Guidance on the use of MRI for treatment planning in radiotherapy clinical trials

Guidance on MRI for treatment planning in RT clinical trials

ABSTRACT

The aim of this article is to propose meaningful guidance covering the technical and safety issues involved when designing or conducting radiotherapy (RT) clinical trials that use magnetic resonance imaging (MRI) for treatment planning. The complexity of imaging requirements will depend on the trial aims, design and MRI methods used.

The use of MRI within the radiotherapy pathway is becoming more prevalent and clinically appropriate as access to MRI increases, treatment planning systems (TPS) become more versatile and potential indications for MRI-planning in RT are documented. Novel MRI-planning opportunities are often initiated and validated within clinical trials.

The guidance in this document is intended to assist researchers designing radiotherapy clinical trials involving MRI to provide sufficient information about the appropriate methods used for image acquisition, post-processing and quality assurance (QA) to complete MRI to consistent standards at participating sites. It has been produced in collaboration with the National Radiotherapy Trials Quality Assurance Group (RTTQA).

As the use of MRI in radiotherapy is developed, it is highly recommended for researchers writing clinical trial protocols to include imaging guidance as part of their clinical trial documentation covering the trial-specific requirements for MRI procedures. Many of the considerations and recommendations in this guidance may well apply to MR-guided treatment machines, where clinical trials will be crucial. Similarly, many of these recommendations will apply to the general use of MRI in radiotherapy, outside of clinical trials.

This document contains a large number of recommendations, not all of which will be relevant to any particular trial. Designers of radiotherapy clinical trials must therefore take this into account. They must also use their own judgement as to the appropriate compromise between accessibility of the trial and its technical rigour.

APPLICATION OF MRI IN RADIOTHERAPY

The use of MRI for RT treatment planning is increasing[1], often with each novel MRI-guidance indication initiated and validated within a clinical trial. Trial groups setting up single or multi-centre trials or studies can take direction from this document. A majority of the content will also be relevant to the use of MRI for RT outside of clinical trials, and for MRI-guided treatment machines[2]. The considerations and recommendations within this guidance document are derived from literature and from the authors' experience.

At the time of writing, the majority of RT planning relies on computed tomography (CT). This imaging modality has a high geometrical accuracy and provides electron density (ED) information that is used for dose calculations during treatment planning. When MRI is introduced to treatment planning it is often used in addition to CT, with the MRI adding soft tissue detail or functional information. Since MRI generally has a lower geometrical accuracy than CT and does not intrinsically provide ED information, it can be spatially registered to the CT to combine the advantages of the two modalities. This has been designated as "indirect" MRI planning within this document.

It is also possible to plan treatments using only MRI. In this case, either the dose calculation is performed without reference to ED (as is typically the case in brachytherapy) or the MRI scans are processed to estimate ED. The resulting images can look very much like CT scans and are often termed pseudo-CT or synthetic-CT (synCT) images[3]. MR vendors and third-party vendors are releasing software that allows the generation of synCT images. These provide the potential to perform "MR-only" RT planning directly on the MR scan, removing the need to register MRI to CT.

RESOURCE REQUIREMENTS

MRI scanner

MRI scanners dedicated for RT planning are marketed by the main MR vendors and are commonly known as MR-simulators. These are wide-bore scanners (nominal 0.7 m diameter bore) with additional hardware and specialised RT software. Alternatively, existing diagnostic scanners can be modified for extracranial RT use by

installing a flat, MR-compatible, indexed couch overlay, MR-compatible immobilisation devices and external positioning lasers[4]. Such modifications are not necessary for intra-cranial radiotherapy planning scans.

Wider-bore MRI systems are wider than the previous standard that used a nominal diameter of 0.6 m. However, even with wide-bore MRI systems, there will be limitations on patient access, due to the limited space within the scanner bore. This space can become even more restricted when using an indexed couch overlay and immobilisation devices.

In most instances, the MR scanner will be located physically, or organisationally, within the radiology department of the healthcare provider. This can pose challenges in terms of patient transfer, image transfer and the interaction of staff from different training backgrounds.

Recommendations:

- Many RT centres will not have access to a dedicated MR-simulator, but radiotherapy planning scans are still possible. For intra-cranial planning a flat couch top is not necessary, and images can be acquired with a standard head coil. Extracranial planning requires a flat couch top, immobilisation devices and lasers.
- Consider the effect on recruitment rate at centres with standard scanner bore sizes that restrict the number of patients who can be comfortably scanned in RT position.
- Consider the bias that may be introduced by a standard scanner bore size restricting patient selection.

Patient positioning equipment

Since MR acquisition times are long, scanning couches are cushioned for patient comfort. For RT purposes, a flat overlay is often placed onto the MR couch, replicating features such as indexed locations to attach immobilisation devices. Placing a flat overlay onto the MR couch has unintended consequences including reduction in patient comfort, thereby increasing the likelihood of motion artefacts, and raising the patient higher within the scanner which affects image quality.

The MR signal that is used to form MR images is received by radiofrequency (RF) coils. These may be built into the structure of the scanner itself or placed onto (or into) the patient. Coils that might normally be used for the examination of a particular body part, such as a head and neck coil, may be impossible to use, due to the flat couch overlay or RT immobilisation devices. Surface coils that would ordinarily be placed onto the patient may need to be suspended to prevent distortion of patient anatomy.

Recommendations:

- Assess requirements for reproducibility and accuracy of patient positioning during imaging and subsequent impact on volume delineation.
- Establish the need for patients to be positioned on a flat couch-top. Doing so may improve image registration but will likely reduce signal to noise ratio (SNR) in the image, require longer scanning times and increase the risk of motion artefacts due to patient discomfort.
- Allow centres to use appropriate additional comfort devices where this will not adversely affect the treatment or clinical trial outcomes.
- For intracranial indirect planning, consider scanning without RT immobilisation, as this is unlikely to improve co-registration with CT and may result in poorer image quality as dedicated head receive coils cannot be used. However, where the lesion is in the brainstem or at the base of skull, be aware that neck flexion may cause significant deformations.
- For extracranial external beam planning, external lasers should be installed to reduce uncertainties in co-registration with the planning CT and to reproduce the patient positioning at treatment. Immobilisation equipment used should be of identical geometry to that used for RT immobilisation.
- External lasers should be turned off during scanning to avoid image artefacts.
- Determine the need for maintaining the external patient contour by suspending surface coils above the patient, using a ‘coil bridge’.

- Centres should optimise MRI sequences to achieve acceptable image quality, while taking into account the non-ideal placement of receive coils.
- For increased accuracy and MR-only planning, centres will require access to a flat, indexed couch overlay, immobilisation devices and external RT laser setup matching those used for external beam RT treatment.

MRI access control and staffing requirements

Individual roles and responsibilities for the provision of RT and imaging procedures will vary depending on local centre arrangements, the mix of staff involved and the level of expertise available. A multidisciplinary approach should be taken and documented to provide consistency and minimise safety concerns.

Recommendations:

- A multi-disciplinary team (MDT) involving an MRI-experienced oncologist, physicist(s) and radiographer(s) experienced in MR and radiotherapy should be formed at an early stage of trial design and work-up at recruiting centres.
- Each centre should develop a detailed patient workflow document with input from their MDT.
- Provide a template or example patient workflow within the image guidance document for the trial.
- The roles within the MR unit should be clearly defined. It may be appropriate for RT staff to set up the immobilisation devices and couch, while MR staff set up the receive coils.
- Input from RT physicists is required to help determine the level of staff training required and additional RT QC. QA is discussed in more detail in a later section of this document.
- Input from MR physicists is very important to assist with the implementation of the recommendations in this document.
- RT radiographers will require MRI safety competence to work within the MR environment.
- There should be the same number of radiographers experienced in RT present for patient setup as for typical CT-simulation, especially where accuracy of patient positioning is critical.
- At least one radiographer trained and qualified in MR operation should be present at all times.
- Recruitment rate may be affected if extensive cross-training is required at a recruiting centre. Where possible it may be prudent to encourage staff members to begin by performing roles according to their existing training and qualifications.
- Consider the extent of imaging support given to recruiting centres, as existing levels of staff training will vary between centres.

MRI SAFETY

This section quickly reviews the hazards that are present in MRI in general, before giving recommendations that are relevant in the context of radiotherapy clinical trials.

MRI uses radiofrequency (RF) electromagnetic fields which deposit energy in the body, leading to a warming of the part of the body within the RF transmit coil. Scanners are designed to limit this heating to safe levels, but these limits do not allow for patients who are particularly sensitive to increases in body temperature or cases where an implant or device absorbs RF energy and causes local heating.

With pulse sequences that use rapid switching of magnetic field gradients, a proportion of patients will experience peripheral nerve stimulation (PNS).

MR scanning is usually noisy. Local policies vary, but may require the use of MR headphones, ear-plugs, or both.

Contrast agents are not always required for trials that use MRI. The contrast agents used in MRI typically contain gadolinium ions chelated with a ligand. Since gadolinium is toxic, the chelating effect of the ligand is critical to the safety of the agent. Gadolinium based contrast agents (GBCAs) have an excellent record of safety, but, as with any pharmaceutical product, there are risks. Patients with pre-existing renal dysfunction are at risk of developing nephrogenic systemic fibrosis (NSF) after the administration of GBCAs. There is growing evidence of

the deposition of gadolinium in the brain following the use of GBCAs[5], which, at the time of writing, has led to the suspension of the licensing of some GBCAs by the European Medicines Agency[6].

Recommendations:

- Where the head is immobilised, the immobilisation device used may prevent use of MR headphones. Consider how this may increase the patient's exposure to noise.
- The RT treatment position may increase the likelihood of the patient forming loops with their hands and arms, increasing the possibility of localised heating. This risk should be assessed and, if possible, mitigated.
- Where patients have difficulty communicating, for instance if they are fitted with a head immobilisation shell, extra care is needed to ensure that the patient has means of alerting the operator.
- Be aware of the risk of patients vomiting while immobilised in a head immobilisation shell. Take steps to mitigate against this and have plans in place should it occur.
- Where PNS is a problem, changes can be made to the scan protocol to reduce its severity, but the effect on image quality (such as on the image contrast) should be assessed.
- Refer to renal function within eligibility criteria for trials that use contrast agents.
- For trials involving brachytherapy implants or applicators, the MR safety implications of these devices must be considered.
- Some patients will have contraindications to MRI due to MR safety considerations or implanted devices. Exclusions from MRI should be stipulated in the trial's eligibility criteria.

IMAGING PROTOCOL DESIGN AND LOGISTICS

Scanning logistics

The inclusion of MRI within the radiotherapy pathway raises some logistical issues. Some patients may be ineligible for an MRI scan, due to contraindications. When consistency of the MRI scans is important, consideration must be given to patient preparation and to the availability of the same scanner for repeated scans of the same patient.

Recommendations:

- Patients undergoing multiple MRI scans to monitor changes over time should be imaged on the same scanner, using the same patient preparation, acquisition & reconstruction procedures as the baseline scan.
- Where bladder or rectum filling is important for RT treatment, a preparation protocol should be defined for MRI.

Imaging protocol

The imaging protocol for an MRI examination consists of an ordered list of imaging sequences and the parameters that control those sequences. The properties of images produced by a particular MRI sequence depend on its precise design (which is manufacturer dependent) and the parameters chosen by the user. The user-adjustable parameters may be chosen in advance of the examination, but can also be changed during the examination, immediately before running the sequence.

The signal intensity (or brightness) within the image created by a pulse sequence will depend on many factors, some anatomical and physiological (such as tissue type or blood flow), some physical (such as receive coil proximity) and some related to the design of the sequence, in terms of the timings and magnitudes of electromagnetic pulses. Whatever the stated weighting (e.g. T1, T2 etc.), a typical pulse sequence will have a contrast that depends on tissue relaxation times, diffusion, perfusion and even morphology.

It is important to note that the requirements for imaging sequences for radiotherapy planning purposes are quite different to those for diagnostic imaging. While low noise, high resolution and good contrast are important for both, low image distortion is particularly important for treatment planning. Also, diagnostic scans are

frequently aligned to anatomical features or planes, whereas transverse slice orientations are usually required for treatment planning.

Recommendations:

- Imaging sequence priority should be defined, either based on anatomical factors or importance to the trial outcomes, in case the patient cannot endure the whole imaging programme.
- It may be necessary to rearrange the sequence order for a patient, to optimise bladder filling, for example. Control software of modern MRI scanners makes such rearrangement straightforward.
- When defining the imaging sequences and their parameters, advice should be sought from MR radiographers, who will be running the examinations, and investigators, who will be using the images.
- A standardised naming scheme for MRI scans should be initiated such that these can be easily interpreted in the TPS, considering any restrictions imposed by the TPS on the length of names.
- To maintain imaging consistency, the scan protocol should be protected from changes and be backed up, such that it can be restored if lost or corrupted. Steps should be taken to ensure that parameters will not be changed inappropriately during an examination. It may be possible to 'lock' a sequence or hide its parameters from view.
- A checklist of items that are essential or valuable to the clinical trial should be provided. This helps to determine when repeat scanning is required, in the case of artefacts or poor image quality.
- Where a functional imaging sequence is to be registered to a planning CT or planning MR, it should be acquired with the same bed position as the anatomical MRI. Functional imaging sequences will have few anatomical landmarks and hence registration will be difficult and prone to errors. An anatomical MRI sequence may be used for the registration to CT, with the transformation (or deformation) matrix applied to the functional image.
- Permissible respiratory motion management techniques should be defined, and examples given of acquisition methods. The techniques may include very fast imaging, breath-holds or respiratory gating.
- For clinical trials that require contrast agent administration, determine whether standardisation will be necessary and advise accordingly. The timing of contrast agent administration is important for subsequent imaging, particularly if perfusion of tissues is being examined using dynamic contrast-enhanced (DCE) imaging.

Image acquisition

Most MRI can be classified as using a 2-dimensional (2D) or 3D acquisition method. In 2D imaging, slices through the volume are acquired and reconstructed one by one before being placed into a 'stack' to create a 3D image. In 3D imaging the entire volume is acquired at once and reconstructed in one operation. An isotropic resolution is easier to achieve with 3D imaging, allowing reconstruction in multiple angled planes with consistent image quality.

In 2D MRI it is common to leave a small gap between adjacent slices to avoid a slice overlap, which would cause artefacts. It is also common not to acquire the slices sequentially, perhaps acquiring every other slice and then returning to fill in the gaps. This also reduces the artefacts caused by slices overlapping in space. When the 2D images are combined to make a 3D image, motion that occurs between the acquisition of each slice will cause artefacts. The nature of these artefacts depend on the slice ordering.

The size of gaps between 2D slices depends on both the displacement between slices and the slice thickness. While these parameters are part of the imaging protocol specified by the operator of the scanner, the actual slice thickness is dependent on the calibration of the scanner's gradient system.

In MRI there is a completely free choice of slice orientation. Slices can be manually or automatically aligned to anatomy. This alignment assists with the interpretation of the images. Automatic alignment can be particularly useful for longitudinal studies, since it is typically more robustly reproducible[7]. MR scanners are able to reconstruct or resample 3D images into arbitrarily-chosen additional slice orientations.

The geometric accuracy of MRI is affected by two properties of the patient: the magnetic susceptibility and the chemical shift. The difference between the magnetic susceptibility of the body and the surrounding air (or

internal gases) leads to distortion and signal intensity changes. Different chemical environments in the body lead to a spatial displacement in the image, particularly between fat and water. Distortion and fat-water shifts both occur in the frequency encoding, or readout, direction and they are both inversely proportional to the readout bandwidth of the imaging sequence. Analogous effects occur during slice excitation, leading to distortion and fat-water shifts in the slice selection direction – the direction normal to the slice plane – for 2D imaging. These effects are inversely proportional to the bandwidth of the RF pulse used to excite the slice.

Recommendations:

- Place a lower limit on the bandwidth of both slice excitation pulse and the readout (the transmit and receive bandwidth). Higher bandwidths reduce the patient-induced distortion and chemical shift artefacts. However, higher receive bandwidths reduce the signal to noise ratio, so a compromise must be struck.
- Correct import into the TPS must be confirmed for each proposed slice orientation.
- Care should be taken when resampling images, since loss of spatial resolution or aliasing artefacts may result.
- The results of 2D or 3D acquisitions may look very similar, but the choice has important implications for image contrast and artefacts. Consider recommending a method within trial documentation.
- For MR-only planning, the ability to calculate dose on the chosen slice orientation must be confirmed. For instance, some planning systems are unable to correctly process oblique slices.
- Consider measuring the actual slice thickness. Gaps or overlaps between slices are detrimental for volumetric imaging, or where very small features (such as metastases) need to be detected.
- Distortion correction should be assessed at local centres, to ensure it functions well, and it must be used for clinical scanning.
- Many techniques are used to accelerate MRI, including parallel imaging, partial *k*-space and echoplanar imaging. If the clinical trial sequences use imaging acceleration techniques, the additional artefacts will need to be assessed in terms of how these may affect clinical, or clinical trial, outcome.
- Fat suppression techniques are widely used in MRI to reduce the signal from fat, often to make the images easier to interpret. Localised suppression of the signal from sub-cutaneous fat is also often used to avoid motion artefacts. While fat suppression techniques may be useful for RT planning purposes, care will need to be taken when images are to be used quantitatively, or for dose calculation.

DATA PROCESSING

Registration

For rigid registration to be optimal, the patient's anatomy on MRI should match that on CT. Improvement in registration accuracy can be achieved when patient immobilisation and setup is consistent across the two modalities[8–10]. Despite efforts to reproduce patient position between scans, there may be difficulties performing rigid registration of MRI to CT images.

Deformable registration (DR) can be used to register images when rigid registration fails, for example due to patient movement. There are many DR algorithms and, amongst other differences, these DR algorithms differ in the way they deal with the properties of human tissue. Often a simple elastic model is used, whereas real tissue may be liquid (blood, CSF), solid (bone) or a complex viscoelastic mixture. There are also tissue interfaces where sliding occurs.

Recommendations:

- Offer guidance for the definition of a suitable region of interest for automatic registration, as this can be crucial for accuracy.
- All automatic image registrations should be visually checked.
- DR techniques are in development stages and must be analysed in depth when used clinically. Many DR packages will not take into account the tissue types involved and their filling or movement properties.

- Define whether DR can be used and, if so, supply QA test cases to each recruitment centre.
- If internal anatomy has moved but is of no interest, it may be possible to exclude it from the registration.
- Indicate when multiple registrations are required for long volumes or when multiple regions need to be translated from MRI to CT.

Delineation

The use of MRI can improve both the accuracy and reproducibility of delineation compared to CT alone and is being adopted into clinical practice and clinical trials. Items of most concern are choice of imaging sequence, quantification and correction of geometric distortion and registration with the planning CT.

Recommendations:

- Ideally, the advice of a radiologist should be available to help with accurate delineation.
- To reduce inter-operator variability within the clinical trial, a delineation guide should be included in the trial documentation. Where CT images are also available, the guide should advise which type of imaging is to be used to define the target or organs at risk – MRI, CT or both.

Response assessment and adaptation

MRI is increasingly being used for intra-treatment response assessment and adaptation within clinical trials[11].

Recommendation:

- For response assessment, the MRI should be performed on the same scanner and under the same conditions as the reference scan.

MR-only treatment planning

MR-only planning allows delineation on MRI without co-registration with a planning CT scan, thus eliminating one source of possible error, but placing extra demands on the MRI process. There are no CT-based ED values, so synCT images often need to be generated from the MRI scan[3], and the possibility to check geometrical accuracy against CT is not available. MR-only treatment planning requires the patient external contour to be imaged, since this will not be available from CT images.

Recommendations:

- MRI-specific markers can be purchased. Where the marker must be placed over an existing skin mark, choose a design that can be easily aligned to such a mark.
- Treatment verification imaging systems are generally designed to use CT scans or digitally reconstructed radiographs (DRRs). The most appropriate images for treatment position verification should be determined. An MRI acquisition or the synCT may be suitable. Differences in file format, image contrast or resolution could cause difficulties, so a test run is advisable.
- The effect of implants on synCT generation should be assessed and, if appropriate, patients with these implants excluded.
- System-based distortions and signal inhomogeneities should be measured within the volume that is relevant for treatment planning purposes. It may be quantified with respect to distance from the MRI isocentre or mapped in space.
- Verification and QA of each synCT algorithm will need to be performed prior to clinical implementation.
- For extra-cranial treatments, or those near to the brainstem, immobilisation and patient setup must be exactly the same as for treatment.

Data transfer and storage

Transfer of MRI data from radiology or picture archiving and communication system (PACS) software to the TPS will likely be required. It is important to understand the systems through which the data will pass and how these might affect image data.

Recommendations:

- A tested and secure method for transferring scans from the MRI scanner to the final location for reporting and/or delineation should be in place to ensure that data integrity is maintained and quantitative information is preserved.
- A template data transfer checklist should be available for the trial to allow local centres to assess transfer accuracy.
- Data exported to an independent central storage system for review should be appropriately anonymised. Considering that MRI data are frequently acquired outside the RT department, the DICOM may contain extra fields of patient identifiable information from a radiology information system.

QUALITY ASSURANCE REQUIREMENTS

Additional tests relating to RT use will need to be incorporated into the existing routine MRI QA programs[12].

Geometrical distortion is a known issue in MR and there are two main sources: inhomogeneity in the static magnetic field (B_0) and non-linearity of the imaging gradient fields. The magnitude of distortion that arises depends on the magnitude of the imperfections as well as the design of the imaging pulse sequence. An accurate measurement of distortion can only be made in a situation that matches the clinical scan, in terms of both the magnetic susceptibility distribution (due to the patient or other objects) and the pulse sequence.

System-related contributions to geometric distortion are expected to be relatively stable over long periods, so less frequent QA may be appropriate for these. However, sudden changes to the static field homogeneity may occur due to magnetic foreign bodies. The intrinsic uniformity of the static magnetic field is usually very high within the imaged volume, but it is markedly degraded by the presence of the patient or other objects.

Recommendations:

- RT planning is particularly demanding in terms of spatial accuracy, so additional geometric distortion QA may be required.
- Since distortion varies depending on the patient morphology and presence of implants, patient specific QA may be required. This can include additional pulse sequences to assess the size of the distortion, or comparisons with CT scans.
- Baseline uniformity of the static magnetic field should be measured. Phase maps should be acquired using a large phantom, ideally filled with oil. The effect of the magnetic susceptibility of the phantom must also be assessed.
- Performance of in-built distortion-correction algorithms should be assessed for a variety of 2D and 3D pulse sequences. Images can be acquired with and without correction, for comparison.
- Long cycle (e.g. 6-monthly) and short-cycle (e.g. weekly) QA should be performed to quantify geometric distortions.
- The uniformity achieved with each imaging pulse sequences should be measured, especially when used for synCT generation or defining a boost volume based on image intensity. Image uniformity is dependent on uniformity of the excitation pulse (B_1) and uniformity of the receive coil sensitivity. Geometrical distortion can also lead to problems with uniformity where signal is displaced, leading to 'signal pile-up'.
- An MRI-visible phantom should be sourced for laser QA. This allows checking of the correspondence between the scanner isocentre and that defined by the lasers.
- For MR-only planning, the MRI scanner should be subject to a routine QA programme that, as a minimum, replicates the departmental CT-simulator QA[13,14].
- When standardisation of image quality across a clinical trial is important, image quality should be assessed using a suitable phantom, since implementations of imaging sequences may vary between scanner models. For instance, when diffusion-weighted imaging is used, phantom measurements can be used to compare quantitative measurements made at different centres. Consider specifying the same field strength scanner for all scans, as the image quality of MRI is affected by the static magnetic field strength (flux density) used.

Advanced imaging techniques

Besides providing structural information, MRI can be used to quantify physical and physiological parameters such as nuclear magnetic relaxation times and rates, diffusion parameters, pharmacokinetic parameters measured using dynamic contrast enhanced (DCE) imaging and metabolite concentrations determined using magnetic resonance spectroscopy (MRS).

To verify the accuracy of these measurements a phantom with known value(s) is required. Construction of phantoms that mimic physiological diffusion and perfusion is technically very difficult and standard phantoms are not readily available. A useful review of phantom designs can be found in IPEM Report 112[12].

Recommendations:

- Where a QA process is being designed for quantitative MRI, reference should be made to guidance provided by national or international bodies, such as the Institute of Physics and Engineering in Medicine (IPEM)[12] and the Quantitative Imaging Biomarkers Alliance (QIBA)[15].
- Where MRI is used for quantitative imaging, QA checks need to verify the accuracy and precision of the quantity being measured.

Protocol compliance

The use of MRI in a clinical trial will require additional auditing procedures to ensure that the trial protocol is adhered to consistently.

Recommendations:

- Researchers should implement central review or ongoing audit procedures to ensure compliance for the trial.
- When MR is used for delineation, co-registration or response assessment, one or more benchmark cases should be used to assess the interpretation of the MRI at each centre.
- A questionnaire should be sent to all centres to understand staffing, patient workflow, image acquisition, frequency and quantitative values for QC tests and data storage provision.
- For multi-centre clinical trials, consider whether MRI scans and subsequent interpretation should be centrally reviewed to reduce the inter-observer variability. The review should be prospective or retrospective, as defined in the guidelines for the trial. For large studies this will not be feasible, in which case a subset of cases should be reviewed.

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