Development of machine learning support for reading whole body diffusion-weighted MRI (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

Laura Satchwell, Linda Wedlake, Emily Greenlay, Xingfeng Li, Christina Messiou, Ben Glocker, Tara Barwick, Theodore Barfoot, Simon Doran, Martin O Leach, Dow Mu Koh, Martin Kaiser, Stefan Winzeck, Talha Qaiser, Eric Aboagye, Andrea Rockall

ABSTRACT

Introduction Whole-body MRI (WB-MRI) is recommended by the National Institute of Clinical Excellence as the first-line imaging tool for diagnosis of multiple myeloma. Reporting WB-MRI scans requires expertise to interpret and can be challenging for radiologists who need to meet rapid turn-around requirements. Automated computational tools based on machine learning (ML) could assist the radiologist in terms of sensitivity and reading speed and would facilitate improved accuracy, productivity and cost-effectiveness. The MALIMAR study aims to develop and validate a ML algorithm to increase the diagnostic accuracy and reading speed of radiological interpretation of WB-MRI compared with standard methods.

Methods and analysis This phase II/III imaging trial will perform retrospective analysis of previously obtained clinical radiology MRI scans and scans from healthy volunteers obtained prospectively to implement training and validation of an ML algorithm. The study will comprise three project phases using approximately 633 scans to (1) train the ML algorithm to identify active disease, (2) clinically validate the ML algorithm and (3) determine change in disease status following treatment via a quantification of burden of disease in patients with myeloma. Phase 1 will primarily train the ML algorithm to detect active myeloma against an expert assessment (‘reference standard’). Phase 2 will use the ML output in the setting of radiology reader study to assess the difference in sensitivity when using ML-assisted reading or human-alone reading. Phase 3 will assess the agreement between experienced readers (with and without ML) and the reference standard in scoring both overall burden of disease before and after treatment, and response.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

⇒ The MALIMAR study has the potential to acquire and characterise what is possibly the largest set of myeloma WB-MRI scans in the UK.
⇒ The cross-sectional diagnostic accuracy design allows for retrospective analysis of previously obtained clinical radiology scans for training and validation of an ML algorithm.
⇒ This study will provide ML outputs that can be tested across the National Health Service in live real-time clinical settings.
⇒ As data will be acquired over a long period of time, scan quality could vary.
⇒ Replicating clinical reporting in a retrospective study setting can be difficult to achieve, particularly for analysis of scan reading time.

INTRODUCTION

There is strong evidence in the existing literature for the use of whole-body MRI (WB-MRI) in the management of patients with multiple myeloma. In 2016, the National Institute of Clinical Excellence (NICE) made the recommendation of using WB-MRI as the first-line
imaging tool for diagnosis, based on the literature. A consensus from the International Myeloma Working Group agreed that identification of focal lesions more than 5 mm on MRI should now be used as an indication to treat. Evidence suggests that diffusion-weighted (DW) WB-MRI (WB-DW-MRI) is the most sensitive magnetic resonance technique for detecting marrow disease and superior to fluorodeoxyglucose positron emission tomography/CT for the detection of small sites of disease and diffuse infiltration. Therefore, WB-MRI is increasingly being adopted at centres worldwide for patients with myeloma. Treatment of high-risk patients is known to improve overall survival, therefore improved diagnostic accuracy is likely to translate into improved patient selection for treatment and prolonged survival.

Despite the acknowledged benefits of WB-MRI for patients with myeloma, with publication of the NICE guidance, one of the major concerns is how these complex scans can be reported by a radiology workforce in crisis. Specificity of disease detection in the marrow is improved by viewing source DW images alongside quantitative apparent diffusion coefficient (ADC) maps. This allows differentiation of active sites of disease with restricted diffusion from treated sites of disease and vertebral haemangiomas, which conversely return a very high ADC. Dixon images are also integral to image interpretation and morphological imaging is also necessary to identify mechanical complications of myeloma bone disease. Therefore, diagnostic accuracy is dependent on viewing multiple imaging sequences and typically over

**Figure 1** MALIMAR study flow diagram. ADC, apparent diffusion coefficient; CNN, convolutional neural network; ML, machine learning; NICE, National Institute of Clinical Excellence; TMG, trial management group; WB-MRI, whole-body MRI.
1200 image slices per WB-MRI scan in order to achieve whole body coverage. Consequently, reading time for the scans may be significant. At least 9% of UK radiology posts are unfilled,13 and in 2015, clinical radiology was placed on the national shortage occupation list. The time-consuming process of reporting WB-MRI scans is a concern for radiologists who need to provide rapid turn around with a high productivity to support the National Health Service (NHS). Automated computational tools based on machine learning (ML) could support reporting of these large data sets and facilitate translation of this valuable imaging technique into the NHS, not only in detecting active disease but also in identifying response to treatment. Ideally, an ML algorithm would automatically detect and highlight suspicious regions and could reduce reading time. An accurate and automatic detection of pathology may also increase diagnostic accuracy.

The possibility of using computer-assisted ML techniques has been considered in aiding interpretation of complex imaging data sets.14–16 Current work in the EME NIHR (Efficacy and Mechanism Evaluation National Institute of Health Research) funded MALIBO study17 18 (13/122/01) has demonstrated fully automatic multiorgan segmentation using WB-MRI in healthy volunteers (HV) and ML detection of primary colorectal cancer and metastatic lesions.

**Aim**

The aim of the MALIMAR study is to develop and validate an ML algorithm to improve the sensitivity of radiologists to detect the presence and extent of active myeloma before and after treatment, with high reproducibility and reduced reading time (WB-MRI with ML, the intervention) when compared with the standard of care radiology read (WB-MRI without ML support, the comparator).

**METHODS AND ANALYSIS**

**Study design**

The study is based on a cross-sectional diagnostic test accuracy design and will comprise three distinct project phases as summarised in figure 1.

- In phase 1, the ML algorithm will be trained using both HV and myeloma patient scans to recognise active myeloma deposits as distinct from cases with no active disease, classifying disease as ‘focal’, ‘diffuse’ or ‘inactive’.
- In phase 2, the ML algorithm will be validated using a second unseen data set against a reference standard (ie, ground truth) to assess how accurately radiologists classify disease using scans with the ML algorithm and compared with readings without ML. Diagnostic accuracy on a per patient and per region (using 16 predefined anatomical sites—table 1) basis and reading time will be measured.
- In phase 3, further development of the ML algorithm to quantify disease burden will be undertaken using data sets from phase 1 and 2. This quantification output will be tested in the phase 3 reader study in which readers will record disease burden and response between paired baseline (new diagnosis or relapse prior to initiation of treatment) and single post-treatment WB-MRI scans, with or without ML support, and tested against the reference standard.

**Participants and recruiting centres**

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

The scan population will comprise of; HV WB-MRI scans acquired from participants prospectively recruited from the sponsor site only (RMH), with the option of the Imperial Site providing previously acquired HV scans; WB-MRI scans acquired as part of clinical care from patients being managed at RMH and ICHT and WB-MRI scans previously acquired for a prospective research study in WB-MRI (iTMM study).9 19 All scans acquired for the study will be done, so using clinical standard of care trust protocols.

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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of MALIMAR anatomical regions between ground truth CRFs and reader CRFs</th>
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<tr>
<td><strong>Anatomical regions</strong></td>
<td><strong>Ground truth CRFs (phases 1 and 2)</strong></td>
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<td>Skull</td>
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<td>Scapula right</td>
<td>Ribs/clavicles/sternum/scapulae</td>
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<td>Clavicle left</td>
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<tr>
<td>Sternum</td>
<td>Ribs/clavicles/sternum/scapulae</td>
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<tr>
<td>Spine upper</td>
<td>Cervical spine</td>
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<td>Spine middle</td>
<td>Dorsal spine</td>
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<tr>
<td>Spine lower</td>
<td>Lumbar spine</td>
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<td>Ribs right</td>
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<td>Sacrum</td>
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Intervention and reference standard

**Intervention (including comparator)**

The comparator in this study is defined as WB-MRI scans read by experienced radiologists, as per standard care (WB-MRI, the COMPARATOR). The intervention will use these standard methods with the addition of ML (WB-MRI+ML, the INTERVENTION). The ML algorithm will be developed during phase 1 of the study following data curation and scan allocation to phases 1 and 2. DW imaging, ADC map and T1-weighted sequences (Dixon fat and water scans) will be used, reflecting the radiological reading tools used by expert readers.

Radiologists or readers are defined as experienced based on their previous clinical radiology reading skills and responsibilities and their length of service in this role. Experienced readers will be required to have completed at least 100 WB-MRI clinical scan reports.

**Reference standard**

There is no available histological reference standard for every site of bone marrow disease, as trephine biopsy is usually restricted to a single site. The proposed reference standard, thus, comprises the interpretation of an expert panel; a radiologist and a haematologist who are experts in myeloma. They will have access to (1) WB-MRI images, (2) bone marrow histopathology reports (with quantitation), (3) serum paraproteins, (4) serum-free light chain (sFLC), in order to categorise per scan:

- Presence or absence of active disease.
- The detailed disease distribution by anatomical site.

**Table 2** Inclusion and exclusion criteria

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<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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| 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  |
| Patients in phases 1 and 2 | Patient with confirmed myeloma with WB-MRI scan previously performed as part of clinical care. Sufficient imaging and clinical data for the expert reference panel to categorise the WB-MRI scan as:  
|                    | 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  
|                    | Patients may be included if the pattern of disease is a combination of focal, diffuse and/or extra-medullary.  |
| Patients in phase 3 | Training set: phase 1 active disease cases and their post-treatment scans from phase 2. Validation set: from iTIMM study. Written informed consent for iTIMM study  
|                    | All patients over the age of 18 with multiple myeloma planned for autograft.  |

Corrupted WB-MRI scan data. Insufficient clinical data to allow the expert reference panel to categorise the scan.

iTIMM, Image-guided Theranostics in Multiple Myeloma; WB-MRI, Whole-Body Magnetic Resonance Imaging.

**Table 3** Number of healthy volunteer (HV) and multiple myeloma (MM) scans in each category for each study phase

<table>
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<tr>
<th>Phase 1†</th>
<th>HV</th>
<th>MM inactive</th>
<th>MM active focal</th>
<th>MM active diffuse</th>
<th>MM new diagnosis</th>
<th>Total</th>
</tr>
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<tr>
<td></td>
<td>40</td>
<td>40</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>Phase 2</td>
<td>50</td>
<td>100</td>
<td>105</td>
<td>70</td>
<td>28</td>
<td>353</td>
</tr>
<tr>
<td>Phase 3 training‡</td>
<td>0</td>
<td>(80 post-treatment)</td>
<td>60</td>
<td>40</td>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>Phase 3 validation</td>
<td>0</td>
<td>60 patients in iTIMM study scanned at baseline and post-treatment</td>
<td></td>
<td></td>
<td></td>
<td>120</td>
</tr>
</tbody>
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*A total of 50 HV will be used, 40 in phase 1, which will be used again in phase 2, with the addition of 10 more HV.  
†The number of scans in phase 1 may increase by 140–180 scans (100 subjects) if there is evidence of over-fitting in the development of the algorithm.  
‡Scans used in phase 3 training are scans that have been previously used in phases 1 and 2.  
HV, Healthy Volunteer; iTIMM, Image-guided Theranostics in Multiple Myeloma; MM, Multiple Myeloma.
Quantification of the burden of disease (using a validated MRI score and sFLC) including category of response to treatment.

Scan and site-level data from these scans will be captured on case report forms (CRFs) for all cases in phases 1 and 2 and used as ‘ground truth’ in the classification of study output. Reference standard for phase 3 will be obtained from the source (iTTiM study).

Objectives
Primary research objectives
Phase 1: to develop a myeloma-specific ML algorithm to detect the presence of active disease on WB-MRI+ML (with machine learning ‘+ML’) with sufficient sensitivity.

Phase 2: to validate WB-MRI+ML against the comparator WB-MRI for sensitivity on a per-patient and per-site basis.

Phase 3: to develop and validate an ML algorithm to automatically quantify the burden of active disease, before and after treatment.

Secondary research objectives (phases 2 and 3 only)
For each of the following, our objective is to compare WB-MRI with and without ML support to the reference standard for:
1. Reading time.
2. Specificity.
4. Agreement of categorising disease as focal, diffuse and/or extramedullary.
5. Agreement of categorising patients as responder or non-responder.

Procedure
Scan acquisition—HV
HV will be recruited to obtain data from normal bone marrow within the age range typical of myeloma. Up to 50 HVs aged 40 years or above will be recruited using approved advertisements at the Sponsor site and consented with the help of clinical research network (CRN) resources (see online supplemental file 1a for consent form). The HV information sheet (online supplemental file 1b) will clearly explain the MRI scanning procedure and the actions that will be taken in the event of incidental (ie, unexpected) findings. Contact details will be supplied on the HV information sheet to enable volunteers to respond to the invitation or ask any questions. A total of 22 HV scans previously acquired are also available for use from ICHT if needed.

Participating HVs will undergo a single whole body MRI scan at RMH according to the trial-specific scanning protocol. HV scans will be acquired in the following sequences (T1, fat/water, Dixon, ADC, etc) to mirror the clinical setting and on Siemens, Avanto and Aero (wide bore) MRI scanners. Subjects with a larger body mass index will be scanned on the Siemens Aero, which has a larger bore diameter to optimise comfort.

Scan acquisition—patients with myeloma
Previously acquired patient scans will be identified by the investigators within the Sponsor’s myeloma clinical service (between 2011 and 2020), supplemented by scans from ICHT, until the required sample size is reached. Scans will normally include the following sequences; T1, fat/water, Dixon, ADC, etc, and on the following MRI machines; Siemens, Avanto and Aero MRI scanners (online supplemental file 2 for sequence details).

Scan classification and allocation to study phase
Patient scans will be categorised by the expert reference panel as showing inactive disease, active focal, active diffuse (focal or diffuse) and new disease. HV scans will be classified as normal (ie, non-diseased). Scans will be allocated to Phase one or two as per table 3. To minimise bias or ‘over-learning’, no more than five scans from the same patient will be allocated to Phase 1. Phase two scans will not include any patient scans that have been used in Phase one and thus comprise only those previously unseen by the ML algorithm. A subset of scans from phase 1 and 2 will be used to further train the algorithm at the start of Phase 3. Phase three validation scans have previously been acquired for the iTTiM trial (NCT02403102) and include a unique series of paired scans, previously unseen by the ML algorithm.

Scan curation (quality control) and anatomical segmentation
Eligible scans will be curated immediately prior to transfer to an online platform for secure storage (ICR XNAT). This will ensure that the ML algorithm is able to interpret all scans consistently. Curation scripts will be written in python and ensure that scans exhibit consistent characteristics such as: correct sequential display of images, no missing slices, noting presence of unusual artefacts that might interrupt ML reads and other factors which might compromise interpretation. Further details on the data curation will be published elsewhere.

Phase 1 scans will then be manually segmented into 16 bone regions (table 1) using a boundary box approach. These scans will be used to teach the ML algorithm to recognise active myeloma disease (focal or diffuse) and precision metrics will be evaluated in order to achieve the optimal algorithm. Initially, scans will be classified by the ML algorithm at scan level (ie, patient level) only.

Testing of ML algorithm—radiology reading process
The ML algorithm will be tested by both experienced and inexperienced radiology readers.

Phase 2 scans will be subjected to the ML algorithm, which will provide an ML overlay on all scans, indicating areas of disease by means of a heat map. For each scan, a ‘standard’ and ‘ML’ version will be available. The trial statistician will randomly allocate reads to each of the (approximately 15–20) readers, using trial-specific algorithms written using Stata software (StataCorp, Texas). The reads will be performed in two batches to incorporate a wash-out period. Each batch will have 50% of cases with...
ML support and 50% without, to avoid reader training bias. The reading process will be described in a reader manual and all readers will receive appropriate training in viewing scans using the Biotronics 3D web-based platform and completing a Read CRF available via Microsoft Forms (see online supplemental file 3a). In the case of ‘inexperienced’ readers, training will comprise a review of the CRFs and the viewing software with a basic training on reporting lexicon. A scribe will be provided to assist readers during the reading process and input data to the CRF in each batch of reads. Following a 4-week wash out period, readers will be presented with the second batch of reads with the opposite reading paradigm with regards to the ML support. The same cases will be allocated to the same readers. A subset of approximately 50 scans will be read a second time by a different reader as an inter-rater check.

In phase 3, scans from the iTIMM study, comprising paired baseline and follow-up post-treatment scans, will be used to test whether the ML algorithm is capable of distinguishing change in disease status (ie, disease burden) between the two time points. Reads will again be randomly allocated to the readers by the trial statistician. Readers will follow similar procedures to that outlined above with one set of paired scans having the ML overlay and the other with no ML overlay (for CRF, see online supplemental file 3b). A 4-week wash out period will again apply between the two batches of reads. A subset of approximately 20 scans will be read a second time by a different reader as an inter-rater check.

Data collection
Reader responses will be captured using MS Forms with responses being transferred directly to an excel spreadsheet. Examples of the CRFs to be used in both ML validation phases are given as online supplemental file 3a,b. All readers will be provided with a manual describing CRF completion (including a lexicon of disease definitions) and use of the software viewing tools and overlay of the ML output heatmap and opportunity for live training using the online platform.

Outcome measures
Phase 1—ML algorithm training phase
Primary: sensitivity for the detection of active myeloma on WB-MRI+ML detection tool against the reference standard.
Secondary: (1) specificity; (2) F1 score (a single measure of precision and recall).

Phase 2—ML algorithm clinical testing phase (presence/absence of active myeloma)
Primary: difference in sensitivity of WB-MRI−/+ML detection tool to diagnose the presence of active myeloma on a per-patient basis, by experienced readers, assessed against the reference standard.
Secondary: for comparison of WB-MRI−/+ML: (1) per-site sensitivity to diagnose active disease, (2) reading time, (3) specificity, (4) agreement with reference standard to categorise disease as focal, diffuse and/or extramedullary, (5) Sensitivity of non-experienced readers for presence of active disease.

Phase 3—ML algorithm for quantification of disease burden with clinical testing
Primary: agreement between experienced readers and the reference standard in scoring overall burden of disease before and after treatment for response categorisation −/+ ML quantification tool.
Secondary: for comparison of WB-MRI −/+ML: (1) reading time, (2) agreement of categorisation of patients as responder or non-responder with the reference standard, (3) agreement of non-experienced readers for burden of disease and categorisation of response, (4) estimated difference in cost for radiology reading time for WB-MRI −/+ML.

Proposed tertiary: verification of the team’s previously published work regarding reverse classification accuracy: predicting segmentation performance in the absence of a reference standard.

Sample size
Phase 1
We will train the ML algorithm on a set of scans without and with active disease that will reflect the categories of disease that may be encountered in clinical practice. The number of cases used for training are arbitrarily chosen reflecting the knowledge that a large number of training data sets will improve training accuracy, counterbalanced with the resources needed to curate and annotate a large number of data sets.

Phase 2
The study is powered on the primary outcome of sensitivity.
In a meta-analysis, Wu et al have reported a pooled sensitivity of 88% and a pooled specificity of 86% (0.86 for WB-MRI with DW-MRI). We anticipate that the addition of ML could increase this by at least 7.5%, from 88% to 95.5%. There is no background data to indicate the expected proportion of discordant pairs, so we have estimated this as (1–0.955)×0.88+0.955×(1–0.88), which is equal to 0.154. To achieve 80% power using a two-sided alpha of 0.05 would require a total of 203 patients positive for myeloma using the gold standard.
If it is assumed that the specificity will be unchanged using ML, a total number of cases with no active disease of 150 (50 HV, 100 inactive treated myeloma) will give 80% power to show that the difference is above a non-inferiority limit of 10%.

Phase 3 training
Approximately 200 cases that have at least two time points will be taken from phases 1 and 2, with active disease present at least at one time point, and used for training and validation for burden of disease; this will ensure efficient use of all data and segmentations.
Phase 3 clinical testing
This sample size is fixed at 60 patients, the full sample size of the iTIMM study, each of whom has a baseline and one post-treatment scan.

Statistical analysis
Phase 1 analysis
The ability to correctly localise and detect active disease will be evaluated by calculating sensitivity, specificity and the F1 score (a single measure of precision (positive predictive value) and recall (sensitivity)) for multiple algorithms and compared against the reference standard. Following Trial Steering Committee (TSC) approval, the optimal algorithm will move forward to phase 2.

Phase 2 analysis
In phase 2, the percentage of patients with active disease on WB-MRI+/−ML support who have positive reference standard will be compared using McNemar’s test with a two-sided alpha of 0.05. Per-patient and per-site sensitivity and specificity with and without ML support will be reported with 95% CIs. Reading time will be compared using Wilcoxon’s test for paired data and described using summary statistics.

The same analysis of sensitivity, specificity and reading time will be repeated for inexperienced readers.

Agreement between experienced and inexperienced readers will be measured in a subset of cases with a Kappa coefficient and overall proportion of concordant cases.

All other endpoints will be summarised using descriptive statistics.

Although the study is powered to detect superiority of the primary endpoint, if sensitivity is shown to be non-inferior using ML and reading time is both clinically and statistically significantly lower using ML, this would be considered as an indication to proceed. Non-inferiority in this context will be defined as having any possible reduction in sensitivity with ML significantly higher than a lower limit of −10% (using Tangos’ test with one-sided alpha of 0.05).

Phase 3 analysis
In phase 3, the difference between the experienced readers’ disease score to the reference standard disease score will be recorded and compared+/−ML support using Wilcoxon’s test. Differences from scores given by experienced readers and the reference standard will be described using Bland-Altman plots for scores±ML support.

All other endpoints will be summarised using descriptive statistics.

A simple cost-effectiveness analysis may be performed depending on study findings, such as the reading time.

Procedure(s) to account for missing or spurious data
If a scan is incomplete or the file is corrupted and not evaluable, it will be excluded from the data set. If a set of radiology reads is incomplete, a new trained reader will be identified to do the full allocation of reads.

Timing and responsibility for analyses
Analyses will take place at both the end of phase 2 and then again at the end of phase 3, when all readings have been completed.

Patient and public involvement
A patient and public involvement (PPI) representative was appointed from an established group at Myeloma UK. The individual gave in-depth feedback on the study, particularly on the relevance to patient care and the use of retrospective patient data and HV scans. Myeloma UK is fully supportive of the project and is willing to assist with dissemination of important findings to the Myeloma UK community.

Safety
As this study is recruiting HV only, an a priori agreement has been reached with the sponsor that safety reporting is not required. Sponsor procedures in respect of incidental (i.e., unexpected) findings in HV will be adhered to and results were captured within the Trust’s Clinical Record.

Monitoring against Source Data will not be required, which is in line with the Sponsor’s policy on non-Clinical Trial of Investigational Medicinal Product trials.

Trial funding, organisation and administration
The study has been awarded funding by Medical Research Council NIHR EME Awards Body (NIHR EME Project ID: 16/68/34). In addition, the department of radiology has agreed to fund the cost of HV WB-MRI scans. The cost of recruitment and consenting of HVs will be requested through the NHS CRN. RMH is the study sponsor responsible for initiating and managing the study and the coordinating centre, including sign-off of the study protocol.

A trial management group (TMG) meeting will be held regularly to ensure satisfactory progress of the study. A TSC will provide independent oversight for the study, review the development of the ML algorithm and advise the TMG where problems may arise. The TSC will include a patient advocate.

Ethics and dissemination
Ethical approval for MALIMAR was granted on 21/11/2017 (REC) and 21/12/2017 (Health Research Authority) Here, we report V.3.0 of the protocol. All participating sites gained local approval prior to study participation.

Any protocol modifications will be submitted for approval to the REC, reflected in the online registration and disseminated by e-mail to site principal investigators and trial coordinators. The statistician will have access to the final linked trial data set. There are no plans to provide public access to the full protocol, participant-level data or statistical code. The researchers aim to publish results in a peer-reviewed journal and share via social media and conferences. Authorship will be determined according to academic standards.
DISCUSSION

This study aims to develop and validate an ML algorithm to augment the performance and efficiency of the radiology reading process using WB-MRI. The results will show the impact of using the ML tool and outcomes of the study will have implications for the application of ML with WB-MRI in patients with patients across the NHS. It is anticipated that feasibility analysis will follow the successful completion of this study to pilot the implementation of the ML tool in a real-time prospective study prior to future clinical setting.

To avoid bias, we ensure: (1) comparator and intervention tests are read by readers that are fully blinded to the reference standard, (2) a mixture of cases with and without disease, (3) the reads will be presented such that radiologists must read a mixture of cases without or with ML support during each round of reading including a wash out period. We will have unavoidable incorporation bias, as the expert reference panel will use the MRI as part of the reference standard. The reference panel will consist of a single person’s opinion, which is a limitation to our study. If resources had allowed, the gold standard would have been to have two blinded opinions with a consensus panel in cases of disagreement. Other limitations include varying scan quality as data are acquired over a 9-year period; and replicating clinical reporting in a retrospective study setting can be challenging.

In conducting this study, we will have acquired possibly the largest set of characterised myeloma patient MRI scans in the UK and we anticipate that this will form the basis of a unique training resource in the future.

ML techniques in WB-MRI scans of patients with myeloma are likely to be transferable to other malignancies. In prostate and breast cancer, quantification of metastatic bone disease is an unmet need as bone only disease is not uncommon and is currently classified as non-measurable by RECIST V.1.1. The participating HVs will be consulted to allow the anonymised datasets to be a future resource for the wider research community.

Study status

The MALIMAR study opened on 26 April 2018 using protocol V.1.0 (30 October 2017). The study was in phase II, using protocol V.3.0 (31 January 2019), at date of submission. Protocol amendments are documented in online supplemental file 4.

Acknowledgements

We acknowledge NHS funding to the NIHR Biomedical Research Centre (BRC) at The Royal Marsden and Institute of Cancer Research and the NIHR Royal Marsden Clinical Research Facility. We acknowledge the support of the Imperial College London NIHR BRC Imaging Theme and the Cancer Research UK (CRUK) Imperial Centre and the Imaging Research Office at ICHT. We acknowledge the support of the CRUK funded National Cancer Imaging Translational Accelerator award (Institute of Cancer Research and Imperial College London).

Contributors

AR, CM, Tab, BG, SW, TG, ThB, SD, MOL, MK and DK: conceptualisation and methodology; AR, CM, Tab, ThB, MK, BG, TG, XF and SW: investigation; EA and AR: resources; ThB and SD: data curation; LS and EG: formal analysis; AR, DK and CM: supervision; LS: writing—original draft; AR, CM, Tab, BG, LW and LS: writing—review and editing; BG, TG, XF and SW: data visualisation; LW project administration; EA and AR: funding acquisition.

Funding

This study (ID: 16/68/34) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. In addition, the Department of Radiology has agreed to fund the cost of healthy volunteer whole body MRI scans. The cost of recruitment and consenting of healthy volunteers will be requested through the NHS Clinical Research Network. The views expressed in this publication are those of the authors and not necessarily those of the MRC, NHS, the NIHR, or the Department of Health and Social Care. ES and LS’s posts are part funded by the National Institute for Health and Care Research (NIHR) Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. SW is supported by the UKRI London Medical Imaging & Artificial Intelligence Centre for Value Based Healthcare.

Competing interests

AR receives honoraria for educational lecture at Garmisch International Symposium, has an unpaid role on the European Society of Radiology Board of Directors and receives travel cost support where necessary. BG receives grants from other entities; EU commission and UKRI London Medical Imaging & Artificial Intelligence Centre for Value Based Healthcare, is a Scientific advisor for Kheiron Medical Technologies (January 2018–September 2021) and receives stock options as part of standard employment packages from both Kheiron Medical Technologies and HeartFlow. EA has a patent pending for Machine Learning in Alzheimer’s disease and has a role on the scientific advisory board for Radiogheath Theranostics Limited. MK receives grants from both Myeloma UK and Celgene/ BMS, and consulting fees or payments from AbbVie, BMS/Celgene, Janssen, GSK, Karyopharm, Takeda and Seagen. CM & DK receive additional funding as a co-investigator on a radiology NIH study and is part of the joint venture Celescan with the Royal Marsden, The Institute of Cancer Research and Sopra Steria. TB receives additional funding from CRUK grant funding (NCITA) and NIHR (HTA) and receives honoraria from Bayer.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Supplemental material

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ORCID iD

Laura Satchwell http://orcid.org/0000-0002-2935-6532

REFERENCES

1. NICE. Myeloma: diagnosis and management NICE guideline [NG35], 2016


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 Healthy Volunteer Consent Form, Version 2.0 07/12/2018
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.
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...
excluded from participating because they will not be a suitable comparator. Once we have confirmed that you are suitable to enter the trial, we will ask you to sign an Informed Consent Form and then book your scan. Some volunteers may be asked to attend early evening or week-end appointments to avoid busy times during the day when the MRI Unit is reserved for patients. There are usually no special preparations and no injection or drugs will be given. All instructions for the scan will be in your MRI appointment letter. When you come for the scan you are advised to wear clothing without metal fastenings and to avoid using make-up or mascara. You can wear glasses, but will need to take these off during the scan. A locker will be provided for your valuables.

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

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

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

**What will happen to the results of this study?**

As soon as there are reliable results, they will be published in a respected peer reviewed medical journal and presented in various scientific meetings. Your identity will not be revealed in any report, publication or presentation. The results will be available on request.

**How is the trial monitored for safety?**

This study has been carefully planned by leading cancer specialists and approved by the Oxford C Research Ethics Committee (REC), the Royal Marsden Hospital Committee for Clinical Research (CCR) and the Health Research Authority (HRA). The members of the study team will be meeting at regular intervals to monitor the progress and safety of the study. Full (100%) monitoring will be carried out to ensure that where incidental findings come to light, both you and your GP are promptly informed.
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.
<table>
<thead>
<tr>
<th>Participant Type</th>
<th>Study name</th>
<th>Site</th>
<th>MRI Machine Name</th>
<th>Sequences acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Volunteers</td>
<td>MALIMAR</td>
<td>Royal Marsden</td>
<td>Siemens Aera</td>
<td>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</td>
</tr>
<tr>
<td>Healthy Volunteers</td>
<td>MALIMAR</td>
<td>Royal Marsden</td>
<td>Siemens Avanto</td>
<td>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</td>
</tr>
<tr>
<td>Myeloma Patients</td>
<td>MALIMAR</td>
<td>Royal Marsden</td>
<td>Siemens Aera</td>
<td>Haste localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and ADC), fl3d_CAIPI_wb_tra_BH_20 and Vertex to knees</td>
</tr>
<tr>
<td>Myeloma Patients</td>
<td>MALIMAR</td>
<td>Royal Marsden</td>
<td>Siemens Avanto</td>
<td>localiser, Sag T1, T2 whole spine, DWI (B50,600,900 and fl3d_vibe_dixon_TRA_15deg 256 256_pocS and T2 HASTE Vertex to knees</td>
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<tr>
<td>Myeloma Patients</td>
<td>MALIMAR</td>
<td>ICHT</td>
<td>Siemens Aera</td>
<td>Axial dixons 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</td>
</tr>
</tbody>
</table>
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)
5. Start time of read - Enter in format: HH:MM using 24 hour clock *


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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt; 10</th>
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</thead>
<tbody>
<tr>
<td>Cervical Spine</td>
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<tr>
<td>Dorsal Spine</td>
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<tr>
<td>Lumbar Spine</td>
<td></td>
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<tr>
<td>Pelvis</td>
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<tr>
<td>Long Bones</td>
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<tr>
<td>Skull</td>
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<tr>
<td>Ribs / Clavicles / Sternum / Scapulae</td>
<td></td>
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</tbody>
</table>
7. Disease status - BONES - Record maximum size of Active / Focal lesions (mm) *

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
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</thead>
<tbody>
<tr>
<td>Cervical Spine</td>
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<td>Dorsal spine</td>
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<td>Lumbar spine</td>
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<td>Pelvis</td>
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<tr>
<td>Long Bones (max. long axis)</td>
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<tr>
<td>Skull</td>
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<td>○</td>
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<tr>
<td>Ribs / Clavicles / Sternum / Scapulae (max. long axis)</td>
<td>○</td>
<td>○</td>
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</tr>
</tbody>
</table>
8. Disease Status - BONES - How confident are you in your assessment of Active / Focal lesions *

<table>
<thead>
<tr>
<th></th>
<th>Not at all confident</th>
<th>Some confidence</th>
<th>Confident</th>
<th>Very Confident</th>
</tr>
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<tbody>
<tr>
<td>Cervical Spine</td>
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<td>Dorsal Spine</td>
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<td>Lumbar Spine</td>
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<td>Long Bones</td>
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<td>Skull</td>
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<td>Ribs / Clavicles / Sternum / Scapulae</td>
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<td>〇</td>
<td>〇</td>
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</tr>
</tbody>
</table>
9. **Disease Status - Record if diffuse disease was present at any of these sites?**

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical Spine</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td><strong>Dorsal Spine</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td><strong>Lumbar Spine</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td><strong>Pelvis</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td><strong>Long Bones</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td><strong>Skull</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td><strong>Ribs / Clavicles / Sternum / Scapulae</strong></td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
</tbody>
</table>
10. How confident were you in your assessment of diffuse disease at these sites? *

<table>
<thead>
<tr>
<th></th>
<th>Not at all confident</th>
<th>Some confidence</th>
<th>Confident</th>
<th>Very confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Dorsal Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pelvis</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Long Bones</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Skull</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Ribs / Clavicles / Sternum / Scapulae</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

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
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
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?

<table>
<thead>
<tr>
<th>Site</th>
<th>Highly likely negative on ML</th>
<th>Probably negative on ML</th>
<th>Probably positive on ML</th>
<th>Highly likely positive on ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Dorsal Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pelvis</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Long Bones</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Skull</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Ribs / Clavicles / Sternum / Scapulae</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
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?

<table>
<thead>
<tr>
<th></th>
<th>Highly likely negative on ML</th>
<th>Probably negative on ML</th>
<th>Probably positive on ML</th>
<th>Highly likely positive on ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Dorsal Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Pelvis</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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<tr>
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<td>○</td>
<td>○</td>
<td>○</td>
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</tr>
<tr>
<td>Skull</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Ribs / Clavicles / Sternum / Scapulae</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Adequate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. B 900</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. ADC</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3. T1 sequences</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>
20. Please enter any specific comments you have on scan quality


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

- Yes
- No

This content is neither created nor endorsed by Microsoft. The data you submit will be sent to the form owner.

Microsoft Forms
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

3/31/2022
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 *

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. CERVICAL SPINE - Was Diffuse Disease present? *

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3/31/2022
10. DORSAL SPINE - Number of Active / Focal Lesions *

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
</tr>
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<tbody>
<tr>
<td>Post-Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12. DORSAL SPINE - Was Diffuse Disease present? *

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3/31/2022
14. LUMBAR SPINE - Maximum size (mm) of Active / Focal Lesions *

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15. LUMBAR SPINE - Was Diffuse Disease present? *

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16. PELVIS - Number of Active / Focal Lesions *

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3/31/2022
18. PELVIS - Was Diffuse Disease present? *

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

21. LONG BONES - Was Diffuse Disease present? *

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3/31/2022
22. SKULL - Number of Active / Focal Lesions *

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
<th>Not Applicable, No Focal lesions seen at this site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24. SKULL - Was Diffuse Disease present?  *

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1 - 4</th>
<th>5 - 10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3/31/2022
26. RIBS / CLAVICLES / STERNUM / SCAPULAE - Maximum size (mm) of Active / Focal Lesions *

<table>
<thead>
<tr>
<th></th>
<th>&lt;10mm</th>
<th>10 - 20mm</th>
<th>&gt;20mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Treatment</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Baseline</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Not Applicable, No Focal lesions seen at this site

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

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Treatment</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Baseline</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

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

3/31/2022
30. 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.

31. OVERALL RESPONSE - Change in Disease Status (Baseline - Post-Treatment) *

<table>
<thead>
<tr>
<th>Response category</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Confidence category</th>
<th>Not at all confident</th>
<th>Some confidence</th>
<th>Confident</th>
<th>Very confident</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

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

3/31/2022
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  

<table>
<thead>
<tr>
<th>Response category</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Adequate</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. B 900</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. ADC</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. T1 sequences</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

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

3/31/2022
38. Reader confirmation: My responses have been accurately reported on this CRF (enter 'yes' if in agreement with this statement) *

- Yes
- No

This content is neither created nor endorsed by Microsoft. The data you submit will be sent to the form owner.
### Supplementary S4 – MALIMAR Amendments

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