Yao Pang, MD
NA
NA

To reduce an MR relaxation metric variability across the multiple‐site studies, it is better to limit the number of acquisition variables as small as possible. This is particularly true for the proposed T1rho and T2 mapping. Given that T2 could be treated as a "specific" T1 that is determined by T1 spin‐lack amplitude (A, 1/2ν) of zero, T2 could, in theory, be derived from T1rho (amplitude) by curve fitting using only the proposed T1rho sequence. Here are two arguments for considering the removal of the proposed CMPS‐based T2 mapping sequence.

First, for clinical MR scanners, the durations of the employed RF pulses in composite [i.e. 10x/10x/99x] CMPS sequence cannot be considered "negligible," and thus a T2 correction scheme was introduced by assuming a constant T1/T2 ratio. It is well known that T1 is mostly constant in human knee cartilage, however, T2 is orientation dependent due to the magic angle effect (MAE). Therefore, the proposed T1 correction will introduce some inevitable dependency by systematic error.

Second, the "spin‐lock" effect in the proposed T2 mapping has never been discussed. An internal‐by‐the‐center of these two adjacent spin echoes becomes shorter, CMPS pulse will behave increasingly like a spin‐lock sequence. It is unclear what extent that the proposed T2 mapping approaches T1‐based measurements.

REFERENCES:

Another comment is about T1rho/T2 image data interpretation (Part 3.8). Although this Profile avoids the "controversial topic," i.e., what does T1/T2 really measure in cartilage? it is necessary to advise the perspective users to take MAE into account when evaluating the longitudinal changes of cartilage composition.

Specifically, for the intra‐subject T1rho/T2 changes, MAE is anticipated to be small when the same imaging protocol is always followed. However, for inter‐subject T1rho/T2 changes, caution should be exercised when interpreting the results since the same imaging protocol is used. This is because that the potential orientation dependent factors, e.g. varied femoral bone shape, may play a role in the observed changes in T2 values (or T1rho values to a lesser extent).

Note provided:

Yao Pang, MD
3.8
NA
M

The focus of the profile is to make recommendations on data acquisition and processing of cartilage T1rho and T2 measures. The specific mechanism of T1rho and T2 relaxation time in cartilage is a topic with active research in the field, which is not the focus of this profile. Magic angle effect will introduce variation in T1rho and T2 measures and the discussion on MAE will be added in the profile.
The profile provides important recommendations for one of the most active areas in MRI imaging research—quantitative, compositional, MRI for knee cartilage—particularly for longitudinal multi-center trials. Although the profile is also intended to apply for clinical practice, there is no solid evidence regarding utility of such techniques for routine clinical care. None provided

These are good points. However, it is noted that there is a T2 mapping product sequence which is used by clinicians.

No action requested

OK

Richard (Marty), D (on behalf of AAPM)

NA

P 1476

NA

Physicists are involved in designing/optimizing the protocols. They should be listed among impacted stakeholders here.

add physicists

done

Richard (Marty), D (on behalf of AAPM)

NA

P5 180

NA

11-14% precision seems a little too much. This value appears to be derived from Appendix B and most of these references are old references.

We recommend against using the precision of 11-14%

reference in Appendix B should support this claim.

change wording

Richard (Marty), D (on behalf of AAPM)

NA

P 1482

NA

For the same manufacturers, different scanner models may have to use different parameters because the hardware and software are different. For example, 60cm vs. 70cm bore size, different slew rate and Gradient waveform, etc. The appendix could apply to vendors vs. specific software.

Reference in Appendix B should support this claim.

change wording

Richard (Marty), D (on behalf of AAPM)

NA

P189 50

NA

The goal of this document appears to be for clinical practice and that point should be clearly stated.

Please clarify "while the emphasis is on clinical trials, this process is also intended to apply for clinical practice." refer to wording

Richard (Marty), D (on behalf of AAPM)

NA

P7 143

177

Both claims of T2 and T1rho variations are within 4-5%. However, there are not so many vendors providing T1rho methods.

Please specify how you can achieve this goal in general clinical practice.

using sequences by manufactures, as outlined

Richard (Marty), D (on behalf of AAPM)

NA

P 1119

NA

Lack of reference values for your calibration phantom of T2 and T1rho.

Please provide reference values for your calibration phantom of T2 and T1rho.

new phantom

Richard (Marty), D (on behalf of AAPM)

NA

P81 160

NA

The impact of segmentation on T2 and T1rho values is obvious.

Please clarify whether the software has been validated.

The variations of T1rho and T2 values with different time of recovery, views per segment, with and without parallel imaging acceleration have been tested in Ref 11 (Kim et al, JMRI 2020). Average CV 10-15% was reported, suggesting minimal variations with changes in these parameters.

add physics

Richard (Marty), D (on behalf of AAPM)

NA

P 1119

NA

Missing actors in Table 1.

In Table 1, add physicians or MRI scientists to install MRI sequences or tools, check the IQ and verify the T1 and T2 values.

add physicians

Richard (Marty), D (on behalf of AAPM)

NA

P 1137

clarification needed...

Please clarify "how study sponsors and others decide to handle deviations..." Specify what kind of deviations.

deviations were discussed

Richard (Marty), D (on behalf of AAPM)

NA

P12 1238

We question whether "A410 grant..." should be included in this profile now.

remove A410 grant and reward as funded study

Richard (Marty), D (on behalf of AAPM)

NA

P 1260

245

In the table, we suggest changing "MRI Physicist" to "MRI Scientists/Physicist."

Richard (Marty), D (on behalf of AAPM)

NA

P1260

245

In the table, there are a lot of segmentation tools. It should state the specific image analysis tool.

no standardised segmentation tools

Richard (Marty), D (on behalf of AAPM)

NA

P 1265

6

Term used.

"AQR phantom" should be changed to "small AQR phantom" or AQR phantom for knee coil.

Richard (Marty), D (on behalf of AAPM)

NA

P 1282

We question whether human volunteer studies should be performed before and after changes.

remove human volunteers, only calibration phantoms

Richard (Marty), D (on behalf of AAPM)

NA

P 12772

Specify how to measure the eddy current and how to perform the gradient calibration.

Option 1.

Provide instructions.

The committee will revise the language and will not recommend that the ida measures eddy current or performs gradient calibration. Per recommendations from the OHA paper (Schneider et al 2008), measurements such as eddy current or phantom scan performed. The MRI system characteristics that were found to affect the ghost level were mechanical vibration and eddy currents, ida software vs. our current. If the measures exceed the set threshold (for example ghosting level > 0.5%), a service call shall be made.

Rewording as: "Measurements should include signal-to-noise ratio (SNR), signal uniformity, spatial accuracy, and ghosting as suggested in LA, T3.

Richard (Marty), D (on behalf of AAPM)

NA

P 1290

245

Specify how to define the calibration factor.

NST phantom and volunteers work in progress

limitation—needs new phantom

Richard (Marty), D (on behalf of AAPM)

NA

P 1180

We recommend listing the subject selection conditions. add more detailed subject selection

change language

done

Richard (Marty), D (on behalf of AAPM)

NA

P 1176

NA

A very specific pulse sequence (MAPS), currently a research sequence, is proposed for T2- and T1rho mapping. Although the involvement of Siemens, GE and Philips is ultimately incorporating this sequence in their systems is applied, it is somewhat concerning that the sequence is currently not generally available to researchers worldwide. The sequence currently is only available through bilateral collaborations with authors of the profile, with the support of vendors.

This is correct and a current limitation of this technology. However, information about access to this research sequence from different vendors is available in the profile.

No action requested

OK

Richard (Marty), D (on behalf of AAPM)

NA

P 1407

NA

Two specific biomarkers, T2 and T1rho mapping, are proposed, both of which seem to be reasonable choices based on the currently literature. However, sensitive alternative techniques for compositional cartilage MRI are available (e.g. GOGST, sodium MRI, 3DASMR, and the others) with active research going on in each of these methods. There is insufficient mentioning of the pros and cons of T2 and T1rho relative to these alternatives, and a solid motivation for the choice of T2 and T1rho as the proposed biomarkers is lacking.

An more balanced introduction with overview of available techniques is encouraged.

Alternative sequences were not discussed in much detail as limited reproducibility data is available. (also response to Gary Gold's comment)

Expand introduction to include other sequences
Richard I. Martin, D (on behalf of AAPM) NA P17 Li500-323 It seems the activities before the exam affect T2 and T1rho values significantly. Please specify whether the environment temperature is also affected. Please take the difference if there is no seated position prior to the scan for 30 minutes. No studies in the literature reported changes with and without seated position for 30 minutes prior to MRI scans. Tegtmeyer et al. reported 7% changes in T1rho with daily activities. Although T1rho and T2 values are affected by temperature, as shown in the abstract by Hardly et al., the committee did not think that the end result temperature in the scanned room would have a noticeable direct effect on body temperature nor T1rho and T2 values. Added reference on T1rho and T2 changes with loading (running or daily activity). Added discussion in the temperature paragraph. Information from Peter Hardy’s poster was added and the poster was referenced. done

Richard I. Martin, D (on behalf of AAPM) NA P18 Li500 MDM is a product for T2 mapping on most of MRI scanners, but the final values here are different among different vendors. Please specify whether this is because of the fitting methods or scanning parameters or the sequence design. This document gives the scanning parameters. We recommend providing the offline fitting/processing method for different vendors. The difference was because different fitting methods by different vendors but also different software/hardware imperfections on each MR systems as the sequence is known to prove to bias introduced by stimulated echo without imperfection refocusing and magnetization transfer, as discussed in AAPM NA P33. It was not seen unless this was not already implemented as this sequence was not recommended in this profile (although it has been discussed as an option if MARS sequences was not accessible). None taken. given that this sequence was not recommended in the profile. done

Richard I. Martin, D (on behalf of AAPM) NA P25 Li484 Please give the recommendation clearly right vs. non-right nigral registration. add more details and references for registration

Richard I. Martin, D (on behalf of AAPM) NA P26 Li485 In the table, it states to perform the segmentation manually, however, in the text, a lot of places reference only for a semi-automatic segmentation. Please clarify. Manual for final revisions. Table 1 was modified and manual was removed for global changes.
done

Richard I. Martin, D (on behalf of AAPM) NA P33 Li662 Do not say “new surface coil.” We recommend saying “new coil” or “new knee coil.” “surface” was removed and replaced by “new”
done

Richard I. Martin, D (on behalf of AAPM) NA P18 Li573 Should T1rho, not T1. Corrected

gary gold, MD, PhD (Stanford) NA NA I wanted to bring to your attention an important point around pulse sequences for T1rho and T2. Although MARS has been widely used and is the most published method, there are many methods out there of input T1rho and T2 acquisition. Different groups and different platforms have different methods. My own group has used many different acquisition methods, and more are under development to improve acquisition speed, resolution, or other factors. Instead of specifying MARS as the recommendation specifically, can we say something like “T1rho and T2 data acquired with XX resolution, etc. that shows repeatability similar to the MARS method.” That leaves space for continued development and application to machine learning and AI methods to the field. Ultimately, we’ll be like these methods to be widely available and be possible that GE, Philips, and Siemens may adopt other methods for T1rho and T2 in product in the future.

Add other available methods or methodologies under development.

The reason the committee made the recommendation on MARS in the current profile, after much discussion, is because you pointed out that MARS is the most published 3D T1rho and T2 method, and because it is the only sequence that has published data as inter- and inter-vendor reproducibility and the QIBA-das are based on these reproducibility data. QIBA profiles recommend specific acquisition protocols that have been applied in multiple studies, have solid reproducibility data and are straightforward for potential future users to follow. The committee also agreed that other available methods and methodologies under development without intra-technician reproducibility data yet shall be added to discussion.

We will add to the Discussion the other available methods or methodologies under development, but without inter/intra inter-vendor reproducibility data. Research is in flow and the committee can provide updates in future profiles to include the newer sequence especially if the vendor come up with some products and inter-vendor reproducibility data is available.

done

Takatoshi Asahi, Tetsuro Inside (Japanese QIBA) NA NA Thank you very much for your e-mail of September 12, 2020. We have read the profile. We think that it is absolutely fine. Thank you again for giving me this kind of opportunity. We look forward to your ongoing support.

none provided

n/a

none required

OK

Frank W. Bauman, MD 3.7 452/465 M Segmentation from high-resolution 3D GRE MRI Protocol will be modified: DED/MENA is recommended (different vendor implementations) as they provide good spatial resolution and contrast - MARS should not be used for segmentation. “Ideally” will be added to the protocol

Frank W. Bauman, MD 3.7 Fig 3 L yellow marking for lateral femur should not include anterior subregions/anterior lateral trochlea but only central and in move Image marking for lateral femur need to correct Figure 3 Figure 3 was corrected

Frank W. Bauman, MD 3.8.1 Table II and Figure 6 M normative value grouped for KD 0 and 1 Figure 6 was corrected

Frank W. Bauman, MD 4.1.3 Feature extraction is keeping T2 and T1rho value Table refers to WORKIN 0 and 1, not KD 0 and 1. no modification required.

OK

Gregory Chang, MD Image Data Analysis 480 L/M Since the document also addresses clinical trials, rheumatologists, orthopedists, it would be helpful to direct them toward software that can perform the image analysis. Provide short list of software that can do the image analysis, e.g. Siemens Mapf, Metalat, etc. Vendors have online reconstruction of T2 maps such as GE Cartigram, Siemens Mapf, and Philips T2 mapping. But no product available by manufacturers for cartilage segmentation add to discussion - provide good additional information but are not well standardized - include studies - discuss problems

Gregory Chang, MD Image Data Analysis 615 L/M Semi-automatic or automatic segmentation software is mentioned. It would be great to also list software for the segmentation, if different from above. see above

Gregory Chang, MD Image Data Acquisition 380 L/M Should the recommendation for number of echoes be mentioned? specify recommended number of echoes. minimum of 4 echoes is recommended - as shown in Table 3, default - for reproducible measurement of mono-exponential decay components 4 echoes is minimum 4 echoes is minimum - can be increased to up to 8 - 6 echoes is default - reproducibility for 4 echoes is good. It may provide more in depth information about cartilage degradation - but this is an area of new research - no discussion to date 4.1

Gregory Chang, MD Installation 230 L/M Even different model 3T scanners from the same vendor could demonstrate variation in measurements. Rheumatologists and orthopedists may not be aware. Clarify that even within a vendor, different model 3T scanners could improve variability in measurements. same vendor and field strength scanners have variability in measurements highlight this surprising - different models from same vendor and different machines, same model have differences

Flavia Couto, PhD, MSc General comment N/A H The approach presented in this document is a very good general/approach and guideline. Good point where should we acknowledge this – our claim is longitudinal This comment was added to the discussion.
The Claim requires presence of a significant amount of cartilage to be present and that there is no significant loss of cartilage volume and there are no major defects in the measured area. In order to focus on subjects with less severe cartilage loss, analyses should be restricted to patients with Knigge Lawrence (KL) Score of 0-2. KL 2 can be associated with significant cartilage loss. The authors need to provide evidence that the Claim is valid in the setting of KL 2.

Heterogeneity of cartilage damage in KL 2 knees and recent research work by Roemer et al. discussed limitations of KL 2 knee regions. According to work by Cicuttini, PhD, MSc N/A 145 N/A FLA 2021, approximately 25% of knees with KL 1 have wide spread full thickness cartilage loss in the medial femoral-tibial joint compartment (FTC) and 13% of the lateral femoral-tibial joint compartment (FTJ). (Roemer, 2021 #1521). Reporting about whether cartilage damage 30% of KL 2 knees is not within cartilage damage in the FTs, while these numbers are 50% for the FTs and 15% for the patellar-femoral joint compartment (PFJ). One third of KL 2 knees exhibit only minimal cartilage damage in the FTs. Given the heterogeneity of cartilage damage in KL 2 knees, radiography as an instrument to define which patients should undergo compositional cartilage imaging has limitations which need to be acknowledged.

The committee acknowledged it is a viable concern. Comments from NIST, Agar (which consists of agarose + agaroptin) is susceptible to bacterial growth. For the proposed phantom, we use agarose (not agar) with G350 and EDTA. EDTA is used here to complex with the G350 and prevent breakage of the agarose bonds (which would cause the gel to degrade). EDTA is also considered a bacterial growth inhibitor. Additionally, the preparation process involves elevated temperatures to above those used for pasteurization and renders the gel free from bacteria. Water hardness may have an impact on the gel structure which we use Good Manufacturing Processes (GMP) to ensure all supplies and equipment are clean and free of contaminants. When assembling the phantom, the gel is placed and there is no partial pressure of oxygen changes also have a significant effect on TF fluid starting in the agarose when stored at an increased temperature? N/A

Please provide additional requirements for hardware specifications needed. May be suggested by the RF amplifier and gradient performance. Please provide additional requirements for hardware specifications such as the RF amplifier and gradient performance. Please consider adding the ACA definition of MR scientist as a potential qualification. scientist was changed to physicist.

Please provide missing info. Spin-echo frequency of 400Hz or 500Hz is added to Table 2. Spin-echo frequency of 400Hz or 500Hz is added to Table 2.
Clarity if patient can walk to the scanner? Or seated the entire time?

Significance of the results?

Is the scan the same?

What is the sign of the scan?

Adding some details of work might result in revision.

Disagree that the reference interval is out of scope. Even if the ideal population is not captured, some effort should be placed to establish a reference interval.

Reference interval is critical.

List of acceptable hardware/software should be identified.

Make a list of acceptable hardware/software. If it is not comprehensive to cover all, the users should use "arrive or better yet repeat the various sert/valid studies to show equivalence (and submit to pipe group to expand list)."

More detail about MRI scanners and NIST phantom was added (under 4.1.1. Imaging equipment and 3.2. Installation).}

Ashley Williams

2 175 8 "site of tumor"?

Fix if this type?

Ashley Williams

2 315 M "Effects of metal artifacts" from metal implants, surgical hardware, shrapnel, etc.

Adds rest... patient was added to the list.

Convered to+tumor? corrected

Mikko Niinimäki, Evelina Lammentausta, Victor Casula (SARR)

2 196-197 M Definition of CV

Provide reference or justification.

Provide update reference for Kim et al manuscript paper.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

2 176 I Discussion of tumor?

Seems irrelevant for the topic. Change to "compositional change" etc.

Already addressed

Type has been corrected

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.3 256-257 H Phantom specs

Technical specifications of the calibration phantom (content, description) should be included here for phantom fabrication.

Add phantom resolos.

Phantom specifications were added to the profile.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.3 357 M Automated software specs

Add what should be the requirements specifications of the automated software to be used (not only reference to commercial software)

This is currently research – no commercial tools

none required

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.5 326 M Landmarks not defined

Add examples of landmarks

The profile referred to landmarking during MRI scans. Not specific landmarks.

Reworded the language to avoid confusion.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 349-345 H Unique sequence for T2/T2rho

Although standardization should be the ultimate aim, refraining the choice of only one sequence for T1rho and T2 quantification is a strict requirement. The use of MAPSS could be recommended so preferred approach, however it should be acknowledged that other methods are acceptable as well if certain criteria are met.

Is MAPSS available for T2/T2rho? Even though the recommended field is T2, there is no reason for not using 1.5 T scanners for cartilage T2 mapping.

Please see response to comment 40. MAPSS is available at 1.5 T

language added

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 355 I Typo

There is a typo in the figure legend of Figure 1: "simen" should be "simen".

type

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 360-371 I Reference to wrong table

Table referred to in the text should be table 3, not table 1

Table number corrected

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.3 276 I Add reference

Cartilage locations with specific abbreviations used, could add ref to Ekmans here to provide into the abbreviations

Reference was added

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 396 I Missing reference to table

Add reference to Table 2 in the text

Reference to Table 2 added in the text.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 330 L Clarification on scanned position for 30 minutes

patient can walk to scanner, pre-scanning before T1rho/T2 includes 10-15 minutes morphological imaging which adds to rest time but may increase motion artifacts.

walking to the scanner and acquisition of morphological sequences before T1rho/T2 sequences was added to the profile.

more detailed information was provided

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.5 325 L What is the sign of the scan?

Adding some details of work might result in revision.

Clarification of the term "arrive" might be required.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.5 305 H Reference interval is critical.

Disagree that the reference interval is out of scope. Even if the ideal population is not captured, some effort should be placed to establish a reference interval.

Reference database would require an additional study – reference data available for OAI study

is beyond the scope of the profile, but required to clinically apply the technology

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

4.1.1 620 M List of acceptable hardware/software should be identified.

Make a list of acceptable hardware/software. If it is not comprehensive to cover all, the users should use "arrive or better yet repeat the various sert/valid studies to show equivalence (and submit to pipe group to expand list)."

More detail about MRI scanners and NIST phantom was added (under 4.1.1. Imaging equipment and 3.2. Installation).}

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

2 169-177 M Reference needed

Provide reference or justification.

Provide updated reference for Kim et al manuscript paper.


Mikko Niinimäki, Evelina Lammentausta, Victor Casula (SARR)

2 176 I Discussion of tumor?

Seems irrelevant for the topic. Change to "compositional change" etc.

Already addressed

Type has been corrected

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.3 256-257 H Phantom specs

Technical specifications of the calibration phantom (content, description) should be included here for phantom fabrication.

add phantom resolos.

Phantom specifications were added to the profile.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.3 357 M Automated software specs

Add what should be the requirements specifications of the automated software to be used (not only reference to commercial software)

This is currently research – no commercial tools

none required

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.5 326 M Landmarks not defined

Add examples of landmarks

The profile referred to landmarking during MRI scans. Not specific landmarks.

Reworded the language to avoid confusion.

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 349-345 H Unique sequence for T2/T2rho

Although standardization should be the ultimate aim, refraining the choice of only one sequence for T1rho and T2 quantification is a strict requirement. The use of MAPSS could be recommended so preferred approach, however it should be acknowledged that other methods are acceptable as well if certain criteria are met.

Is MAPSS available for T2? Even though the recommended field is T2, there is no reason for not using 1.5 T scanners for cartilage T2 mapping.

Please see response to comment 40. MAPSS is available at 1.5T

language added

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.6 355 I Typo

There is a typo in the figure legend of Figure 1: "simen" should be "simen".

type

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

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Table referred to in the text should be table 3, not table 1

Table number corrected

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)

3.3 276 I Add reference

Cartilage locations with specific abbreviations used, could add ref to Ekmans here to provide into the abbreviations

Location of regions - line 363 in current version

Reference was added

Mikko Niinimäki, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARR)
Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.6.3 406 H Parameters for T2/T1rho sequences

Some general recommendation for parameters for conventional multi-echo spin-echo and spin-echo sequences, including instructions on TR and longitudinal/T2/T1rho values, and spin-lock amplitude (sensitivity to cartilage degeneration varies with frequency).

Included in Table 3 for MAPSS parameters. OAI protocol is recommended to use for MSME.

Information was added in Table 3, and in discussion 3.6.3 for MSME
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 16.3 439 L Parameters for T2/T1rho sequences

Siemens→Siemens

Type

Type has been corrected
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3 464 M Reconstruction of relaxation maps

"With or without noise components", This, the use of, or not using noise should be very precisely defined, as well as the exact way of handling noise, as this will affect the fitted data values.

This is a stable comment. However currently there is no consensus on optimized fitting algorithm for cartilage T2rho and T2 especially regarding how to handle the noise component. More studies are needed in the field. Could be this paper as a discussion of various ways to fit data to derive a relaxation time when the signal comes from multi-element coils. HDR, AH, Anderson AH. Calculating T2 in images from a Phase Array Receiver. Mag Reson Med. 2005;54(1):982-6.

More discussion and references are added to section 3.6.1 regarding fitting methods.
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.7 466 H Definition of compartments

1. Definitions of the regions are too vague. In figure 2, the images on the left are not showing any anatomical landmarks, while in the images on the right there are no lines indicating boundaries between regions.

2. The proposed regions are very large, resulting in averaging out most of the local changes and reduced sensitivity to early cartilage degeneration. At least load-bearing cartilage should be divided and alternative approaches should be mentioned (e.g. Vector Sciv et al. Evaluation of semi-quantitative white joint assessment of knee OA. Osteoart (Osteoart. Cartilage. 2011;19(8):990-1000. doi: 10.1016/j.joca.2011.05.004. Hannula et al. Topographical variation of T2 relaxation time in the young adult knee cartilage at 1.5 T. Osteoart. Cartilage. 2008;16(12):1678-81. doi: 10.1016/j.joca.2008.05.011.)

Division into layers (i.e. superficial and deep/hub) should also be mentioned. *

Figure 2 was changed and regions were better defined, may need some more detailed definitions of regions, also added a citation-
definitions - should we subdivide femoral region - weight-bearing/non-weight-bearing, deep and superficial cartilage layers.

More discussion and references are added to section 3.7.1 regarding fitting methods.
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 511 L Missing reference to table

Add reference to the Table in the text

Reference was added
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 511 L Significant decimals

number of significant digits seems too high

Table was taken from publication

Left as is

OK

done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 515 L Missing reference to figure

Add reference to the figure 4 in the text

Reference to Fig. 4 was added
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 563 L Missing reference to figure

Add reference to the figure 5 in the text

Reference to Fig. 5 was added
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 566 M "The table" is referred

Figure caption refers to an unnumbered / inconsistent table. The reference should be removed, or the table added.

Substituted table with figure

done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 565 L Missing reference to figure

Add reference to the figure 6 in the text

Reference to Fig. 6 was added
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 595 L Missing reference to figure

Add reference to the figure 7 in the text

Reference to Fig. 7 was added
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 3.8 595 L Risk calculator

It is not clear how the risk calculator tool fits with the purpose of this claim, it seems rather handwaving

This part of the discussion of 3.8. Image Data interpretation and how T1rho and T2 can be used in the future - similar to FRAX for BMD measurements.

None required

Ok

done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 4.1.1 621 M Field dependence

It might be worth to mention that relaxation times are field dependent

T1rho and T2 relaxation time and field strength.

This added to 4.1.1. That relaxation times are field dependent.
done

Miika Nieminen, Mikko Nissi, Evelina Lammentausta, Victor Casula (SARQ) 4.2 675 M upper bound of wCV?

Check the conformance criteria. Less than 5k seems conformant if target is between 4-5k

Not sure what is meant here

None required

Ok
The findings of two recent systematic reviews and meta-analyses should be considered:


MacKay reference was included in our previous discussion, both references were discussed.

References were added to Appendix B.

James MacKay | James.A.macKay@uva.ac.uk
Title page, 1
6, 74, L Prefer term ‘osteoarthritis’ to degenerative joint disease which is a little vague
Change ‘Degenerative joint disease’ to ‘osteoarthritis’

James MacKay, MiKKCHIR, MRCF
1, 2
78, 135-6, H Does the reproducibility of 4 T1 refer to global, compartmental or laminae (e.g. superficial, deep) values? One would expect reproducibility to women with more granular analyses
Clarify what type of analysis the 4 T1 refers to.

James MacKay, MiKKCHIR, MRCF
2
139-40, M Suggest a caveat is added or elsewhere to clarify that many studies have demonstrated bidirectional changes in T2/T1 with increasing degeneration (particularly with more granular compartmental/subcompartmental analysis) and no one-sided analyses should only be performed with caution.
Add caveat regarding the indiscriminate use of one-sided analyses giving likelihood of bi-directional change

James MacKay, MiKKCHIR, MRCF
2
180, M Similar to comment 1, should at least acknowledge that we frequently see concurrent increases and decreases in T2/T1 in different regions of the same knee
There is sound biological rationale for this: in early osteoarthritis the synthesis of proteoglycan and type II collagen actually increases (dx.doi.org/10.1016/j.rcl.2009.04.003). In addition, disruption of the normal cartilage structure may cause a counterintuitive increase in the amount of bound water molecules by increasing the number of accessible hydrophilic binding sites (dx.doi.org/10.1016/j.rcl.2009.04.003). acknowledge that we frequently see concurrent increases and decreases in T2/T1 in different regions of the same knee in clinical studies.

James MacKay, MiKKCHIR, MRCF
2
201-2, H In my experience the flexible coils demonstrate improved image quality compared to some rigid coils. They also permit simultaneous biplane imaging. If including this statement, the QA data needs to be included to justify.
Remove statement on flexible coils not being recommended or provide supporting data

James MacKay, MiKKCHIR, MRCF
3
304-5, M Bland Altman analysis would be preferable here. A tone would not tell you anything about the magnitude of any systematic difference between different hardware/software settings, which Bland-Altman analysis would
Change Student’s t-test to Bland-Altman analysis

James MacKay, MiKKCHIR, MRCF
3
320, M I have found defining what constitutes ‘exercise’ difficult to define, and is something which study participants often ask about. For example, is walking to their MRI appointment okay? How much ‘exercise’ is too much? Perhaps we could try to define this a little more here
Clarity of what is meant by ‘should not have exercised’
Patients should not have exercised on the day of the exam (no high impact sports and no running, no exercise gym). They should not have performed any unusual, atypical physical activities (such as a marathon or an extended hike) 48 hours before the MRI examination.
Discussion was added under 3.1.3.1 Subject handling

James MacKay, MiKKCHIR, MRCF
3
370-85, M Should also mention dQISS sequence here which allows simultaneous acquisition of morphological data and T2 maps for free!
Mention dQISS sequence

James MacKay, MiKKCHIR, MRCF
3
455-60, M Should we provide thresholds for implausible values (e.g. T2 > 100 msec) or poor fits (e.g. squared-e < 0.8) above/below which pixels should be excluded from analysis
Consider specifying exclusion thresholds for implausible value/parameter fit

Dimitrios Karampinos, PhD
34.1
380, M The severely delayed dQISS sequence may be used here. Some more clear statements on the use of the dQISS for cartilage T2 mapping should be included.
MSE in MAPSS: previous discussions - MAPSS is recommended as the preferred method based on reproducibility evaluation. Other sequences including MSE may be used when MAPSS T2 and T2 are not accessible, provided the Test–ReTest Concordance can be met.

Dimitrios Karampinos, PhD
410, M N/A
It would be useful to include some statements regarding the use of parallel imaging and compressed sensing for T2/T1rho mapping, as they are nowadays mainstream tools for accelerating image acquisitions across platforms.
Parallel imaging is a standard - we can recommend this in the discussion - acceleration factor of 2 in phase direction were commonly used, if higher acceleration factors (with compressed sensing) are used make sure that there are no
As coils have a significant impact on signal and measurements, quadrature transceive (array of coils) is used for the 8Ch system. However, the results, from the current setup, seem better and more repeatable with the quadrature coils than with the single coil setup (Table 1). This may be because the quadrature coils provide a more uniform excitation across the field of view, which is important for achieving reproducible results. In contrast, the single coil setup can lead to variations in the excitation profile, which can affect the reproducibility of the measurements. Therefore, it is recommended to use quadrature coils for reproducible results.

Furthermore, the SNR of the quadrature coils is also better than that of the single coil. This is because the quadrature coils can capture more of the signal, which improves the overall SNR of the measurement system.

In conclusion, using quadrature coils is recommended for reproducible results, especially in long-term studies where consistency is crucial. This approach ensures that the results obtained are reliable and can be compared across different measurements, which is essential for research and clinical applications.