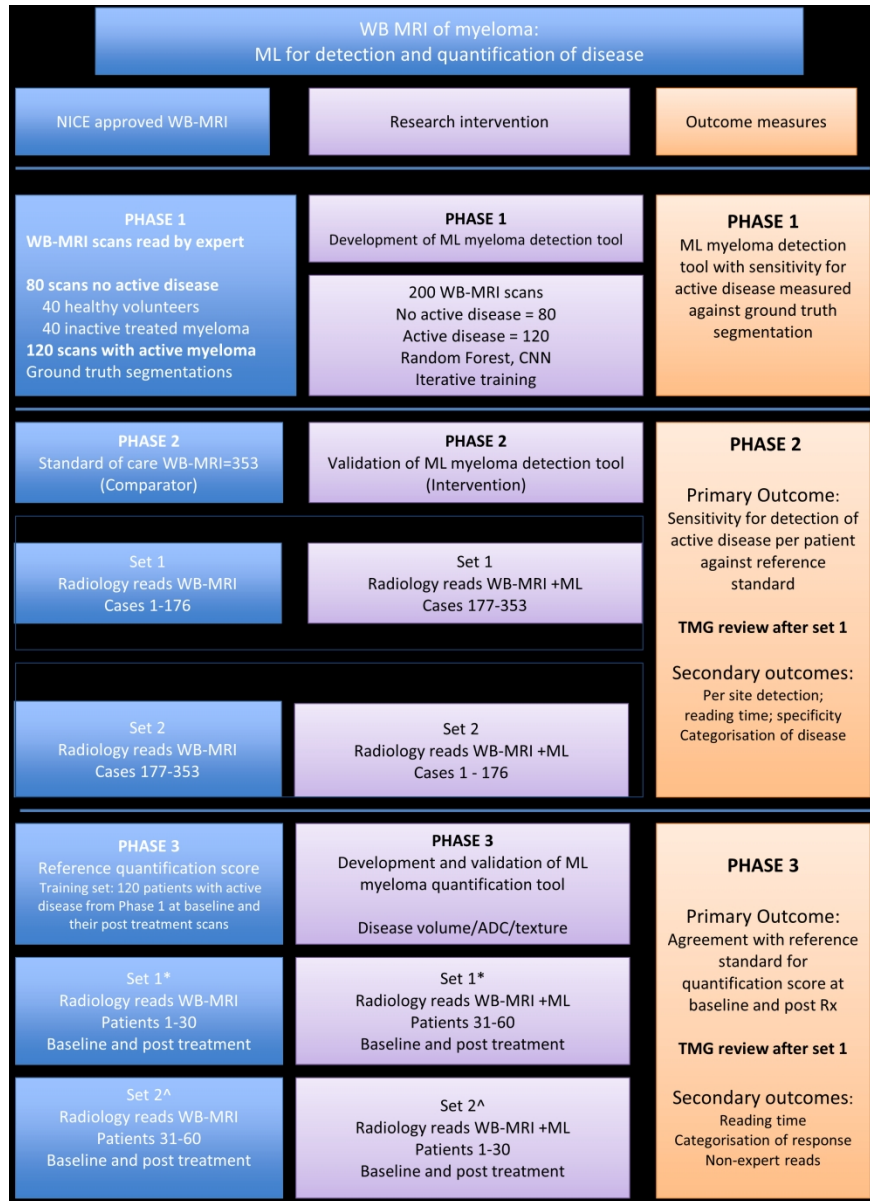


Figure 1: Study Flow Chart

526x723mm (130 x 130 DPI)

The MALIMAR Study Healthy Volunteer Consent Form

Study Reference Numbers: CCR 4820: IRAS No.: 233501

NHS No.

Healthy volunteer Trial ID:

Name of Lead Researcher:

Please initial box

- 1. I confirm that I have read and understand the Healthy Volunteer Information Sheet version 2.0 dated 07/12/18 for the above study and have had the opportunity to ask questions.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3. If I request withdrawal from the study, I give permission that my data already collected within the study can be anonymised and used.
- 4. I understand that relevant sections of my medical notes may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
- 5. I consent to undergo an MRI scan under the supervision of the responsible clinician for this research. I understand that if any health related issues come to light as a result of undergoing this scan, otherwise known as 'incidental findings', that I and my General Practitioner will be promptly informed of these issues.
- 6. I agree to participate in the MALIMAR study.
- 7. I give permission for the data collected during the study to be used in further ethically approved research within and outside the UK in the field of imaging research. I understand this will not include any personal data from which I could be identified.

Name of Healthy Volunteer	Date	Signature
Name of person taking consent (PI or approved signatory)	Date	Signature

Original for Investigator's Site File; 1 copy for volunteer; 1 copy for hospital notes; 1 copy to be sent to RM-CTU

MALIMAR (CCR 4820, IRAS: 233501)

The ROYAL MARSDEN
NHS Foundation Trust

MALIMAR

Healthy Volunteer Information Sheet

Development of machine learning support for reading whole body diffusion weighted magnetic resonance imaging (WB-DW-MRI) in myeloma for the detection and quantification of the extent of disease before and after treatment.

Short Title: MAchine Learning In MyelomA Response

7th December 2017

Version 2.0

CCR Number: 4820

IRAS (Integrated Research Application System) No. 233501

You are being invited to take part in a research study. Before you decide whether or not to take part it is important for you to understand why we are doing this research and what it involves. Please take time to read the following information carefully and discuss it with relatives, friends, and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time deciding whether or not you wish to take part.

You can learn more about clinical research on the Cancer Research UK's patient website (www.cancerhelp.org.uk)

MALIMAR (CCR 4820, IRAS: 233501)

Invitation

If you are 40 years or above the Radiology Department at the Royal Marsden hospital would like to invite you to take part in a research study. This will involve you having a particular type of Magnetic Resonance Imaging (MRI) scan known as a Whole-Body Diffusion Weighted MRI scan or 'WB-DW-MRI'.

Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Thank you for reading this Information Sheet.

What is the purpose of the study?

There have been enormous advances in recent years in the technology used to take pictures (images) of the internal anatomy of cancer patients to better identify sites of disease. These images (or scans) can now provide a more accurate indication of the scope or spread of disease. They can also be used for assessing disease response to different drugs or treatments.

MRI (magnetic resonance imaging) has the advantage over other types of scanning (e.g. computerised tomography or 'CT') in that it does not involve the delivery of any radiation dose. In particular, a new type of MRI, called Whole Body Diffusion Weighted MRI (WB-DW-MRI) can provide especially precise images of diseased compared to healthy tissues. As a result, it is now being more widely used in cancer treatment centers throughout the world.

Despite these advantages, WB-DW-MRI has an important disadvantage. Each scan is made up from over a thousand images, each of which needs to be read and interpreted by an expert Radiologist. Thus, the time taken to read a single WB-DW-MRI scan is much longer than for a normal MRI scan, meaning that few NHS treatment centres (or hospitals) are able to offer them to patients.

MALIMAR (CCR 4820, IRAS: 233501)

Members of the research team from the Royal Marsden Hospital and Imperial College London have already undertaken some work to ascertain how computers can reduce the time taken to read WB-DW-MRI scans. The technique is called 'machine learning' and basically teaches a computer to detect areas of suspicion or concern for disease on WB-DW-MRI scans. The 'trained' computer can then make an initial and very rapid interpretation of the images taken during a scan. These images can then be presented to the expert radiologist to make the final interpretation. In addition to training computers to read scans more quickly, we also want to train computers to interpret differences between scans taken from the same patient at different time-points. This will allow us to accurately assess change in disease extent or response to treatment over time.

However, in order to train the computers, we need examples of WB-DW-MRI images taken from both diseased (cancerous) and healthy tissues. In this study we are concentrating on patients with myeloma (cancer of white blood cells). We have already acquired WB-DW-MRI images from many patients with this type of cancer. **So now, we are seeking your help to acquire WB-DW-MRI images from healthy tissues for the Machine Learning In MyelomA Response (MALIMAR) study.**

What will happen to me if I decide that I would like to take part?

Before we can enter you to the study, we will need to check that you can have an MRI scan and that you are suitable to take part. Some people cannot have an MRI scan. These include people with a pacemaker, metal heart valves, aneurysm clips in the brain or people who have had metal fragments in their eyes. In addition, we are unable to include volunteers who have had or have a significant illness as this may affect the scan.

It may also not be appropriate for you to take part if you have had extensive surgery previously. Our study researcher will confirm these points with you before you are admitted to the trial. As advised above we are only recruiting volunteers aged 40 and above: anyone under this age will have to be

MALIMAR (CCR 4820, IRAS: 233501)

1
2
3 excluded from participating because they will not be a suitable comparator.
4
5 Once we have confirmed that you are suitable to enter the trial, we will ask
6
7 you to sign an Informed Consent Form and then book your scan. Some
8
9 volunteers may be asked to attend early evening or week-end appointments
10
11 to avoid busy times during the day when the MRI Unit is reserved for patients.
12
13 There are usually no special preparations and no injection or drugs will be
14
15 given. All instructions for the scan will be in your MRI appointment letter.
16
17 When you come for the scan you are advised to wear clothing without metal
18
19 fastenings and to avoid using make-up or mascara. You can wear glasses,
20
21 but will need to take these off during the scan. A locker will be provided for
22
23 your valuables.

24
25 The MRI scan will be carried out by radiographers who are trained to carry out
26
27 the scans. MRI uses a magnetic field and radio waves to build up detailed
28
29 images of your internal anatomy by detecting signals sent out by water
30
31 molecules. It is not painful, but you will have to lie still for the duration of the
32
33 scan which can be up to 60 minutes. The scanner produces a variety of loud
34
35 noises during the scan which are made by the magnetic coils that switch on
36
37 and off during the scan. These are important in measuring the signals from
38
39 your body to create the images. They are switched on and off very quickly and
40
41 they vibrate, which is what causes the noise.

42
43 Some people may find the noise level uncomfortable and the table quite hard
44
45 to lie on. You will be provided with earplugs to help reduce the noise. The
46
47 scanner is open at both ends, but some people may find it claustrophobic.
48
49 During the scan the radiographer can see you from the control room and can
50
51 talk to you through an intercom. You will be given a call button to press to
52
53 alert attention and can listen to music during the scan. You can leave as soon
54
55 as your scan is finished and can eat and drink as normal. There are no side
56
57 effects from the MRI scan itself.

Why am I being invited to take part?

MALIMAR (CCR 4820, IRAS: 233501)

You will be reading this Information Sheet because you have responded to one of our advertisements for Healthy Volunteers to take part. If we invite you to sign a Consent Form then you are eligible to take part in the study. If you are not eligible to participate we will explain the reason.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do choose to take part you will be asked to sign a consent form, a copy of which will be given to you for your records along with this information sheet about the study. Your legal rights are not affected by participation in the study.

What happens if I change my mind during the study?

Your participation in this study is entirely voluntary. If you agree to take part and then change your mind and wish to withdraw, you may do so at any time. If you decide to not join the study or to discontinue in the study, this will not affect any future care or treatment you receive.

What are the risks and the benefits of taking part in this study?

A possible risk in taking part is a degree of discomfort you may encounter in undergoing the MRI scan. As we said above, unlike other forms of imaging (e.g. CT scans) MRI does not deliver radiation and no drugs or other medication will be given. You will be registered on the Royal Marsden Hospital Information System and a report of your scan results will be held on this system. If an unexpected finding of concern is discovered, a doctor will call you to discuss your scan report. We will also send a copy of the report to your GP who will then advise you regarding any follow-up investigations that may be needed. This could lead to some anxiety. If unexpected findings are discovered which are not concerning, we will send you a letter to explain the findings and copy this letter to your GP. You may then wish to call us or your GP for more information. If there are no unexpected findings we will not contact you or your GP.

MALIMAR (CCR 4820, IRAS: 233501)

In general, the research will not be of direct benefit to you, but may prove to be of benefit to others in the future. However, possible benefits are that you may find it satisfying to have contributed to medical research and, should an unexpected finding be discovered you may feel that the early detection and diagnosis will result in a better outcome. If you wish to have a copy of your scan report, you may ask for this.

What if something goes wrong?

It is unlikely that anything will go wrong but, if you wish to complain, you can do so using the normal NHS complaints procedure. If taking part harms you in any way, there are no special compensation arrangements, but the hospital would be liable for any negligence on the part of hospital staff. Your legal rights are not affected by giving your consent to participate in this study.

Who is organizing and funding the research?

This study is being organised by The Royal Marsden NHS Foundation Trust with participation from The Institute of Cancer Research, Imperial College London and Imperial Healthcare NHS Foundation Trust. The study is being funded by a National Institute for Health Research grant as part of their Efficacy and Mechanism Evaluation programme.

Will my taking part in this study be kept confidential?

1) Clinical Information: You will need to be given a Royal Marsden hospital number in order to receive the WB-DW-MRI scan. The resulting scan report will be held on our clinical Hospital Information (NHS PACS) System which is the system we use for holding all NHS patient information. Access to this system is subject to the normal Trust-based information governance controls. If, in the event of unexpected findings, you require further diagnostic investigations, your GP will be informed and your scans and accompanying data will be made available to the hospital treating you.

MALIMAR (CCR 4820, IRAS: 233501)

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5 **2) Research Information:** Your scan data will be anonymised and identified
6 by a unique trial identification number. Your unique trial number will be used
7 to make sure you cannot be identified by members of the research team that
8 are not part of the NHS staff at RMH. The data from your scan which will be
9 used in the MALIMAR study will only be available to authorised members of
10 our research team so they can collect information needed for this research
11 study and also to check that it is correct. All information will be kept
12 confidential, and your name, date of birth and other identifiable information will
13 be removed from your scans prior to archiving. We will also ask you to
14 consent to allow your data that has been collected in the study to be sent
15 outside of the UK and to be used in future ethically approved studies. This
16 information will not include any personal information that could directly identify
17 you.
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What will happen to the results of this study?

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32 As soon as there are reliable results, they will be published in a respected
33 peer reviewed medical journal and presented in various scientific meetings.
34 Your identity will not be revealed in any report, publication or presentation.
35 The results will be available on request.
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How is the trial monitored for safety?

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44 This study has been carefully planned by leading cancer specialists and
45 approved by the Oxford C Research Ethics Committee (REC), the Royal
46 Marsden Hospital Committee for Clinical Research (CCR) and the Health
47 Research Authority (HRA). The members of the study team will be meeting at
48 regular intervals to monitor the progress and safety of the study. Full (100%)
49 monitoring will be carried out to ensure that where incidental findings come to
50 light, both you and your GP are promptly informed.
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MALIMAR (CCR 4820, IRAS: 233501)

What do I do now?

We would be happy to answer any questions you may have about the study. You can telephone us, or speak to us again. Please discuss this information with your family, friends or your GP if you wish. If you require further information about this study please contact:

Professor Andrea Rockall,
Chief Investigator,
Clinical Chair Radiology,
ICTEM Building,
Imperial College Healthcare HNS Trust,
Du Cane Road
London, W12 0NN
Tel: 0207 59 42792 (Personal Assistant to Professor Rockall)

Dr Christina Messiou,
Principal Investigator,
Consultant Radiologist,
The Royal Marsden NHS Foundation Trust,
Fulham Road
London, SW3 6JJ
Tel: 0208 661 3216

Veronica Morgan
MRI Research Superintendent Radiographer
Clinical Magnetic Resonance Unit, Sutton
The Royal Marsden NHS Foundation Trust
Tel 02089156493

Thank you for reading and considering taking part in this study.

Funding Acknowledgement: Funding from the National Institute for Health Research – Efficacy and Mechanism Evaluation (NIHR – EME) programme for the MALIMAR study is acknowledged.

MALIMAR (CCR 4820, IRAS: 233501)

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For peer review only

Participant Type	Study name	Site	MRI Machine Name	Sequences acquired
Healthy Volunteers	MALIMAR	Royal Marsden	Siemens Aera	Haste localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_CAIPi_wb_tra_BH_20 and T2 HASTE Vertex to knees
Healthy Volunteers	MALIMAR	Royal Marsden	Siemens Avanto	localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_vibe_dixon_TRA_15deg 256_pocS and T2 HASTE Vertex to knees
Myeloma Patients	MALIMAR	Royal Marsden	Siemens Aera	Haste localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_CAIPi_wb_tra_BH_20 and Vertex to knees
Myeloma Patients	MALIMAR	Royal Marsden	Siemens Avanto	localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and fl3d_vibe_dixon_TRA_15deg 256 Vertex to knees
Myeloma Patients	MALIMAR	ICHT	Siemens Aera	Axial dixon's x 4 350 slices each (total: 1400) B 50 248 slices B900 248 slices ADC 248 slices Sag T1 spine 15 slices Sag T2 spine 15 slices

MALIMAR Radiology Reads - CRF

Phase 2

Version 4, 06 September 2021

* Required

1. Scan ID *

2. Reader ID *

3. Round *

Round 1

Round 2

4. Date of Read *

Please input date (dd/MM/yyyy)



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5. Start time of read - Enter in format: HH:MM using 24 hour clock *

6. Disease status - BONES - Record Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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7. Disease status - BONES - Record maximum size of Active / Focal lesions (mm) *

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones (max. long axis)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae (max. long axis)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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8. Disease Status - BONES - How confident are you in your assessment of Active / Focal lesions *

	Not at all confident	Some confidence	Confident	Very Confident
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. Disease Status - Record if diffuse disease was present at any of these sites?

*

	Yes	No
Cervical Spine	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>

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10. How confident were you in your assessment of diffuse disease at these sites? *

	Not at all confident	Some confidence	Confident	Very confident
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

11. Was extramedullary disease present at any site? *

Yes

No

12. If extramedullary disease was present at any site - state location(s) separated by a semi-colon

1
2
3 13. If extramedullary disease was present, what was your level of confidence in
4 assessing this? *

- 5
6
7 Not confident at all
8
9 Some confidence
10
11 Confident
12
13 Very confident
14
15 Not Applicable, no extramedullary disease is seen.
16
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22 14. Confidence in assessing overall disease status on this scan (i.e. in
23 determining the presence or absence of ANY active disease) *

- 24
25
26 Not confident at all
27
28 Some confidence
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30 Confident
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32 Very confident
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40 15. Stop time of read - RECORD IMMEDIATELY AFTER COMPLETING CLINICAL
41 READ - Enter in format: HH:MM using 24 hour clock *

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51 16. TO BE COMPLETED FOLLOWING THE CLINICAL READ:
52 Was a Machine Learning Image available *

- 53
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55 Yes
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57 No
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17. If a Machine Learning 'ML' Image was available, please indicate whether sites were positive for active / focal disease, i.e. was there an ML finding?

	Highly likely negative on ML	Probably negative on ML	Probably positive on ML	Highly likely positive on ML
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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3 18. If a Machine Learning 'ML' image was available, please indicate whether
4 sites were positive for diffuse disease, i.e. was there an ML finding?
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	Highly likely negative on ML	Probably negative on ML	Probably positive on ML	Highly likely positive on ML	
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
	Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

19. Scan Quality: What was the quality of the WB-MRI used for this read? *

	Good	Adequate	Poor
1. B 900	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. ADC	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. T1 sequences	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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3 20. Please enter any specific comments you have on scan quality
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14 21. Reader confirmation: My responses have been accurately reported on this
15 CRF (enter 'yes' if in agreement with this statement) *

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18 Yes

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29 This content is neither created nor endorsed by Microsoft. The data you submit will be sent to the form
30 owner.
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MALIMAR Radiology Reads - CRF

Phase 3

Version 2, 31 March 2022

* Required

1. Scan ID Post Treatment Scan (PT) *

2. Scan ID - Baseline Scan (BL) *

3. Reader ID *

4. Phase 3 - Round *

Round 1

Round 2

5. Date of Read *



Format: M/d/yyyy

6. Start time of read - Enter in format: HH:MM using 24 hour clock *

7. CERVICAL SPINE - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

8. CERVICAL SPINE - Maximum size (mm) of Active / Focal Lesions *

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. CERVICAL SPINE - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

10. DORSAL SPINE - Number of Active / Focal Lesions *

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	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

11. DORSAL SPINE - Maximum size (mm) of Active / Focal Lesions *

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

12. DORSAL SPINE - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

13. LUMBAR SPINE - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

14. LUMBAR SPINE - Maximum size (mm) of Active / Focal Lesions *

				Not Applicable, No Focal lesions seen at this site
	<10mm	10 - 20mm	>20mm	
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

15. LUMBAR SPINE - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

16. PELVIS - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

17. PELVIS - Maximum size (mm) of Active / Focal Lesions *

				Not Applicable, No Focal lesions seen at this site
	<10mm	10 - 20mm	>20mm	
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

18. PELVIS - Was Diffuse Disease present? *

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Yes

No

Post Treatment

Baseline

19. LONG BONES - Number of Active / Focal Lesions *

0

1 - 4

5 - 10

>10

Post Treatment

Baseline

20. LONG BONES - Maximum size (mm) of Active / Focal Lesions *

<10mm

10 - 20mm

>20mm

Not Applicable,
No Focal lesions
seen at this site

Post-Treatment

Baseline

21. LONG BONES - Was Diffuse Disease present? *

Yes

No

Post Treatment

Baseline

22. SKULL - Number of Active / Focal Lesions *

		0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

23. SKULL - Maximum size (mm) of Active / Focal Lesions *

		<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

24. SKULL - Was Diffuse Disease present? *

		Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

25. RIBS / CLAVICLES / STERNUM / SCAPULAE - Number of Active / Focal Lesions *

		0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

26. RIBS / CLAVICLES / STERNUM / SCAPULAE - Maximum size (mm) of Active / Focal Lesions *

Not Applicable,
No Focal lesions
seen at this site

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

27. RIBS / CLAVICLES / STERNUM / SCAPULAE - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

28. Was extramedullary disease present at any site? *

Yes

No

29. If extramedullary disease was present at any site - state location(s) separated by a semi-colon

30. If extramedullary disease was present, what was your level of confidence in assessing this? *

- 1
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4 Not confident at all
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6 Some confidence
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8 Confident
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11 Very confident
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14 Not Applicable, no extramedullary disease is seen.
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20 31. OVERALL RESPONSE - Change in Disease Status (Baseline - Post-Treatment) *

- | | Complete Response | Partial Response | Stable Disease | Disease Progression |
|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Response category | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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33 32. OVERALL RESPONSE - CONFIDENCE - How confident were you in assessing overall response? *

- | | Not at all confident | Some confidence | Confident | Very confident |
|---------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Confidence category | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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47 33. Stop time of read - RECORD IMMEDIATELY AFTER COMPLETING CLINICAL READ -
48 Enter in format: HH:MM using 24 hour clock *
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34. TO BE COMPLETED FOLLOWING THE CLINICAL READ:

Was a Machine Learning Image available *

Yes

No

35. If Machine Learning 'ML' Images were available, please indicate category of response suggested by ML

	Complete Response	Partial Response	Stable Disease	Progressive Disease
Response category	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

36. Scan Quality: What was the quality of the WB-MRI used for this read? *

	Good	Adequate	Poor
1. B 900	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. ADC	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. T1 sequences	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

37. Please enter any specific comments you have on scan quality

38. Reader confirmation: My responses have been accurately reported on this CRF (enter 'yes' if in agreement with this statement) *

Yes

No

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Supplementary S4 – MALIMAR Amendments

No. and Type of Amendment	Date approved	Brief Details of amendment
1. Non-substantial	25/06/2018	Protocol administrative updates
2. Non-substantial	15/01/2019	Communications to HVs
3. Non-substantial	19/03/2019	Update on scan numbers for protocol
4. Non-substantial	16/10/2019	Addition of ICHT site
5. Non-substantial	28/06/2019	Extension of project time-line and uplift in costs

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SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: <http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/>

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item		Page and Line Number	Reason if not applicable
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line 1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 7, line 141
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a Not a RCT
Protocol version	#3	Date and version identifier	Page 22, line 488

1 2 3 4 5 6 7 8 9	Funding	#4	Sources and types of financial, material, and other support	Page 4, line 71	
10 11 12 13 14	Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 4, line 65	
15 16 17 18 19 20 21 22 23	Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 4, line 86	
24 25 26 27 28 29 30 31 32 33	Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 4, line 86 Page 20, line 452	
34 35	Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 20, line 440	
Introduction					
36 37 38 39 40 41 42 43 44	Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 8, line 156	

1 2 3 4 5	Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 9, line 181 - 191	
6 7	Objectives	#7	Specific objectives or hypotheses	Page 9, line 191	
8 9 10 11 12 13 14 15	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 9, line 199 Page 12 line 254	
16	Methods: Participants, interventions, and outcomes				
17 18 19 20 21 22 23 24	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 10, line 216	
25 26 27 28 29 30 31	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 10-11, line 221-228 and Table 1	
32 33 34 35 36	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11, line 229	
37 38 39 40 41 42 43	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a	No modifications

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1 2 3 4 5 6	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a	No strategies or monitoring of adherence
7 8 9 10	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a	Use of scans only
11 12 13 14 15 16 17 18 19 20 21 22	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 15, line 343	
23 24 25 26 27 28 29 30	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and Table 3	Schedule and assessment of scans rather than participants
31 32 33 34 35 36 37 38	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 16, lines 366	
39 40 41 42 43 44	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 12, line 271 Page 13, line 285	

Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 10, lines 194-210	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 10, lines 200-210	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 14, line 316 Page 15, line 327	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 14, line 318 Page 21, line 470	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a	No blinding of intervention
Methods: Data collection, management, and analysis				

1 2 3 4 5 6 7 8 9 10 11 12 13	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 15, line 337	
14 15 16 17 18 19 20 21 22	Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a	No participant retention/follow-up
23 24 25 26 27 28 29 30 31	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 15, line 340	
32 33 34 35 36 37 38	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17, line 391-428	
39 40 41 42	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a	Primary and secondary analysis included only

1 2 3 4 5 6	Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 19, line 421	
7 8 9	Methods: Monitoring				
10 11 12 13 14 15 16 17 18 19 20 21	Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 19 line 433 – line 450	
22 23 24 25 26 27 28	Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page 18, line 396 Page 18, line 408	
29 30 31 32 33 34	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 19, line 433	No adverse event reporting as not an interventional study on participants. Specified in manuscript.
35 36 37 38 39 40	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 19, line 438	
41 42 43 44 45 46 47	Ethics and dissemination				

1 2 3	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 20, line 452	
4 5 6 7 8 9 10 11	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Page 20, line 456	
12 13 14 15 16 17	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 13, lines 272-279	
18 19 20 21 22	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a	No ancillary studies
23 24 25 26 27 28 29	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 20, line 458-461 Page 22, line 484	
30 31 32 33 34	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 5, line 102	
35 36 37 38 39 40 41 42 43 44 45 46 47	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 20, line 457-458	

1 2 3 4 5	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a	No participant level intervention
6 7 8 9 10 11 12 13 14 15 16	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 20, lines 457-461	
17 18 19 20	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 20, lines 457-461	
21 22 23 24 25	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 20, lines 457-461	
26 27	Appendices				
28 29 30 31 32	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material S1a, S1b	
33 34 35 36 37 38 39	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a	No biological specimens collected

It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-](#)

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BMJ Open

Development of machine learning support for reading whole body diffusion weighted magnetic resonance imaging (WB-MRI) in myeloma for the detection and quantification of the extent of disease before and after treatment (MALIMAR): protocol for a cross-sectional diagnostic test accuracy study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067140.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Aug-2022
Complete List of Authors:	Satchwell, Laura; Royal Marsden Hospital NHS Trust Wedlake, Linda; Royal Marsden Hospital NHS Trust Greenlay, Emily; Royal Marsden Hospital NHS Trust Li, Xingfeng; Imperial College London, Department of Cancer and Surgery Messiou, Christina; Royal Marsden Hospital NHS Trust; Institute of Cancer Research Glocker, Ben ; Imperial College London Department of Computing Barwick, Tara; Imperial College London, Department of Cancer and Surgery; Imperial College Healthcare NHS Trust, Department of Radiology Barfoot, Theodore; King's College London Doran, Simon; Institute of Cancer Research Leach, Martin O; Institute of Cancer Research Koh, Dow Mu; Royal Marsden Hospital NHS Trust; Institute of Cancer Research Sutton Kaiser, Martin; Institute of Cancer Research; Royal Marsden Hospital NHS Trust Winzeck, Stefan; Imperial College London Department of Computing Qaiser, Talha; Imperial College London Department of Computing Aboagye, Eric; Imperial College London Department of Surgery and Cancer ROCKALL, ANDREA; Imperial College London Department of Surgery and Cancer; Imperial College Healthcare NHS Trust, Department of Radiology
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Oncology
Keywords:	Myeloma < HAEMATOLOGY, Diagnostic radiology < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, ONCOLOGY

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3 1 Development of machine learning support for reading whole body diffusion weighted magnetic
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5 2 resonance imaging (WB-MRI) in myeloma for the detection and quantification of the extent of
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7 3 disease before and after treatment (MALIMAR): protocol for a cross-sectional diagnostic test
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9 4 accuracy study
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13 **Authors:**
14

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16
17 7 Tara Barwick^{3,4}; Theodore Barfoot⁵; Simon Doran⁶; Martin O Leach⁶; Dow Mu Koh^{1,6}; Martin Kaiser^{1,6};
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43 16 6532**
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58 23 Creative Commons licence will apply to this Work are set out in our licence referred to above.
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1
2
3 24 **Abbreviations:**
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6 25 **ADC:** Apparent Diffusion Coefficient
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9 26 **BRC:** Biomedical Research Centre
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12 27 **CCR:** Committee for Clinical Research
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15 28 **CPMS:** Central Portfolio Management System
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18 29 **CRF:** Case Report Form
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21 30 **CRN:** Clinical Research Network
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24 31 **CRUK:** Cancer Research UK
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27 32 **CT:** Computerised Tomography
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30 33 **CTIMP:** Clinical Trial of Investigational Medicinal Product
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33 34 **DWI:** Diffusion Weighted Imaging
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36 35 **EME:** Efficacy and Mechanism Evaluation
37

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39 36 **FDG:** Fluorodeoxyglucose
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42 37 **HV:** Healthy Volunteer
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45 38 **ICHT:** Imperial College Healthcare Trust
46

47
48 39 **ICR:** The Institute of Cancer Research
49

50
51 40 **ML:** Machine Learning
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54 41 **MM:** Multiple Myeloma
55

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57 42 **MRC:** Medical Research Council
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60 43 **MRI:** Magnetic Resonance Imaging

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3 44 **NHS:** National Health Service
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6 45 **NICE:** National Institute of Clinical Excellence
7
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9 46 **NIHR:** National Institute of Health Research
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12 47 **PET:** Positron Emission Tomography
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15 48 **PPI:** Patient and Public Involvement
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18 49 **REC:** Research Ethics Committee
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21 50 **sFLC:** serum Free Light Chain
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24 51 **TMG:** Trial Management Group
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27 52 **TSC:** Trial Steering Committee
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30 53 **WB-DW-MRI:** Whole Body Diffusion Weighted Magnetic Resonance Imaging
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33 54 **UKRI:** UK Research and Innovation
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36 55 **Acknowledgements:**
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38 56 We acknowledge NHS funding to the NIHR Biomedical Research Centre (BRC) at The Royal Marsden
39 and Institute of Cancer Research and the NIHR Royal Marsden Clinical Research Facility.
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42 58 We acknowledge the support of the Imperial College London NIHR BRC Imaging Theme and the
43 Cancer Research UK (CRUK) Imperial Centre and the Imaging Research Office at ICHT.
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46 59 We acknowledge the support of the CRUK funded National Cancer Imaging Translational Accelerator
47 award (Institute of Cancer Research and Imperial College London).
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50 61
51 62 **Availability of data and materials:**
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53

54 63 Not applicable.
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57 64 **Ethics approval and consent to participate:**
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3 65 The Royal Marsden NHS Foundation Trust is the study sponsor and responsible for initiating and
4
5 66 managing the study, for oversight of the conduct of the study including submission of financial
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7 67 returns to NIHR, for reporting trial progress in line with NIHR EME requirements, for submitting and
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10 68 co-ordinating amendments to the trial protocol and for oversight of closure and archiving of all trial
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12 69 materials. All publications must have the consent of the NIHR. The study protocol was reviewed by
13
14 70 the Royal Marsden NHS Foundation Trust and Institute of Cancer Research Combined Committee for
15
16 71 Clinical Research (CCR) and underwent proportionate review by the South Central – Oxford C
17
18 72 Research Ethics Committee in November 2017 (Integrated Research Application System Project ID:
19
20 73 233501) and the Health Research Authority. The study was also approved for Central Portfolio
21
22 74 Management System (CPMS) Portfolio adoption (CPMS ID: 36766). This research will be carried out
23
24 75 in accordance with the Declaration of Helsinki (1996). The study will be conducted in accordance
25
26 76 with the conditions of ethical approval. Participation is limited to Healthy Volunteers only. Before
27
28 77 participation all participants will be provided with a Healthy Volunteer Participation Sheet and will
29
30 78 give written informed consent.
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35 79 **Consent for publication:**

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38 80 Not applicable.
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41 81 **Protocol version:** 3.0 31/01/2019
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3 **83 Abstract:**
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6 **84 Introduction:** Whole-body MRI (WB-MRI) is recommended by the National Institute of Clinical
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8 **85** Excellence (NICE) as the first-line imaging tool for diagnosis of multiple myeloma. Reporting WB-MRI
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10 **86** scans requires expertise to interpret and can be challenging for radiologists who need to meet rapid
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12 **87** turn-around requirements. Automated computational tools based on machine learning (ML) could
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14 **88** assist the radiologist in terms of sensitivity and reading speed and would facilitate improved
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16 **89** accuracy, productivity and cost-effectiveness. The MALIMAR study aims to develop and validate a
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18 **90** ML algorithm to increase the diagnostic accuracy and reading speed of radiological interpretation of
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20 **91** WB-MRI compared to standard methods.
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24 **92 Methods and analysis:** This phase II/III imaging trial will perform retrospective analysis of previously
25
26 **93** obtained clinical radiology magnetic resonance imaging (MRI) scans and scans from healthy
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28 **94** volunteers obtained prospectively to implement training and validation of a machine learning
29
30 **95** algorithm. The study will comprise three project phases using approximately 633 scans to 1) train
31
32 **96** the ML algorithm to identify active disease; 2) clinically validate the ML algorithm; and 3) determine
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34 **97** change in disease status following treatment via a quantification of burden of disease in myeloma
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36 **98** patients. Phase 1 will primarily train the ML algorithm to detect active myeloma against an expert
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38 **99** assessment ('reference standard'). Phase 2 will utilise the ML output in the setting of radiology
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40 **100** reader study to assess the difference in sensitivity when using ML-assisted reading or human-alone
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42 **101** reading. Phase 3 will assess the agreement between experienced readers (with and without ML) and
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44 **102** the reference standard in scoring both overall burden of disease before and after treatment, and
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46 **103** response.
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52 **104 Ethics and dissemination:** MALIMAR has ethical approval from South Central – Oxford C Research
53
54 **105** Ethics Committee (REC Reference: 17/SC/0630). MALIMAR is funded by National Institute for
55
56 **106** Healthcare Research Efficacy and Mechanism Evaluation funding (NIHR EME Project ID: 16/68/34).
57
58 **107** Findings will be made available through peer-reviewed publications and conference dissemination.
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3 108 **Trial registration:** The study was registered at clinicaltrials.gov (NCT03574454) on 2 July 2018.
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6 109 **Strengths and limitations of this study:**
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- 9 110 • The MALIMAR study has the potential to acquire and characterise what is possibly the
10
11 111 largest set of myeloma WB-MRI scans in the UK.
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13 112 • The cross-sectional diagnostic accuracy design allows for retrospective analysis of previously
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15 113 obtained clinical radiology scans for training and validation of a ML algorithm.
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17 114 • This study will provide ML outputs that can be tested across the National Health Service in
18
19 115 live real-time clinical settings.
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22 116 • As data will be acquired over a long period of time, scan quality could vary.
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25 117 • Replicating clinical reporting in a retrospective study setting can be difficult to achieve,
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27 118 particularly for analysis of scan reading time.
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119 Introduction

120 There is strong evidence in the existing literature for the use of whole-body magnetic resonance
121 imaging (WB-MRI) in the management of patients with multiple myeloma. In 2016, the National
122 Institute of Clinical Excellence (NICE) made the recommendation of using WB-MRI as the first line
123 imaging tool for diagnosis, based on the literature(1). A consensus from the International Myeloma
124 Working Group agreed that identification of focal lesions more than 5mm on MRI should now be
125 used as an indication to treat (2,3). Evidence suggests that diffusion weighted (DW) WB-MRI (WB-
126 DW-MRI) is the most sensitive magnetic resonance technique for detecting marrow disease (4–8)
127 and superior to Fluorodeoxyglucose Positron Emission Tomography / Computerised Tomography
128 (FDG-PET/CT) for the detection of small sites of disease and diffuse infiltration (9,10). Therefore, WB-
129 MRI is increasingly being adopted at centres worldwide for patients with myeloma. Treatment of
130 high-risk patients is known to improve overall survival (11), therefore improved diagnostic accuracy
131 is likely to translate into improved patient selection for treatment and prolonged survival.

132 Despite the acknowledged benefits of WB-MRI for patients with myeloma, with publication of the
133 NICE guidance, one of the major concerns is how these complex scans can be reported by a
134 radiology workforce in crisis. Specificity of disease detection in the marrow is improved by viewing
135 source DW images alongside quantitative Apparent Diffusion Coefficient (ADC) maps. This allows
136 differentiation of active sites of disease with restricted diffusion from treated sites of disease and
137 vertebral haemangiomas which conversely return a very high ADC (12). Dixon images are also
138 integral to image interpretation and morphological imaging is also necessary to identify mechanical
139 complications of myeloma bone disease. Therefore, diagnostic accuracy is dependent on viewing
140 multiple imaging sequences (7) and typically over 1200 image slices per WB-MRI scan in order to
141 achieve whole body coverage. Consequently, reading time for the scans may be significant. At least
142 9% of UK radiology posts are unfilled (13) and in 2015 clinical radiology was placed on the national
143 shortage occupation list. The time-consuming process of reporting WB-MRI scans is a concern for

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3 144 radiologists who need to provide rapid turn-around with a high productivity to support the National
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5 145 Health Service (NHS). Automated computational tools based on machine learning (ML) could support
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7 146 reporting of these large datasets and facilitate translation of this valuable imaging technique into the
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9 147 NHS, not only in detecting active disease but also in identifying response to treatment. Ideally, a ML
10
11 148 algorithm would automatically detect and highlight suspicious regions and could reduce reading
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13 149 time. An accurate and automatic detection of pathology may also increase diagnostic accuracy.
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17 150 The possibility of using computer-assisted ML techniques has been considered in aiding
18
19 151 interpretation of complex imaging datasets (14–16). Current work in the EME NIHR (Efficacy and
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21 152 Mechanism Evaluation National Institute of Health Research) funded MALIBO study
22
23 153 (17,18)(13/122/01) has demonstrated fully automatic multi-organ segmentation using WB-MRI in
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25 154 healthy volunteers (HV) and ML detection of primary colorectal cancer and metastatic lesions.
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29 155 **Aim**

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32 156 The aim of the MALIMAR study is to develop and validate a Machine Learning (ML) algorithm to
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34 157 improve the sensitivity of radiologists to detect the presence and extent of active myeloma before
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36 158 and after treatment, with high reproducibility and reduced reading time (WB-MRI with ML, the
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38 159 intervention) when compared with the standard of care radiology read (WB-MRI without ML
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40 160 support, the comparator).
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46 162 **Methods and analysis**

48 163 **Study design**

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52 164 The study is based on a cross-sectional diagnostic test accuracy design and will comprise three
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54 165 distinct project phases as summarised in Figure 1.
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3 166 • In **Phase 1** the ML algorithm will be trained using both HV and myeloma patient scans to
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5 167 recognise active myeloma deposits as distinct from cases with no active disease, classifying
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7 168 disease as ‘focal’, ‘diffuse’ or ‘inactive’.
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10 169 • In **Phase 2** the ML algorithm will be validated using a second unseen dataset against a
11
12 170 reference standard (i.e. ground truth) to assess how accurately radiologists classify disease
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14 171 using scans with the ML algorithm and compared to readings without ML. Diagnostic
15
16 172 accuracy on a per patient and per region (using 16 pre-defined anatomical sites – Table 1)
17
18 173 basis and reading time will be measured.
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21 174 • In **Phase 3**, further development of the ML algorithm to quantify disease burden will be
22
23 175 undertaken using datasets from phase 1 and 2. This quantification output will be tested in
24
25 176 the phase 3 reader study in which readers will record disease burden and response between
26
27 177 paired baseline (new diagnosis or relapse prior to initiation of treatment) and single post
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29 178 treatment WB-MRI scans, with or without ML support, and tested against the reference
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31 179 standard.

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35 **Table 1: Comparison of MALIMAR anatomical regions between ground truth CRFs and reader CRFs**

Anatomical Regions	
Ground Truth CRFs (Phase 1 and 2)	Reader CRFs (Phase 2)
Skull	Skull
Scapula right	Ribs / clavicles / sternum / scapulae
Scapula left	Ribs / clavicles / sternum / scapulae
Clavicle right	Ribs / clavicles / sternum / scapulae
Clavicle left	Ribs / clavicles / sternum / scapulae
Sternum	Ribs / clavicles / sternum / scapulae
Spine upper	Cervical spine
Spine middle	Dorsal spine
Spine lower	Lumbar spine
Ribs right	Ribs / clavicles / sternum / scapulae

Ribs left	Ribs / clavicles / sternum / scapulae
Sacrum	Pelvis
Femur right	Long bones
Femur left	Long bones
Humerus right	Long bones
Humerus left	Long bones

181

182 Participants and Recruiting Centres

183 The study will be run at The Royal Marsden NHS Foundation Trust across two Royal Marsden

184 Hospital (RMH) sites; Chelsea and Sutton, and Imperial College Healthcare Trust (ICHT). Patient and

185 HV scans will make up the study population, and disease classification will be at both the scan and

186 anatomical site level.

187 The scan population will comprise of; HV WB-MRI scans acquired from participants prospectively

188 recruited from the Sponsor site only (RMH), with the option of the Imperial Site providing previously

189 acquired HV scans; WB-MRI scans acquired as part of clinical care from patients being managed at

190 RMH and ICHT; and WB-MRI scans previously acquired for a prospective research study in WB-MRI

191 (iTMM study). All scans acquired for the study will be done so using clinical standard of care Trust

192 protocols.

193 The inclusion/exclusion criteria for the HV and patient scans are detailed in Table 2 and the planned

194 number of scans for each study phase is detailed in Table 3.

195 Table 2: Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Healthy volunteers	Written informed consent No contra-indication to MRI 40 years or above in age (attempts will be made to include similar age range as myeloma patients) No known significant illness No known metallic implant	Significant artifact on scan Corrupted scan data
Patients in	Patient with confirmed myeloma with WB-MRI scan	Corrupted WB-MRI scan

phase 1 & 2	<p>previously performed as part of clinical care.</p> <p>Sufficient imaging and clinical data for the expert reference panel to categorise the WB-MRI scan as:</p> <ol style="list-style-type: none"> 1. Previously treated inactive disease with no evidence of active disease based on expert reference panel 2. Active disease – focal 3. Active disease – diffuse 4. Active disease – extra-medullary 5. New active myeloma, no previous treatment <p>Patients may be included if the pattern of disease is a combination of focal, diffuse and/or extra-medullary.</p>	<p>data.</p> <p>Insufficient clinical data to allow the expert reference panel to categorise the scan.</p>
Patients in phase 3	<p>Training set: Phase 1 active disease cases and their post treatment scans from phase 2.</p> <p>Validation set: from iTIMM study.</p> <p>Written informed consent for iTIMM study</p> <p>All patients over the age of 18 with multiple myeloma planned for autograft.</p>	<p>Corrupted scan data.</p> <p>MRI incompatible metal implants</p> <p>Claustrophobia</p> <p>Diagnosis of other malignancy within 5 yrs</p>

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197 **Table 3: Number of Healthy Volunteer (HV) and Multiple Myeloma (MM) scans in each category**
 198 **for each study phase.**

	HV**	MM inactive	MM active focal	MM active diffuse	MM new diagnosis	Total
Phase 1*	40	40	60	40	20	200
Phase 2	50	100	105	70	28	353
Phase 3 training***	0	(80 post treatment)	60	40	20	200
Phase 3 validation	0	60 patients in iTIMM study scanned at baseline and post treatment				120

199 *The number of scans in phase 1 may increase by 140-180 scans (100 subjects) if there is evidence
 200 of over-fitting in the development of the algorithm.

201 ** A total of 50 HV will be used, 40 in phase 1, which will be used again in phase 2, with the addition
 202 of 10 more HV.

203 ***Scans used in phase 3 training are scans that have been previously used in phase 1 and 2

204 **Intervention and Reference Standard**

205 *Intervention (including comparator)*

206 The comparator in this study is defined as WB-MRI scans read by experienced radiologists, as per
 207 standard care (WB-MRI, the COMPARATOR). The intervention will use these standard methods with
 208 the addition of machine learning (WB-MRI+ML, the INTERVENTION). The ML algorithm will be

209 developed during phase 1 of the study following data curation and scan allocation to phase 1 and 2.

210 DW imaging (DWI), ADC map and T1 weighted sequences (Dixon fat and water scans) will be used,

211 reflecting the radiological reading tools used by expert readers.

212 Radiologists or readers are defined as experienced based on their previous clinical radiology reading

213 skills and responsibilities, and their length of service in this role. Experienced readers will be required

214 to have completed at least 100 WB-MRI clinical scan reports.

215 *Reference standard*

216 There is no available histological reference standard for every site of bone marrow disease, as

217 trephine biopsy is usually restricted to a single site. The proposed reference standard thus

218 comprises the interpretation of an expert panel; a radiologist and a haematologist who are experts

219 in myeloma. They will have access to 1) WB-MR images; 2) bone marrow histopathology reports

220 (with quantitation); 3) serum paraproteins; 4) serum free light chain (sFLC), in order to categorise

221 per scan:

- 222 • Presence or absence of active disease
- 223 • The detailed disease distribution by anatomical site
- 224 • Quantitation of the burden of disease (using a validated MRI score (19,20) and sFLC)
- 225 including category of response to treatment .

226 Scan and site level data from these scans will be captured on Case Report Forms (CRFs) for all cases

227 in phases 1 and 2 and used as 'ground truth' in the classification of study output. Reference standard

228 for phase 3 will be obtained from the source (iTMM study).

229 **Objectives**

230 *Primary research objectives*

231 Phase 1: To develop a myeloma-specific ML algorithm to detect the presence of active disease on

232 WB-MRI+ML (with machine learning '+ML') with sufficient sensitivity.

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3 233 Phase 2: To validate WB-MRI+ML against the comparator WB-MRI for sensitivity on a per-patient
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5 234 and per site basis.

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8 235 Phase 3: To develop and validate a ML algorithm to automatically quantify the burden of active
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10 236 disease, before and after treatment.

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13 237 *Secondary research objectives (Phase 2 and 3 only)*

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16 238 For each of the following, our objective is to compare WB-MRI with and without ML support to the
17
18 239 reference standard for:

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21 240 1) Reading time

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24 241 2) Specificity

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27 242 3) Sensitivity of non-experienced readers

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30 243 4) Agreement of categorising disease as focal, diffuse and/or extramedullary.

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32
33 244 5) Agreement of categorising patients as responder or non-responder

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36 245 **Procedure**

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39 246 *Scan Acquisition – Healthy Volunteers*

40 247 Healthy Volunteers (HV) will be recruited to obtain data from normal bone marrow within the age
41
42 248 range typical of myeloma. Up to 50 HVs aged 40 years or above will be recruited using approved
43
44 249 advertisements at the Sponsor site and consented with the help of Clinical Research Network (CRN)
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46 250 resources (See Supplementary S1a for consent form). The HV Information Sheet (Supplementary file
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48 251 S1b) will clearly explain the MRI scanning procedure and the actions that will be taken in the event
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50 252 of incidental (i.e. unexpected) findings. Contact details will be supplied on the HV Information Sheet
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52 253 to enable volunteers to respond to the invitation or ask any questions. A total of 22 HV scans
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54 254 previously acquired are also available for use from ICHT if needed.
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3 255 Participating HVs will undergo a single whole body MRI scan at RMH according to the trial specific
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5 256 scanning protocol. HV scans will be acquired in the following sequences (T1, fat/water, Dixon, ADC,
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7 257 etc) to mirror the clinical setting and on Siemens, Avanto and Aero (wide bore) MRI scanners
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10 258 (Supplementary S2 details sequences). Subjects with a larger Body Mass Index will be scanned on
11
12 259 the Siemens Aero which has a larger bore diameter to optimise comfort.

15 260 *Scan Acquisition– Myeloma Patients*

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17 261 Previously acquired patient scans will be identified by the investigators within the Sponsor's
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19 262 myeloma clinical service (between 2011 and 2020), supplemented by scans from ICHT, until the
20
21 263 required sample size is reached. Scans will normally include the following sequences; T1, fat/water,
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23 264 Dixon, ADC, etc, and on the following MRI machines; Siemens, Avanto and Aero MRI scanners
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25
26 265 (Supplementary S2 for sequence details).

29 266 *Scan Classification and Allocation to Study Phase*

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31 267 Patient scans will be categorised by the expert reference panel as showing inactive disease, active
32
33 268 focal, active diffuse (focal or diffuse) and new disease. HV scans will be classified as normal (i.e. non-
34
35 269 diseased). Scans will be allocated to Phase 1 or 2 as per Table 3. To minimise bias or 'over-learning',
36
37 270 no more than 5 scans from the same patient will be allocated to Phase 1. Phase 2 scans will not
38
39
40 271 include any patient scans that have been used in Phase 1 and thus comprise only those previously
41
42 272 unseen by the ML algorithm. A subset of scans from phase 1 and 2 will be used to further train the
43
44 273 algorithm at the start of Phase 3. Phase 3 validation scans have previously been acquired for the
45
46
47 274 iTTiM trial (NCT02403102) and include a unique series of paired scans, previously unseen by the ML
48
49 275 algorithm.

52 276 *Scan Curation (Quality Control) and Anatomical Segmentation*

53
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55 277 Eligible scans will be curated immediately prior to transfer to an online platform for secure storage
56
57 278 (ICR XNAT). This will ensure the ML algorithm is able to interpret all scans consistently. Curation
58
59 279 scripts will be written in python and ensure that scans exhibit consistent characteristics such as:

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3 280 correct sequential display of images, no missing slices, noting presence of unusual artifacts that
4
5 281 might interrupt ML reads and other factors which might compromise interpretation. Further details
6
7 282 on the data curation will be published elsewhere.
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10 283 Phase 1 scans will then be manually segmented into 16 bone regions (Table 1) using a boundary box
11
12 284 approach. These scans will be used to teach the ML algorithm to recognise active myeloma disease
13
14 285 (focal or diffuse) and precision metrics will be evaluated in order to achieve the optimal algorithm.
15
16 286 Initially, scans will be classified by the ML algorithm at scan level (i.e. patient level) only.
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20 287 *Testing of ML Algorithm – Radiology Reading Process*

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23 288 The ML algorithm will be tested by both experienced and inexperienced radiology readers.
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26 289 Phase 2 scans will be subjected to the ML algorithm which will provide an ML overlay on all scans
27
28 290 indicating areas of disease by means of a heat map. For each scan, a ‘standard’ and ‘machine
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30 291 learning’ version will be available. The trial statistician will randomly allocate reads to each of the
31
32 292 (approximately 15 – 20) readers, using trial-specific algorithms written using Stata software
33
34 293 (StataCorp, Texas). The reads will be performed in two batches to incorporate a wash-out period.
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36 294 Each batch will have 50% of cases with ML support and 50% without, to avoid reader training bias.
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38 295 The reading process will be described in a Reader Manual and all readers will receive appropriate
39
40 296 training in viewing scans using the Biotronics 3D Web-based platform and completing a Read CRF
41
42 297 available via Microsoft Forms (see supplementary file S3a). In the case of “inexperienced” readers,
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44 298 training will comprise a review of the CRFs and the viewing software with a basic training on
45
46 299 reporting lexicon. A scribe will be provided to assist readers during the reading process and input
47
48 300 data to the CRF in each batch of reads. Following a 4-week wash out period, readers will be
49
50 301 presented with the second batch of reads with the opposite reading paradigm with regards to the
51
52 302 ML support. The same cases will be allocated to the same readers. A subset of approximately 50
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54 303 scans will be read a second time by a different reader as an interrater check.
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3 304 In Phase 3, scans from the iTIMM study, comprising paired baseline and follow-up post treatment
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5 305 scans, will be used to test whether the ML algorithm is capable of distinguishing change in disease
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7 306 status (i.e. disease burden) between the two time-points. Reads will again be randomly allocated to
8
9
10 307 the readers by the trial statistician. Readers will follow similar procedures to that outlined above
11
12 308 with one set of paired scans having the ML overlay and the other with no ML overlay (for CRF see
13
14 309 supplementary file S3b). A 4-week wash-out period will again apply between the two batches of
15
16 310 reads. A subset of approximately 20 scans will be read a second time by a different reader as an
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18
19 311 interrater check.

21 312 *Data collection*

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24 313 Reader responses will be captured using MS Forms with responses being transferred directly to an
25
26 314 excel spreadsheet. Examples of the CRFs to be used in both ML validation phases are given as
27
28 315 supplemental files (S3a, S3b). All readers will be provided with a manual describing CRF completion
29
30 316 (including a lexicon of disease definitions) and use of the software viewing tools and overlay of the
31
32 317 ML output heatmap and opportunity for live training using the online platform.

33 34 35 36 318 **Outcome measures**

37 38 39 319 *Phase 1 – ML Algorithm Training Phase*

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41
42 320 Primary: Sensitivity for the detection of active myeloma on WB-MRI + ML detection tool against the
43
44 321 reference standard.

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47 322 Secondary: 1. Specificity; 2. F1 score (a single measure of precision and recall).

48 49 50 323 *Phase 2 – ML Algorithm Clinical Testing Phase (Presence /Absence of active myeloma)*

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53 324 Primary: Difference in sensitivity of WB-MRI +/- ML detection tool to diagnose the presence of
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55 325 active myeloma on a per-patient basis, by experienced readers, assessed against the reference
56
57 326 standard.

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2
3 327 Secondary: For comparison of WB-MRI +/-ML: 1. Per-site sensitivity to diagnose active disease; 2.
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5 328 Reading time; 3. Specificity; 4. Agreement with reference standard to categorise disease as focal,
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7 329 diffuse and/or extramedullary; 5. Sensitivity of non-experienced readers for presence of active
8
9 330 disease.

11
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13 331 *Phase 3 – ML Algorithm for quantification of disease burden with clinical testing*

14
15 332 Primary : agreement between experienced readers and the reference standard in scoring overall
16
17 333 burden of disease before and after treatment for response categorisation +/- ML quantification tool.

18
19 334 Secondary: For comparison of WB-MRI +/-ML: 1. Reading time; 2. Agreement of categorisation of
20
21 335 patients as responder or non-responder with the reference standard; 3. Agreement of non-
22
23 336 experienced readers for burden of disease and categorisation of response; 4. Estimated difference in
24
25 337 cost for radiology reading time for WB-MRI +/-ML.

26
27 338 Proposed tertiary: Verification of the team's previously published work regarding reverse
28
29 339 classification accuracy: predicting segmentation performance in the absence of a reference standard
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31 340 (21).

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35 341 **Sample size**

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38 342 *Phase 1:*

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41 343 We will train the ML algorithm on a set of scans without and with active disease that will reflect the
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43 344 categories of disease that may be encountered in clinical practice. The number of cases used for
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45 345 training is arbitrarily chosen reflecting the knowledge that a large number of training datasets will
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47 346 improve training accuracy, counterbalanced with the resources needed to curate and annotate a
48
49 347 large number of datasets.

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52 348 *Phase 2:*

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55 349 The study is powered on the primary outcome of sensitivity.
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3 350 In a meta-analysis, Wu et al have reported a pooled sensitivity of 88% and a pooled specificity of
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5 351 86% (0.86 for WB-MRI with DW-MRI) (8). We anticipate that the addition of ML could increase this
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7 352 by at least 7.5%, from 88% to 95.5%. There is no background data to indicate the expected
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9
10 353 proportion of discordant pairs so we have estimated this as $(1-0.955)*0.88 + 0.955*(1-0.88)$, which is
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12 354 equal to 0.154. To achieve 80% power using a two-sided alpha of 0.05 would require a total of 203
13
14 355 patients positive for myeloma using the gold standard.

16
17 356 If it is assumed that the specificity will be unchanged using ML, a total number of cases with no
18
19 357 active disease of 150 (50 HV, 100 inactive treated myeloma), will give 80% power to show that the
20
21 358 difference is above a non-inferiority limit of 10%.

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25 359 *Phase 3 training:*

26
27 360 Approximately 200 cases that have at least two time points will be taken from phase 1 and 2, with
28
29 361 active disease present at least at one time point, and used for training and validation for burden of
30
31 362 disease; this will ensure efficient use of all data and segmentations.

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35 363 *Phase 3 clinical testing:*

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37 364 This sample size is fixed at 60 patients, the full sample size of the iTIMM study, each of whom has a
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39 365 baseline and one post treatment scan.

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43 366 **Statistical Analysis**

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46 367 *Phase 1 analysis*

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48 368 The ability to correctly localise and detect active disease will be evaluated by calculating sensitivity,
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50 369 specificity and the F1 score (a single measure of precision (positive predictive value) and recall
51
52 370 (sensitivity)) for multiple algorithms and compared against the reference standard. Following Trial
53
54 371 Steering Committee (TSC) approval, the optimal algorithm will move forward to phase 2.

55
56
57
58 372 *Phase 2 analysis*

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2
3 373 In phase 2, the percentage of patients with active disease on WB-MRI +/- ML support who have
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5 374 positive reference standard will be compared using McNemar's test with a two-sided alpha of 0.05.
6
7 375 Per patient and per site sensitivity and specificity with and without ML support will be reported with
8
9 376 95% confidence intervals. Reading time will be compared using Wilcoxon's test for paired data and
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11 377 described using summary statistics.
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15 378 The same analysis of sensitivity, specificity and reading time will be repeated for inexperienced
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17 379 readers.
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20 380 Agreement between experienced and inexperienced readers will be measured in a subset of cases
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22 381 with a Kappa coefficient, and overall proportion of concordant cases.
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25 382 All other endpoints will be summarised using descriptive statistics.
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27

28 383 Although the study is powered to detect superiority of the primary endpoint, if sensitivity is shown
29
30 384 to be non-inferior using ML and reading time is both clinically and statistically significantly lower
31
32 385 using ML, this would be considered as an indication to proceed. Non-inferiority in this context will be
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34 386 defined as having any possible reduction in sensitivity with ML significantly higher than a lower limit
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36 387 of -10% (using Tangos' test with one-sided alpha 0.05)
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40 388 *Phase 3 analysis*

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43 389 In phase 3, the difference between the experienced readers' disease score to the reference standard
44
45 390 disease score will be recorded and compared +/- ML support using Wilcoxon's test. Differences from
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47 391 scores given by experienced readers and the reference standard will be described using Bland-
48
49 392 Altman plots for scores +/- ML support.
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52 393 All other endpoints will be summarised using descriptive statistics.
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55 394 A simple cost-effectiveness analysis may be performed depending on study findings, such as the
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57 395 reading time.
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3 396 *Procedure(s) to account for missing or spurious data*

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5
6 397 If a scan is incomplete or the file is corrupted and not evaluable, it will be excluded from the dataset.

7
8 398 If a set of radiology reads is incomplete, a new trained reader will be identified to do the full

9
10 399 allocation of reads.

11
12
13 400 *Timing and responsibility for analyses*

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15
16 401 Analyses will take place at both the end of phase 2 and then again at the end of phase 3, when all

17
18 402 readings have been completed.

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21 403 **Patient and public involvement (PPI)**

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24 404 A PPI representative was appointed from an established group at Myeloma UK. The individual gave

25
26 405 in-depth feedback on the study, particularly on the relevance to patient care and the use of

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28 406 retrospective patient data and HV scans. Myeloma UK is fully supportive of the project and is willing

29
30 407 to assist with dissemination of important findings to the Myeloma UK community.

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34 408 **Safety**

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36 409 As this study is recruiting healthy volunteers only, an a-priori agreement has been reached with the

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38 410 Sponsor that safety reporting is not required. Sponsor procedures in respect of incidental (i.e.

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40 411 unexpected) findings in healthy volunteers will be adhered to and results captured within the Trust's

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42 412 Clinical Record.

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45 413 Monitoring against Source Data will not be required which is in line with the Sponsor's policy on

46
47 414 non-CTIMP (Clinical Trial of Investigational Medicinal Product) trials.

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49
50 415 **Trial funding, organisation and administration**

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52 416 The study has been awarded funding by Medical Research Council (MRC) NIHR EME Awards Body

53
54 417 (NIHR EME Project ID: 16/68/34). In addition, the Department of Radiology has agreed to fund the

55
56 418 cost of HV WB-MRI scans. The cost of recruitment and consenting of HVs will be requested through

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3 419 the NHS CRN. RMH is the study sponsor responsible for initiating and managing the study and the
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5 420 coordinating centre, including sign-off of the study protocol.
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8 421 A Trial Management Group (TMG) meeting will be held regularly to ensure satisfactory progress of
9
10 422 the study. A TSC will provide independent oversight for the study, review the development of the
11
12 423 ML algorithm, and advise the TMG where problems may arise. The TSC will include a Patient
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14 424 Advocate.
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19 426 **Ethics and dissemination**

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23 427 Ethical approval for MALIMAR was granted on 21/11/2017 (REC) and 21/12/2017 (Health Research
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25 428 Authority) Here, we report version 3.0 of the protocol. All participating sites gained local approval
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27 429 prior to study participation.
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30 430 Any protocol modifications will be submitted for approval to the REC, reflected in the online
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32 431 registration and disseminated by e-mail to site principal investigators and trial coordinators. The
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34 432 statistician will have access to the final linked trial dataset. There are no plans to provide public
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36 433 access to the full protocol, participant-level data, or statistical code. The researchers aim to publish
37
38 434 results in a peer-reviewed journal and share via social media and conferences. Authorship will be
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40 435 determined according to academic standards.
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44 436 **Discussion**

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46 437 This study aims to develop and validate a ML algorithm to augment the performance and efficiency
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48 438 of the radiology reading process using WB-MRI. The results will show the impact of using the ML tool
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50 439 and outcomes of the study will have implications for the application of ML with WB-MRI in myeloma
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52 440 patients across the NHS. It is anticipated that feasibility analysis will follow the successful completion
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54 441 of this study to pilot the implementation of the ML tool in a real-time prospective study prior to
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56 442 future clinical setting.
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3 443 To avoid bias we ensure: 1) comparator and intervention tests are read by readers that are fully
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5 444 blinded to the reference standard; 2) a mixture of cases with and without disease; 3) the reads will
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7 445 be presented such that radiologists must read a mixture of cases without or with ML support during
8
9 446 each round of reading including a wash-out period. We will have unavoidable incorporation bias, as
10
11 447 the expert reference panel will use the MRI as part of the reference standard. The reference panel
12
13 448 will consist of a single person's opinion which is a limitation to our study. If resources had allowed,
14
15 449 the gold standard would have been to have two blinded opinions with a consensus panel in cases of
16
17 450 disagreement. Other limitations include varying scan quality as data is acquired over a 9-year period;
18
19 451 and replicating clinical reporting in a retrospective study setting can be challenging.
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24 452 In conducting this study, we will have acquired possibly the largest set of characterised myeloma
25
26 453 patient MRI scans in the UK and we anticipate this will form the basis of a unique training resource in
27
28 454 the future.
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31 455 Machine learning techniques in WB-MRI scans of patients with myeloma is likely to be transferable
32
33 456 to other malignancies. In prostate and breast cancer, quantification of metastatic bone disease is an
34
35 457 unmet need as bone only disease is not uncommon and is currently classified as non-measurable by
36
37 458 RECIST 1.1 (22). The participating HVs will be consented to allow the anonymised datasets to be a
38
39 459 future resource for the wider research community.
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43 460 **Study status**

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45 461 The MALIMAR study opened on 26 April 2018 using protocol version 1.0 (30 Oct 2017). The study
46
47 462 was in phase II, using protocol version 3.0 (31 Jan 2019), at date of submission. Protocol
48
49 463 amendments are documented in Supplementary S4.
50

51 464 **Author contributions:**

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53
54 466 AR, CM, TaB, BG, SW, TQ, ThB, SD, ML, MK and DK conceptualization and methodology; AR,
55
56 467 CM, TaB, ThB, MK, BG, TQ, XF and SW investigation; EA and AR resources; ThB and SD data
57
58 468 curation; LS and EG formal analysis; AR, DK and CM supervision; LS writing – original draft; AR,
59
60

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2
3 469 CM, TaB, BG, LW and LS writing – review and editing; BG, TQ, XF and SW data visualisation; LW
4
5 470 project administration; EA and AR funding acquisition.
6
7

8 471 **Competing interests:**
9

10 472 AR receives honoraria for educational lecture at Garmisch International Symposium, has an unpaid
11
12 473 role on the European Society of Radiology Board of Directors and receives travel cost support where
13
14 474 necessary. BG receives grants from other entities; EU commission and UKRI London Medical Imaging
15
16 475 & Artificial Intelligence Centre for Value Based Healthcare, is a Scientific advisor for Kheiron Medical
17
18 476 Technologies (Jan 2018 – Sep 2021) and receives stock options as part of standard employment
19
20 477 packages from both Kheiron Medical Technologies and HeartFlow. EA has a patent pending for
21
22 478 Machine Learning in Alzheimer’s disease and has a role on the scientific advisory board for
23
24 479 Radiopharm Theranostics Limited. MK receives grants from both Myeloma UK and Celgene/BMS,
25
26 480 and consulting fees or payments from AbbVie, BMS/Celgene, Janssen, GSK, Karyopharm, Takeda and
27
28 481 Seagen. CM & DK receive additional funding as a co-investigator on a radiology NIHR study and is
29
30 482 part of the joint venture Celescan with the Royal Marsden, The Institute of Cancer Research and
31
32 483 Sopra Steria. TB receives additional funding from CRUK grant funding (NCITA) and NIHR (HTA) and
33
34 484 receives honoraria from Bayer.
35
36
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39

40 485 **Funding:**
41

42
43 486 This study (ID: 16/68/34) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an
44
45 487 MRC and NIHR partnership. In addition, the Department of Radiology has agreed to fund the cost of
46
47 488 healthy volunteer whole body MRI scans. The cost of recruitment and consenting of healthy
48
49 489 volunteers will be requested through the NHS Clinical Research Network. The views expressed in this
50
51 490 publication are those of the authors and not necessarily those of the MRC, NHS, the NIHR, or the
52
53 491 Department of Health and Social Care.
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56
57 492 EG and LS’s posts are part funded by the National Institute for Health and Care Research (NIHR)
58
59 493 Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer
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3 494 Research, London. The views expressed are those of the author(s) and not necessarily those of the
4
5 495 NIHR or the Department of Health and Social Care.

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7
8 496 SW is supported by the UKRI London Medical Imaging & Artificial Intelligence Centre for Value Based
9
10 497 Healthcare.

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13 498 **Data sharing statement:**

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15
16 499 Anonymised data are available upon reasonable request as a resource for the wider research
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18 500 community from Andrea Rockall (ORCID ID: 0000-0001-8270-5597), providing consent has been
19
20 501 granted from all participants.

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23 502 **References**

- 24
25
26 503 1. NICE. Myeloma: diagnosis and management NICE guideline [NG35]. 2016.
27
28 504 2. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International
29 505 Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The lancet*
30 506 *oncology*. 2014;15(12):e538–48.
31
32 507 3. Dimopoulos MA, Hillengass J, Usmani S, Zamagni E, Lentzsch S, Davies FE, et al. Role of
33 508 magnetic resonance imaging in the management of patients with multiple myeloma: a
34 509 consensus statement. 2015;
35
36 510 4. Pearce T, Philip S, Brown J, Koh DM, Burn PR. Bone metastases from prostate, breast and
37 511 multiple myeloma: differences in lesion conspicuity at short-tau inversion recovery and
38 512 diffusion-weighted MRI. *Br J Radiol*. 2012;85(1016):1102–6.
39
40 513 5. Squillaci E, Manenti G, di Stefano F, Miano R, Strigari L, Simonetti G. Diffusion-weighted MR
41 514 imaging in the evaluation of renal tumours. *Journal of Experimental and Clinical Cancer*
42 515 *Research*. 2004;23(1):39–46.
43
44 516 6. Dutoit JC, Vanderkerken MA, Anthonissen J, Dochy F, Verstraete KL. The diagnostic value of
45 517 SE MRI and DWI of the spine in patients with monoclonal gammopathy of undetermined
46 518 significance, smouldering myeloma and multiple myeloma. *Eur Radiol*. 2014;24(11):2754–65.
47
48 519 7. Messiou C, Hillengass J, Delorme S, Lecouvet FE, Moulopoulos LA, Collins DJ, et al. Guidelines
49 520 for acquisition, interpretation, and reporting of whole-body MRI in myeloma: myeloma
50 521 response assessment and diagnosis system (MY-RADS). *Radiology*. 2019;291(1):5–13.
51
52 522 8. Wu L, Gu H, Zheng J, Xu X, Lin L, Deng X, et al. Diagnostic value of whole-body magnetic
53 523 resonance imaging for bone metastases: a systematic review and meta-analysis. *Journal of*
54 524 *Magnetic Resonance Imaging*. 2011;34(1):128–35.
55
56 525 9. Messiou C, Porta N, Sharma B, Levine D, Koh DM, Boyd K, et al. Prospective evaluation of
57 526 whole-body MRI versus FDG PET/CT for lesion detection in participants with myeloma.
58 527 *Radiology: Imaging Cancer*. 2021;3(5).

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3 528 10. Pawlyn C, Fowkes L, Otero S, Jones JR, Boyd KD, Davies FE, et al. Whole-body diffusion-
4 529 weighted MRI: a new gold standard for assessing disease burden in patients with multiple
5 530 myeloma? *Leukemia*. 2016;30(6):1446–8.
- 7 531 11. Mateos MV, Hernández MT, Giraldo P, de la Rubia J, de Arriba F, Corral LL, et al. Lenalidomide
8 532 plus Dexamethasone for High-Risk Smoldering Multiple Myeloma. *New England Journal of*
9 533 *Medicine*. 2013 Aug;369(5):438–47.
- 11 534 12. Padhani AR, Koh DM, Collins DJ. Whole-body diffusion-weighted MR imaging in cancer:
12 535 current status and research directions. *Radiology*. 2011;261(3):700–18.
- 14 536 13. Radiologists RC of. Clinical radiology UK workforce census 2015 report. The Royal College of
15 537 Radiologists London; 2016.
- 17 538 14. Juntu J, Sijbers J, de Backer S, Rajan J, van Dyck D. Machine learning study of several
18 539 classifiers trained with texture analysis features to differentiate benign from malignant
19 540 soft-tissue tumors in T1-MRI images. *Journal of Magnetic Resonance Imaging: An Official*
20 541 *Journal of the International Society for Magnetic Resonance in Medicine*. 2010;31(3):680–9.
- 22 542 15. Pauly O, Glocker B, Criminisi A, Mateus D, Möller AM, Nekolla S, et al. Fast multiple organ
23 543 detection and localization in whole-body MR Dixon sequences. In: *International Conference*
24 544 *on Medical Image Computing and Computer-Assisted Intervention*. Springer; 2011. p. 239–47.
- 26 545 16. Lavdas I, Rockall AG, Castelli F, Sandhu RS, Papadaki A, Honeyfield L, et al. Apparent diffusion
27 546 coefficient of normal abdominal organs and bone marrow from whole-body DWI at 1.5 T: the
28 547 effect of sex and age. *American Journal of Roentgenology*. 2015;205(2):242–50.
- 30 548 17. Lavdas I, Glocker B, Rueckert D, Taylor SA, Aboagye EO, Rockall AG. Machine learning in
31 549 whole-body MRI: experiences and challenges from an applied study using multicentre data.
32 550 *Clin Radiol*. 2019;74(5):346–56.
- 34 551 18. Lavdas I, Glocker B, Kamnitsas K, Rueckert D, Mair H, Sandhu A, et al. Fully automatic,
35 552 multiorgan segmentation in normal whole body magnetic resonance imaging (MRI), using
36 553 classification forests (CF s), convolutional neural networks (CNN s), and a multi-atlas (MA)
37 554 approach. *Med Phys*. 2017;44(10):5210–20.
- 39 555 19. Giles SL, Desouza NM, Collins DJ, Morgan VA, West S, Davies FE, et al. Assessing myeloma
40 556 bone disease with whole-body diffusion-weighted imaging: comparison with x-ray skeletal
41 557 survey by region and relationship with laboratory estimates of disease burden. *Clin Radiol*.
42 558 2015;70(6):614–21.
- 44 559 20. Giles SL, Messiou C, Collins DJ, Morgan VA, Simpkin CJ, West S, et al. Whole-body diffusion-
45 560 weighted MR imaging for assessment of treatment response in myeloma. *Radiology*.
46 561 2014;271(3):785–94.
- 48 562 21. Valindria V v, Lavdas I, Bai W, Kamnitsas K, Aboagye EO, Rockall AG, et al. Reverse
49 563 classification accuracy: predicting segmentation performance in the absence of ground truth.
50 564 *IEEE Trans Med Imaging*. 2017;36(8):1597–606.
- 52 565 22. Lecouvet FE, Talbot JN, Messiou C, Bourguet P, Liu Y, de Souza NM, et al. Monitoring the
53 566 response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear
54 567 medicine techniques: a review and position statement by the European Organisation for
55 568 Research and Treatment of Cancer imaging group. *Eur J Cancer*. 2014;50(15):2519–31.

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570 **Figure 1: MALIMAR Study Flow Diagram**

For peer review only

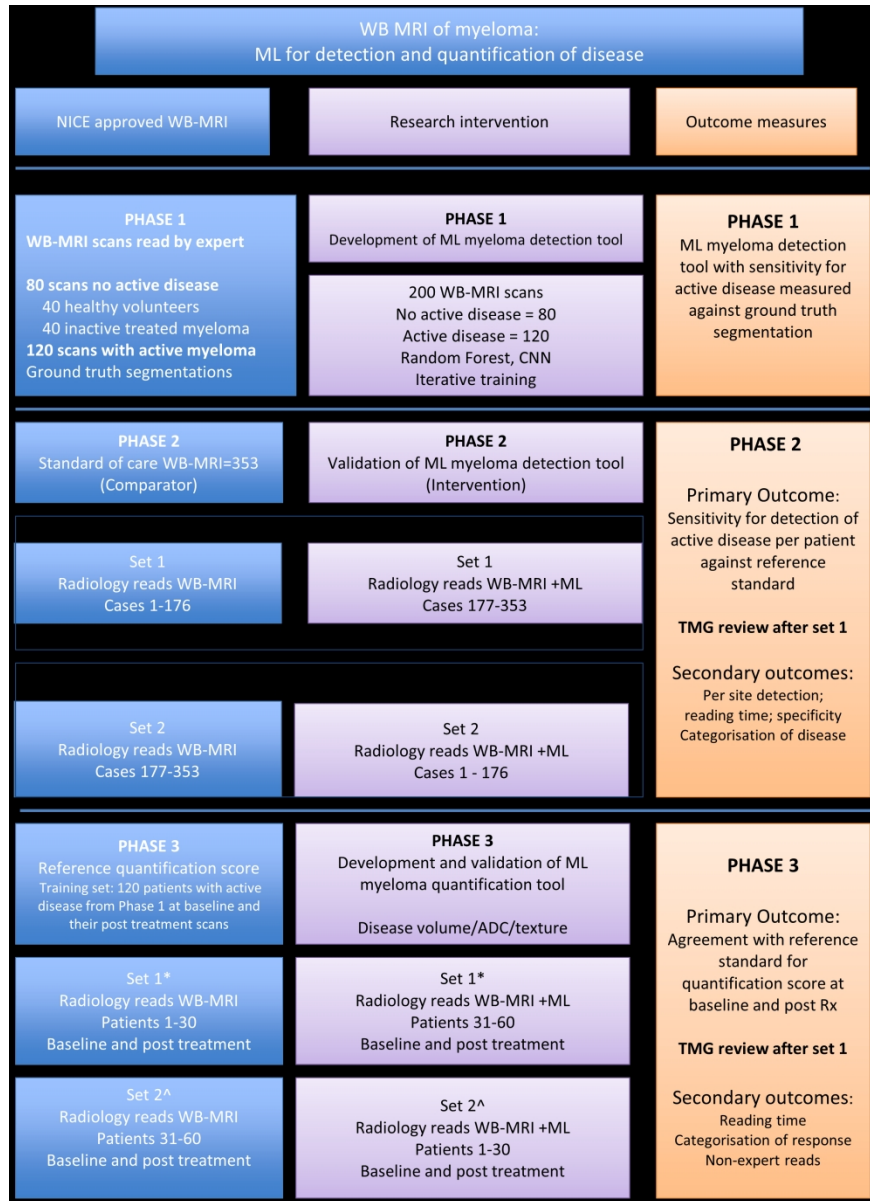


Figure 1: Study Flow Chart

526x723mm (130 x 130 DPI)

The MALIMAR Study Healthy Volunteer Consent Form**Study Reference Numbers: CCR 4820: IRAS No.: 233501**NHS No. Healthy volunteer Trial ID:

Name of Lead Researcher:

Please initial box

1. I confirm that I have read and understand the Healthy Volunteer Information Sheet version 2.0 dated 07/12/18 for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. If I request withdrawal from the study, I give permission that my data already collected within the study can be anonymised and used.
4. I understand that relevant sections of my medical notes may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
5. I consent to undergo an MRI scan under the supervision of the responsible clinician for this research. I understand that if any health related issues come to light as a result of undergoing this scan, otherwise known as 'incidental findings', that I and my General Practitioner will be promptly informed of these issues.
6. I agree to participate in the MALIMAR study.
7. I give permission for the data collected during the study to be used in further ethically approved research within and outside the UK in the field of imaging research. I understand this will not include any personal data from which I could be identified.

Name of Healthy Volunteer	Date	Signature
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Name of person taking consent (PI or approved signatory)	Date	Signature
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Original for Investigator's Site File; 1 copy for volunteer; 1 copy for hospital notes; 1 copy to be sent to RM-CTU

MALIMAR (CCR 4820, IRAS: 233501)

The ROYAL MARSDEN
NHS Foundation Trust

MALIMAR

Healthy Volunteer Information Sheet

Development of machine learning support for reading whole body diffusion weighted magnetic resonance imaging (WB-DW-MRI) in myeloma for the detection and quantification of the extent of disease before and after treatment.

Short Title: MACHine Learning In MyelomA Response

7th December 2017

Version 2.0

CCR Number: 4820

IRAS (Integrated Research Application System) No. 233501

You are being invited to take part in a research study. Before you decide whether or not to take part it is important for you to understand why we are doing this research and what it involves. Please take time to read the following information carefully and discuss it with relatives, friends, and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time deciding whether or not you wish to take part.

You can learn more about clinical research on the Cancer Research UK's patient website (www.cancerhelp.org.uk)

Invitation

If you are 40 years or above the Radiology Department at the Royal Marsden hospital would like to invite you to take part in a research study. This will involve you having a particular type of Magnetic Resonance Imaging (MRI) scan known as a Whole-Body Diffusion Weighted MRI scan or 'WB-DW-MRI'.

Before you decide to participate it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Thank you for reading this Information Sheet.

What is the purpose of the study?

There have been enormous advances in recent years in the technology used to take pictures (images) of the internal anatomy of cancer patients to better identify sites of disease. These images (or scans) can now provide a more accurate indication of the scope or spread of disease. They can also be used for assessing disease response to different drugs or treatments.

MRI (magnetic resonance imaging) has the advantage over other types of scanning (e.g. computerised tomography or 'CT') in that it does not involve the delivery of any radiation dose. In particular, a new type of MRI, called Whole Body Diffusion Weighted MRI (WB-DW-MRI) can provide especially precise images of diseased compared to healthy tissues. As a result, it is now being more widely used in cancer treatment centers throughout the world.

Despite these advantages, WB-DW-MRI has an important disadvantage. Each scan is made up from over a thousand images, each of which needs to be read and interpreted by an expert Radiologist. Thus, the time taken to read a single WB-DW-MRI scan is much longer than for a normal MRI scan, meaning that few NHS treatment centres (or hospitals) are able to offer them to patients.

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Members of the research team from the Royal Marsden Hospital and Imperial College London have already undertaken some work to ascertain how computers can reduce the time taken to read WB-DW-MRI scans. The technique is called 'machine learning' and basically teaches a computer to detect areas of suspicion or concern for disease on WB-DW-MRI scans. The 'trained' computer can then make an initial and very rapid interpretation of the images taken during a scan. These images can then be presented to the expert radiologist to make the final interpretation. In addition to training computers to read scans more quickly, we also want to train computers to interpret differences between scans taken from the same patient at different time-points. This will allow us to accurately assess change in disease extent or response to treatment over time.

However, in order to train the computers, we need examples of WB-DW-MRI images taken from both diseased (cancerous) and healthy tissues. In this study we are concentrating on patients with myeloma (cancer of white blood cells). We have already acquired WB-DW-MRI images from many patients with this type of cancer. **So now, we are seeking your help to acquire WB-DW-MRI images from healthy tissues for the Machine Learning In MyelomA Response (MALIMAR) study.**

What will happen to me if I decide that I would like to take part?

Before we can enter you to the study, we will need to check that you can have an MRI scan and that you are suitable to take part. Some people cannot have an MRI scan. These include people with a pacemaker, metal heart valves, aneurysm clips in the brain or people who have had metal fragments in their eyes. In addition, we are unable to include volunteers who have had or have a significant illness as this may affect the scan.

It may also not be appropriate for you to take part if you have had extensive surgery previously. Our study researcher will confirm these points with you before you are admitted to the trial. As advised above we are only recruiting volunteers aged 40 and above: anyone under this age will have to be

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2
3 excluded from participating because they will not be a suitable comparator.
4
5 Once we have confirmed that you are suitable to enter the trial, we will ask
6
7 you to sign an Informed Consent Form and then book your scan. Some
8
9 volunteers may be asked to attend early evening or week-end appointments
10
11 to avoid busy times during the day when the MRI Unit is reserved for patients.
12
13 There are usually no special preparations and no injection or drugs will be
14
15 given. All instructions for the scan will be in your MRI appointment letter.
16
17 When you come for the scan you are advised to wear clothing without metal
18
19 fastenings and to avoid using make-up or mascara. You can wear glasses,
20
21 but will need to take these off during the scan. A locker will be provided for
22
23 your valuables.

24
25 The MRI scan will be carried out by radiographers who are trained to carry out
26
27 the scans. MRI uses a magnetic field and radio waves to build up detailed
28
29 images of your internal anatomy by detecting signals sent out by water
30
31 molecules. It is not painful, but you will have to lie still for the duration of the
32
33 scan which can be up to 60 minutes. The scanner produces a variety of loud
34
35 noises during the scan which are made by the magnetic coils that switch on
36
37 and off during the scan. These are important in measuring the signals from
38
39 your body to create the images. They are switched on and off very quickly and
40
41 they vibrate, which is what causes the noise.

42
43 Some people may find the noise level uncomfortable and the table quite hard
44
45 to lie on. You will be provided with earplugs to help reduce the noise. The
46
47 scanner is open at both ends, but some people may find it claustrophobic.
48
49 During the scan the radiographer can see you from the control room and can
50
51 talk to you through an intercom. You will be given a call button to press to
52
53 alert attention and can listen to music during the scan. You can leave as soon
54
55 as your scan is finished and can eat and drink as normal. There are no side
56
57 effects from the MRI scan itself.

Why am I being invited to take part?

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You will be reading this Information Sheet because you have responded to one of our advertisements for Healthy Volunteers to take part. If we invite you to sign a Consent Form then you are eligible to take part in the study. If you are not eligible to participate we will explain the reason.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do choose to take part you will be asked to sign a consent form, a copy of which will be given to you for your records along with this information sheet about the study. Your legal rights are not affected by participation in the study.

What happens if I change my mind during the study?

Your participation in this study is entirely voluntary. If you agree to take part and then change your mind and wish to withdraw, you may do so at any time. If you decide to not join the study or to discontinue in the study, this will not affect any future care or treatment you receive.

What are the risks and the benefits of taking part in this study?

A possible risk in taking part is a degree of discomfort you may encounter in undergoing the MRI scan. As we said above, unlike other forms of imaging (e.g. CT scans) MRI does not deliver radiation and no drugs or other medication will be given. You will be registered on the Royal Marsden Hospital Information System and a report of your scan results will be held on this system. If an unexpected finding of concern is discovered, a doctor will call you to discuss your scan report. We will also send a copy of the report to your GP who will then advise you regarding any follow-up investigations that may be needed. This could lead to some anxiety. If unexpected findings are discovered which are not concerning, we will send you a letter to explain the findings and copy this letter to your GP. You may then wish to call us or your GP for more information. If there are no unexpected findings we will not contact you or your GP.

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In general, the research will not be of direct benefit to you, but may prove to be of benefit to others in the future. However, possible benefits are that you may find it satisfying to have contributed to medical research and, should an unexpected finding be discovered you may feel that the early detection and diagnosis will result in a better outcome. If you wish to have a copy of your scan report, you may ask for this.

What if something goes wrong?

It is unlikely that anything will go wrong but, if you wish to complain, you can do so using the normal NHS complaints procedure. If taking part harms you in any way, there are no special compensation arrangements, but the hospital would be liable for any negligence on the part of hospital staff. Your legal rights are not affected by giving your consent to participate in this study.

Who is organizing and funding the research?

This study is being organised by The Royal Marsden NHS Foundation Trust with participation from The Institute of Cancer Research, Imperial College London and Imperial Healthcare NHS Foundation Trust. The study is being funded by a National Institute for Health Research grant as part of their Efficacy and Mechanism Evaluation programme.

Will my taking part in this study be kept confidential?

1) Clinical Information: You will need to be given a Royal Marsden hospital number in order to receive the WB-DW-MRI scan. The resulting scan report will be held on our clinical Hospital Information (NHS PACS) System which is the system we use for holding all NHS patient information. Access to this system is subject to the normal Trust-based information governance controls. If, in the event of unexpected findings, you require further diagnostic investigations, your GP will be informed and your scans and accompanying data will be made available to the hospital treating you.

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5 **2) Research Information:** Your scan data will be anonymised and identified
6 by a unique trial identification number. Your unique trial number will be used
7 to make sure you cannot be identified by members of the research team that
8 are not part of the NHS staff at RMH. The data from your scan which will be
9 used in the MALIMAR study will only be available to authorised members of
10 our research team so they can collect information needed for this research
11 study and also to check that it is correct. All information will be kept
12 confidential, and your name, date of birth and other identifiable information will
13 be removed from your scans prior to archiving. We will also ask you to
14 consent to allow your data that has been collected in the study to be sent
15 outside of the UK and to be used in future ethically approved studies. This
16 information will not include any personal information that could directly identify
17 you.
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What will happen to the results of this study?

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32 As soon as there are reliable results, they will be published in a respected
33 peer reviewed medical journal and presented in various scientific meetings.
34 Your identity will not be revealed in any report, publication or presentation.
35 The results will be available on request.
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How is the trial monitored for safety?

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44 This study has been carefully planned by leading cancer specialists and
45 approved by the Oxford C Research Ethics Committee (REC), the Royal
46 Marsden Hospital Committee for Clinical Research (CCR) and the Health
47 Research Authority (HRA). The members of the study team will be meeting at
48 regular intervals to monitor the progress and safety of the study. Full (100%)
49 monitoring will be carried out to ensure that where incidental findings come to
50 light, both you and your GP are promptly informed.
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MALIMAR (CCR 4820, IRAS: 233501)

What do I do now?

We would be happy to answer any questions you may have about the study. You can telephone us, or speak to us again. Please discuss this information with your family, friends or your GP if you wish. If you require further information about this study please contact:

Professor Andrea Rockall,
Chief Investigator,
Clinical Chair Radiology,
ICTEM Building,
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Thank you for reading and considering taking part in this study.

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MALIMAR (CCR 4820, IRAS: 233501)

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For peer review only

Participant Type	Study name	Site	MRI Machine Name	Sequences acquired
Healthy Volunteers	MALIMAR	Royal Marsden	Siemens Aera	Haste localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_CAIPi_wb_tra_BH_20 and T2 HASTE Vertex to knees
Healthy Volunteers	MALIMAR	Royal Marsden	Siemens Avanto	localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_vibe_dixon_TRA_15deg 256_pocS and T2 HASTE Vertex to knees
Myeloma Patients	MALIMAR	Royal Marsden	Siemens Aera	Haste localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_CAIPi_wb_tra_BH_20 and Vertex to knees
Myeloma Patients	MALIMAR	Royal Marsden	Siemens Avanto	localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and fl3d_vibe_dixon_TRA_15deg 256 Vertex to knees
Myeloma Patients	MALIMAR	ICHT	Siemens Aera	Axial dixon x 4 350 slices each (total: 1400) B 50 248 slices B900 248 slices ADC 248 slices Sag T1 spine 15 slices Sag T2 spine 15 slices

MALIMAR Radiology Reads - CRF

Phase 2

Version 4, 06 September 2021

* Required

1. Scan ID *

2. Reader ID *

3. Round *

Round 1

Round 2

4. Date of Read *

Please input date (dd/MM/yyyy)



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3 5. Start time of read - Enter in format: HH:MM using 24 hour clock *

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6. Disease status - BONES - Record Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

7. Disease status - BONES - Record maximum size of Active / Focal lesions (mm) *

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones (max. long axis)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae (max. long axis)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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8. Disease Status - BONES - How confident are you in your assessment of
Active / Focal lesions *

	Not at all confident	Some confidence	Confident	Very Confident
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. Disease Status - Record if diffuse disease was present at any of these sites?

*

	Yes	No
Cervical Spine	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>

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3 10. How confident were you in your assessment of diffuse disease at these
4 sites? *

	Not at all confident	Some confidence	Confident	Very confident
11 Cervical 12 Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15 Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18 Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21 Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24 Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
27 Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
30 Ribs / 31 Clavicles / 32 Sternum / 33 Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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39 11. Was extramedullary disease present at any site? *

41 Yes

42 No

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51 12. If extramedullary disease was present at any site - state location(s)
52 separated by a semi-colon

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13. If extramedullary disease was present, what was your level of confidence in assessing this? *

- Not confident at all
- Some confidence
- Confident
- Very confident
- Not Applicable, no extramedullary disease is seen.

14. Confidence in assessing overall disease status on this scan (i.e. in determining the presence or absence of ANY active disease) *

- Not confident at all
- Some confidence
- Confident
- Very confident

15. Stop time of read - RECORD IMMEDIATELY AFTER COMPLETING CLINICAL READ - Enter in format: HH:MM using 24 hour clock *

16. TO BE COMPLETED FOLLOWING THE CLINICAL READ:

Was a Machine Learning Image available *

- Yes
- No

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3 17. If a Machine Learning 'ML' Image was available, please indicate whether
4 sites were positive for active / focal disease, i.e. was there an ML finding?
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	Highly likely negative on ML	Probably negative on ML	Probably positive on ML	Highly likely positive on ML
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18. If a Machine Learning 'ML' image was available, please indicate whether sites were positive for diffuse disease, i.e. was there an ML finding?

	Highly likely negative on ML	Probably negative on ML	Probably positive on ML	Highly likely positive on ML
Cervical Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dorsal Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lumbar Spine	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pelvis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Long Bones	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Skull	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Ribs / Clavicles / Sternum / Scapulae	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

19. Scan Quality: What was the quality of the WB-MRI used for this read? *

	Good	Adequate	Poor
1. B 900	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. ADC	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. T1 sequences	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

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3 20. Please enter any specific comments you have on scan quality
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14 21. Reader confirmation: My responses have been accurately reported on this
15 CRF (enter 'yes' if in agreement with this statement) *

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30 owner.
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MALIMAR Radiology Reads - CRF

Phase 3

Version 2, 31 March 2022

* Required

1. Scan ID Post Treatment Scan (PT) *

2. Scan ID - Baseline Scan (BL) *

3. Reader ID *

4. Phase 3 - Round *

Round 1

Round 2

5. Date of Read *

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Format: M/d/yyyy

6. Start time of read - Enter in format: HH:MM using 24 hour clock *

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7. CERVICAL SPINE - Number of Active / Focal Lesions *

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	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

8. CERVICAL SPINE - Maximum size (mm) of Active / Focal Lesions *

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	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

9. CERVICAL SPINE - Was Diffuse Disease present? *

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	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

10. DORSAL SPINE - Number of Active / Focal Lesions *

		0	1 - 4	5 - 10	>10
5	Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8	Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

11. DORSAL SPINE - Maximum size (mm) of Active / Focal Lesions *

		<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
22	Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25	Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

12. DORSAL SPINE - Was Diffuse Disease present? *

		Yes	No
36	Post Treatment	<input type="radio"/>	<input type="radio"/>
39	Baseline	<input type="radio"/>	<input type="radio"/>

13. LUMBAR SPINE - Number of Active / Focal Lesions *

		0	1 - 4	5 - 10	>10
51	Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
54	Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

14. LUMBAR SPINE - Maximum size (mm) of Active / Focal Lesions *

Not Applicable,
No Focal lesions
seen at this site

	<10mm	10 - 20mm	>20mm	
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

15. LUMBAR SPINE - Was Diffuse Disease present? *

Yes

No

Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

16. PELVIS - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

17. PELVIS - Maximum size (mm) of Active / Focal Lesions *

Not Applicable,
No Focal lesions
seen at this site

	<10mm	10 - 20mm	>20mm	
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

18. PELVIS - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

19. LONG BONES - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

20. LONG BONES - Maximum size (mm) of Active / Focal Lesions *

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

21. LONG BONES - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

22. SKULL - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

23. SKULL - Maximum size (mm) of Active / Focal Lesions *

	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

24. SKULL - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

25. RIBS / CLAVICLES / STERNUM / SCAPULAE - Number of Active / Focal Lesions *

	0	1 - 4	5 - 10	>10
Post Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

26. RIBS / CLAVICLES / STERNUM / SCAPULAE - Maximum size (mm) of Active / Focal Lesions *

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	<10mm	10 - 20mm	>20mm	Not Applicable, No Focal lesions seen at this site
Post-Treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

27. RIBS / CLAVICLES / STERNUM / SCAPULAE - Was Diffuse Disease present? *

	Yes	No
Post Treatment	<input type="radio"/>	<input type="radio"/>
Baseline	<input type="radio"/>	<input type="radio"/>

28. Was extramedullary disease present at any site? *

- Yes
- No

29. If extramedullary disease was present at any site - state location(s) separated by a semi-colon

30. If extramedullary disease was present, what was your level of confidence in assessing this? *

- 1
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4 Not confident at all
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6 Some confidence
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9 Confident
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11 Very confident
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14 Not Applicable, no extramedullary disease is seen.
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20 31. OVERALL RESPONSE - Change in Disease Status (Baseline - Post-Treatment) *

- | | Complete Response | Partial Response | Stable Disease | Disease Progression |
|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Response category | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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33 32. OVERALL RESPONSE - CONFIDENCE - How confident were you in assessing overall response? *

- | | Not at all confident | Some confidence | Confident | Very confident |
|---------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Confidence category | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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47 33. Stop time of read - RECORD IMMEDIATELY AFTER COMPLETING CLINICAL READ -
48 Enter in format: HH:MM using 24 hour clock *
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34. TO BE COMPLETED FOLLOWING THE CLINICAL READ:

Was a Machine Learning Image available *

Yes

No

35. If Machine Learning 'ML' Images were available, please indicate category of response suggested by ML

	Complete Response	Partial Response	Stable Disease	Progressive Disease
Response category	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

36. Scan Quality: What was the quality of the WB-MRI used for this read? *

	Good	Adequate	Poor
1. B 900	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. ADC	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. T1 sequences	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

37. Please enter any specific comments you have on scan quality

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38. Reader confirmation: My responses have been accurately reported on this CRF (enter 'yes' if in agreement with this statement) *

Yes

No

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peer review only

Supplementary S4 – MALIMAR Amendments

No. and Type of Amendment	Date approved	Brief Details of amendment
1. Non-substantial	25/06/2018	Protocol administrative updates
2. Non-substantial	15/01/2019	Communications to HVs
3. Non-substantial	19/03/2019	Update on scan numbers for protocol
4. Non-substantial	16/10/2019	Addition of ICHT site
5. Non-substantial	28/06/2019	Extension of project time-line and uplift in costs

For peer review only

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: <http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/>

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

Reporting Item		Page and Line Number	Reason if not applicable
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, line 1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 7, line 141
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a Not a RCT
Protocol version	#3	Date and version identifier	Page 22, line 488

1 2 3 4 5 6 7 8 9	Funding	#4	Sources and types of financial, material, and other support	Page 4, line 71	
10 11 12 13 14	Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 4, line 65	
15 16 17 18 19 20 21 22 23	Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 4, line 86	
24 25 26 27 28 29 30 31 32 33	Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Page 4, line 86 Page 20, line 452	
34 35	Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page 20, line 440	
36 37 38 39 40 41 42 43 44	Introduction				
45 46 47	Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 8, line 156	

1 2 3 4 5	Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 9, line 181 - 191	
6 7	Objectives	#7	Specific objectives or hypotheses	Page 9, line 191	
8 9 10 11 12 13 14 15	Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	Page 9, line 199 Page 12 line 254	
16	Methods: Participants, interventions, and outcomes				
17 18 19 20 21 22 23 24	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 10, line 216	
25 26 27 28 29 30 31	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 10-11, line 221-228 and Table 1	
32 33 34 35 36	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 11, line 229	
37 38 39 40 41 42 43	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a	No modifications

1 2 3 4 5 6	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a	No strategies or monitoring of adherence
7 8 9	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a	Use of scans only
10 11 12 13 14 15 16 17 18 19 20 21 22	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 15, line 343	
23 24 25 26 27 28 29 30	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and Table 3	Schedule and assessment of scans rather than participants
31 32 33 34 35 36 37 38	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 16, lines 366	
39 40 41 42 43 44	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 12, line 271 Page 13, line 285	

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Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 10, lines 194-210	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 10, lines 200-210	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 14, line 316 Page 15, line 327	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 14, line 318 Page 21, line 470	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a	No blinding of intervention
Methods: Data collection, management, and analysis				

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1 2 3 4 5 6 7 8 9 10 11 12 13	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 15, line 337	
14 15 16 17 18 19 20 21 22	Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a	No participant retention/follow-up
23 24 25 26 27 28 29 30 31	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 15, line 340	
32 33 34 35 36 37 38	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 17, line 391-428	
39 40 41 42	Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a	Primary and secondary analysis included only

1 2 3 4 5 6	Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 19, line 421	
7 8 9	Methods: Monitoring				
10 11 12 13 14 15 16 17 18 19 20 21	Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 19 line 433 – line 450	
22 23 24 25 26 27 28	Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page18, line 396 Page 18, line 408	
29 30 31 32 33 34	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 19, line 433	No adverse event reporting as not an interventional study on participants. Specified in manuscript.
35 36 37 38 39 40	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 19, line 438	
41 42 43 44 45 46 47	Ethics and dissemination				

1 2 3	Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 20, line 452	
4 5 6 7 8 9 10 11	Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	Page 20, line 456	
12 13 14 15 16 17	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 13, lines 272-279	
18 19 20 21 22	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a	No ancillary studies
23 24 25 26 27 28 29	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 20, line 458-461 Page 22, line 484	
30 31 32 33 34	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 5, line 102	
35 36 37 38 39 40 41 42 43 44 45 46 47	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 20, line 457-458	

1 2 3 4 5	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a	No participant level intervention
6 7 8 9 10 11 12 13 14 15 16	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 20, lines 457-461	
17 18 19 20	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 20, lines 457-461	
21 22 23 24 25	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 20, lines 457-461	
26 27	Appendices				
28 29 30 31 32	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material S1a, S1b	
33 34 35 36 37 38 39	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a	No biological specimens collected

It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.

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