

Multi-centre imaging measurements for oncology and in brain

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Multicentre imaging studies of brain tumours (and other tumour and brain studies) can enable a large group of patients to be studied, yet they present challenging technical problems. Between centre differences can be characterised, understood and minimised by use of phantoms (test objects) and normal control subjects. Normal white matter forms an excellent standard for some MRI parameters (diffusion, magnetisation transfer), since the normal biological range is low (<2-3%), and measurements will reflect this, provided the acquisition sequence is controlled. MR phantoms have benefits, and are necessary for some parameters (e.g. tumour volume). Techniques for temperature monitoring and control are given. In a multi-centre study or treatment trial, between-centre variation should be minimised. In a cross-sectional study, all groups should be represented at each centre, and the effect of centre added as a covariate in the statistical analysis. In a serial study of disease progression or treatment effect, individual patients should receive all of their scans at the same centre; the power is then limited by the within-subject reproducibility (test-retest difference). Sources of variation that are generic to any imaging method and analysis parameters include MR sequence mismatch, B_1 errors, CT effective kV, ROI generation and segmentation procedure. Specific tissue parameters are analysed in detail, to identify the major sources of variation, and the most appropriate phantoms or normal studies. These include DCE and DSC Gd imaging (for K^{trans} , blood volume and blood flow or perfusion), T_1 , diffusion, magnetisation transfer, spectroscopy, tumour volume, ASL (for blood flow) and CT perfusion.

1. Introduction.

There have been many approaches to carrying out multi-centre studies. The difficulty soon found is that a measurement made at one centre is often not reproducible at another centre, and thus to pool measurements from several centres into a large trial reduces its statistical power. Yet there is a strong imperative to be able to carry out meaningful multi-centre studies, in order that clinical drug trials with a large number of subjects can take place in a reasonable time. By analysing the sources of inter-centre variation, with insight into the MR physics aspects of the imaging process, and then reducing them where possible, progress has been made. By measuring actual quantities (such as volume, relaxation time or transfer constant), then in principle we obtain values independent of the scanner used and of the particular way the measurement was carried out.

Multi-centre imaging studies are desirable for several reasons. 1. In clinical treatment trials, they are usually the only way of achieving the large number of patients that is needed to statistically power the study. 2. Measurement of good inter-centre agreement demonstrates that imaging technique is good and that the results of clinical or scientific research can be applied to other centres. 3. Good inter-centre agreement also demonstrates that the physical factors involved in the measurement process are relatively well understood and controlled, and therefore the process is relatively reliable and robust, and serial measurements through imager upgrades are also likely to be reliable. 4. Pharmaceutical companies will sometimes recruit a large number of

clinical centres in order to engage with many potential buyers of the treatment (although this can actually *reduce* the power of the study – see below).

Multi-centre studies have considerable difficulties[1]. These are primarily related to *logistics* and *variance*. Logistical problems relate to the interfacing required by the reading centre to the many different imaging centres, each with a potentially different imaging hardware and protocol, system of controlling and documenting the protocol, and image data format. The resources required for this scale approximately with the number of imaging centres. Variance problems relate to the way that image measurements of a given subject can vary between centres (the *between-centre variance*), and how such variance can mask the effects of treatment. A small number of carefully selected and controlled centres, which give data of high quality, might give better statistical power than a large number of relatively low quality centres. Minimising between-centre variance (and also within-centre variance) is therefore at the heart of this paper.

In this paper we discuss measurement variance in general terms, including how it affects cross-sectional and serial measurements. The principle sources in MR and CT measurements are identified. Concepts of quality assurance using normal human controls and phantoms (test objects that seek to simulate human tissue) are presented. For individual imaging parameters, the major sources of variance are identified, and published measurements are reviewed. Recommendations for the design of multi-centre studies are given.

2. Concepts in multi-centre studies

A good ('qualified') *biomarker* should have three properties (reference[2] page 68): i) biological relevance to the disease process under study, ii) sensitivity to the disease process and iii) reliability (i.e. good reproducibility). Relevance and sensitivity will have been established in single-centre studies. Reproducibility (i.e. a small difference between repeated measurements) will have been good at single centres where the initial studies were carried out (in order to establish the sensitivity); however at multiple centres this has to be established again.

In a *serial study* to establish treatment effect, each subject will normally be imaged at the same centre for each time point, and thereafter it is the within-subject variance (i.e. reproducibility), measured at a given centre, over the duration of the study, that is important. (This is also true for a single-centre study). The between-centre effects constitute a confounding variable; these effects, if small, can be accounted for by including centre as a covariate (reference [3] page 44) in the statistical analysis. However between-centre variance should also be reasonably controlled, otherwise between-centre effects that alter sensitivity might be suspected, and cross terms containing centre and sensitivity (or effect) would be needed in the analysis. In a *cross-sectional study*, between-centre variance could dominate the power of the study, although the effect of centre as a confounding variable could again be reduced by using centre as a covariate in the statistical analysis, and ensuring that each subject group is well represented at each centre. In summary, within-subject variance should already be controlled in any (single-centre) study; if the study is to be multi-centre then between-centre variance should also be controlled.

The *within-centre variance* for a subject can most straightforwardly be measured using the Bland-Altman analysis method[4,5]. Repeated measurements are made (usually pairs), over a set of subjects (typically 5-20), to establish the difference between repeats, and whether this depends on the mean value of the parameter being estimated. This variance can then be used directly in a power calculation. This variance usually depends (sometimes quite dramatically) on the time period over which it is measured. A repeated image data collection, whilst the subject remains on the scanning couch, will only be vulnerable to image noise, and perhaps movement; conversely a pair of measurements separated by several years could also be vulnerable to factors such as imager hardware upgrade, change of radiographer (technologist), and change of image analysis procedure.

Protocol-matching is the most straightforward way of reducing between centre differences. Thus in reporting Multiple Sclerosis (MS) hypointense lesions from T₂-weighted MRI, differences in qualitative image appearance could be reduced by standardising the acquisition parameters thought to be relevant (TR, TE, slice thickness, type of radiofrequency coil etc) and also the analysis procedure (by defining rules) [6-9]. The

MAGNIMS Study group defined many guidelines for multicentre MR studies in MS[10,11], and at times this involved MR physicists travelling to different sites within Europe, sometimes with phantoms, to improve the protocol matching[12]. Differences between imaging hardware produced by different manufacturers (vendors) may prevent identical protocols being used at every site. Alternatively, acquisition parameters may be compromised, giving a protocol that is common across all sites, but is less than optimal for most sites.

Quantitative imaging maps (derived from source image data and a common post-processing software package) may further reduce between centre differences, since parameter maps of particular quantities are calculated, which in principle are independent of the exact imaging protocol used. For example, Apparent Diffusion Coefficient maps are approximately independent of the particular imaging parameters used (e.g. TE, gradient strength, b-value and static field B₀). In some cases there may be a conflict between requirements to minimise within-and between-centre variances. For example, spectroscopic metabolite peak ratios usually have better within-subject reproducibility than do absolute metabolite concentrations (since the latter quantity involves input from more potentially variable sources related to the instrument calibration); conversely the between-centre performance of absolute concentrations is often better, since more centre-specific factors have been taken account of in the calculation.

3. Sources of variation

3.1 The magnitude of genuine *biological variation* in a subject is usually unknown. This is the variance that would be measured with an instrument having perfect reproducibility (or at least negligible variance of its own), and represents how much the biology of a tissue varies with time over a short period (say one day) during. For example, it is likely that blood flow or blood volume do change over short periods of time (e.g. in response to cardiac output); conversely tumour volume probably does not. Other factors which could alter tissue biology in the short term include state of hydration and menstrual cycle. These effects all appear as random effects which can mask the effect of treatment.

If the instrumental variance is well below this biological variance, then it constitutes a '*perfect instrument*'; the power of a study is no longer limited by instrumental imperfections. Thus we can aspire to this situation. In multiple sclerosis (MS), the visible lesions vary enormously with time (by maybe 50%; this is the phenomenon of relapse and remission), and therefore a 'perfect instrument' can easily be achieved (the requirements on instrumental reproducibility are very lax). Conversely, the observed changes in Normal-Apparent Brain Tissue in MS are very small (typically 3%), instrumental performance probably limits what can currently be observed, and there is a premium on improving instrumental performance. Thus the magnitude of instrumental variance compared to the

biological changes seen as a result of disease determines the importance of instrumental imperfections for each tissue parameter, and the amount of effort that should be expended in reducing such imperfections. Such effort might include setting up and maintaining Quality Assurance (QA) at each centre, and improving the acquisition procedure. For a technically demanding parameter this might be done at only a few high-quality centres, whilst for a parameter where instruments are already 'perfect', many more centres could easily be included in the study.

The process of imaging (whether for qualitative reporting or for quantitative measurement) can conceptually be split into the sub-processes of *data collection* and *image analysis*. This is convenient for identifying the sources of variation, since the analysis process (for a given dataset) can usually be repeated (e.g. for a Bland-Altman analysis), whilst data collection often can not (particularly if it involves administration of contrast agent, or the use of ionising radiation).

3.2 All image *data collection* procedures are potentially vulnerable to the following sources of variation[3,13] :

- i) differences in acquisition parameters
- ii) patient repositioning errors between examinations
- iii) patient gross movement during the scan (e.g. moving the head slightly); this can be minimised by careful attention to patient comfort.
- iv) patient involuntary movement during the scan
 - a. respiratory motion
 - b. cardiac motion and ensuing blood vessel and ventricular pulsation
- v) image noise
- vi) upgrades to imager hardware or acquisition software

MR acquisition is also vulnerable to the following effects:

- vii) The prescan procedure to set imaging parameters (e.g. flip angle (FA) and shimming) may be variable
- viii) Changes in static field strength: some tissue parameters are in principal independent of field strength (K^{trans} , diffusivity, volume, metabolite concentration, blood volume and flow), although an altered measurement protocol, and the increased signal-to-noise ratio at 3T compared to 1.5T may be evident; other parameters are certainly dependent on field strength (e.g. T_1 , magnetisation transfer)
- ix) RF coil architecture, which affects the B_1 and hence FA distribution (whether head or body coil excitation is used). Body coil excitation is preferable[14] , although there can still be differences between vendors, particularly at 3T.

CT acquisition is also vulnerable to:

- x) Changes in X-ray tube output. Although a daily calibration for water CT number is usually carried out, changes in the beam energy

spectrum will not be compensated for. Any resulting change in beam effective energy will alter the measured CT number of tissues containing significant amounts of high atomic number elements.

3.3 *Image analysis* results often depend on the observer carrying out the procedure. Sources of variation can include:

- xi) Image viewing conditions (display window, image magnification, viewing distance, ambient lighting)
- xii) The set of rules used to define (segment) a Region of Interest (ROI) around an area of abnormality (e.g. tumour outline), and to generate a histogram[15] (if used)
- xiii) Mode of operation of analysis software
- xiv) Changes in analysis software over time

In multi-centre trials, the trend is towards using a single centre for analysis (the 'Clinical Research Organisation - CRO'). If multiple tissue parameters are being evaluated, then distinct centres are often used for each parameter, in order to spread the analysis load. Observers are trained to a well-defined set of rules and procedures, and their performance in repeated analysis is monitored. With manual analysis of serial data, there may be long-term drift (reference[16] figure 1), and best practice is to repeat the analysis each time there is a new time point for a given subject, in addition to continuously monitoring the QA results. Software for semi-automated analysis clearly reduces variance compared to a manual procedure (and an entirely automatic procedure must necessarily be completely reproducible, for the same image dataset). In multi-centre scientific studies, several centres may wish to carry out analysis, and then these sources of variation would be identified and controlled as much as possible, particularly by moving towards using a single software analysis system (e.g. in IDL or java languages) which can be run on many platforms; this also has the benefit that ROI are all generated in a common format, with a common naming convention. Batch processing files (for example in XML language) are often used to drive the analysis process; such a file records the entire processing procedure, a way that can be read by a human.[17]. The file might include information on the analysis model used, the kind of T_1 calculation, and the software version used. Thus an 'audit trail' is available, as required for FDA approved clinical trials, and a result can be exactly reproduced at a later date.

4. Quality Assurance

Accuracy and *precision* are determined in QA procedures which determine the quality of the imaging process. They can be cross-sectional (across several centres) to estimate between-centre effects, or serial (at a single centre, to monitor stability over time). They can be used to monitor two quantities. Accuracy (i.e. closeness to the truth, or systematic error) can be found using a phantom with known properties (e.g. volume or diffusion

coefficient). Precision (stability, reproducibility, test-retest difference, or random error) can be found with phantoms (which often need temperature control) or human subjects (provided they are known to be stable over the period of the repeated measurement). Stability can be measured over various time periods, from a few minutes (with a repeated scan keeping the subject on the scanner bed) to several years (through scanner upgrades). Tumours usually change quickly enough that long term measurement stability is not important. Note that if accuracy can be established at each centre (for example if measured values of a tumour volume standard, or of normal white matter T_1 , are close to the known values), and if precision (i.e. within-centre reproducibility) is good, then the between-centre differences will necessarily be small, and need not be measured explicitly.

Human control subjects have some benefits over phantoms (at least for MR studies). (i) They can be an almost completely realistic simulation of the clinical measurement process in a multi-centre study (depending on the tissue parameter). The white matter of healthy controls (frontal or parietal lobes) often has a narrow range of tissue parameters, and thus can be used at different centres without the need to transport the subjects from centre-to-centre. The normal range can be estimated from published high quality measurements made on a number of controls at a single centre (ideally where within-subject reproducibility has also been measured), and age and gender may need to be controlled for. Some recent single-centre studies of normal subjects report encouragingly narrow ranges of values, with measured normal coefficients of variation (CV's) for MTR and diffusivity down to about 2-3%; see tables 2,3 below. Reported values usually include the effect of instrumental variation (although this could in principle be removed with an analysis of variance); thus the lower published values probably approach an upper limit to the true biological variation (which could in fact be considerably lower). (ii) Homeostasis provides inbuilt temperature control, and the demands of temperature stabilisation are bypassed. (iii) Human controls are often more readily available than phantoms. Disadvantages of using human subjects include (i) a lack of stability over time for tumour-related parameters in patients (e.g. for K^{trans} and volume); thus the stability of a measurement procedure cannot be evaluated, (ii) imaging humans may be more demanding of resources than imaging of phantoms, depending on the operating policy of the imaging centre (iii) if the imaging procedure includes incidental hazards such as contrast agent injection or the use of ionising radiation then the availability of normal controls, and the number of repeated exams that can be made, will be limited by ethical constraints.

Phantoms exist for some of the tissue properties that can be measured in tumours, but not all[2]. They have the benefits (over human control measurements) of i) being conveniently scanned, as many times as required, without any ethical constraints, (particularly important for CT),

ii) of having known physical properties and (iii) being relatively easily transported from centre to centre. Their potential disadvantages include i) there may be a lack of realism compared with in-vivo measurements; some quantities (e.g. blood flow) are extremely difficult to simulate in a phantom, and the measurement process, even for a simple quantity like volume, does not replicate the complexity of the in-vivo process. (ii) The MR properties may vary with time, caused by either a temperature dependence of the parameter under study (e.g. diffusion), or by instability of the material over time (for example caused by fungal attack, chemical decay, or gel breakdown). For liquids or gels, failure of the container cap seal can lead to evaporation, oxidation, or ingress of water vapour. (iii) The time and expertise required to manufacture phantoms may be prohibitive at some centres. Note that these phantoms are designed to directly monitor imager performance in measuring tissue parameters; they are distinct from those designed to measure instrumental parameters such as slice thickness or image noise[18].

Temperature control of MR phantoms is now recognised as being crucial if imager stability is to be measured precisely (i.e. within <1%). The temperature coefficient of MR diffusion and T_1 phantoms is about $2.5\%/^{\circ}\text{C}$ [2]; thus temperature must be monitored and controlled to within about 0.2°C to confirm a stability or precision of 0.5% in these parameters. Storage of phantoms in the magnet room, at as close a temperature to that of the magnet bore as possible, reduces phantom temperature changes during scanning. RF power deposition in phantoms can usually be ignored (unless they have been deliberately made electrically conducting by the addition of NaCl); this can be confirmed by monitoring the phantom temperature before and after scanning. Measurements near to body temperature can be made by placing the phantom and containers of warm water (or saline) inside an insulating container. Phantom temperature can be monitored by using thermocouples (or the more expensive and brittle optical probes) attached to the surface of the container (provided there is plenty of thermal insulation around the container), or else thermocouples can be placed inside the phantom (if liquid), although this involves breaking into the container. A thin T-type thermocouple has signal dropout limited to within about 3 mm of the tip[19].

Thermal insulation can conveniently be achieved by re-using packaging made of expanded polystyrene (Styrofoam), or else can be custom-made for better performance. Thermal insulation slabs (about 100 mm thick) used in the building construction industry for cavity wall insulation are readily available and perform well, although they may have a layer of aluminium foil attached which has to be painstakingly removed first. Expanded polystyrene is commonly available and cheap. Expanded urethane or phenolic foam, although slightly more expensive, has considerably lower values of thermal conductivity[20] (about 60% of that for expanded polystyrene), and the fine mechanical structure

makes it easier to machine. Values for thermal conductivity k ($\text{W m}^{-1} \text{K}^{-1}$) (from an internet search) are approximately as follows: mineral wool 0.041, expanded polystyrene 0.037, rigid urethane foam 0.023 and rigid phenolic foam 0.022. For comparison, air has $k=0.024$. One of the authors (PT) has successfully used Kingspan Kooltherm K8 phenolic 50 mm thick cavity board, which is easily available in the UK from builders merchants. Thermal time constants greater than 10 hours can be obtained by using a 5 cm bottle in a head coil, and filling all the available space with insulation. Machining is straightforward using a bandsaw and slow drill bit, although care should be taken to avoid any small ferromagnetic chards becoming embedded in the phantom.

Provided phantom temperature has been measured during QA measurements, then phantom parameter values (e.g. ADC) can be converted to a standard temperature for realistic comparison with those made at other times (which will inevitably have been made at slightly different temperatures)[21]. In some cases the phantom can be made using available liquids from a chemical supplier[21,22]; this has the convenience of being able to leave the liquids sealed in the delivery bottle (although slightly magnetic labels might have to be removed).

Reanalysis of acquired image data (both human and phantom) enables the contribution of the analysis process to variation to be estimated. Generally this process can be refined and semi-automated to the extent that the majority of the measurement variance then derives from acquisition. Analysis of the same image data at different centres can identify between centre effects that derive from analysis rather than acquisition.

5. Specific QA procedures for each tissue parameter

5.1 Qualitative weighted images (e.g. qualitative T_2 -weighted images) are often used in multi-centre studies because they are straightforward to implement at each centre. Lesion dimensions can be estimated manually. By controlling the acquisition parameters (TR, TE, TI, voxel dimensions etc), the display parameters (grey scale windowing, image magnification, ambient lighting etc), and the rules for radiological analysis (e.g. how to identify the border of a tumour, and maximising the use of automated analysis software), then a reasonable between centre agreement can often be achieved[6], without the need for a large amount of technical input.

5.2 T_1 weighted-DCE

T_1 weighted-DCE (T_1 w-DCE) measurements may be used to calculate semi-quantitative parameters (such as Initial Area under the Gadolinium Curve IAUGC[23]) or the transfer coefficient K^{trans} [24]. Within-centre variance may be better for AUGC (since variation from sources such as the Arterial Input Function AIF may be reduced); conversely K^{trans} may be successful at removing the effects of varying AIF at different centres and thus have

better multi-centre performance. The major sources of variance are likely to be: the injection procedure (a power injector makes this more reproducible); the image acquisition procedure (this determines spatial and temporal resolution and image noise); the way that T_{10} (the tumour T_1 before injection of Gd) is measured, if at all; the way that the AIF is derived from a ROI over a major blood vessel (the descending aorta or a carotid can be imaged using a different coil from that used for the brain); the way that ROI's are defined on the tumour; and the modelling procedure used to estimate IAUGC or K^{trans} .

Table 1: recommended QA procedures for each tissue parameter – phantoms, normal subjects and tumours. Phantom measurements can be used in an initial evaluation where they exist (T_1 , diffusion, MTR, MRS and volume). Measurements in normal brain give precision (from repeated measurements) and accuracy (by comparison with published values) in T_1 , diffusion, MTR, MRS and ASL, with more realism than phantoms. Measurements in tumours are particularly important where no phantom or normal tissue measurements are appropriate (K^{trans} and volume).

quantity	phantom	normal brain	tumour
T_1 w-DCE ^g	none	no	yes
T_1	yes	yes	
T_2 w DSC ^a	none	no ^c	yes
diffusion	yes ^b	yes	
MTR	yes	yes ^c	
spectroscopy	yes	yes	
volume	yes	no	yes
ASL	none	yes ^d	
CT perfusion	no	no ^f	yes

^a for blood flow and volume rCBF and rCBV

^b ADC or mean diffusivity only

^c results depend on sequence

^d NB large normal variation

^e it may sometimes be possible to give Gd to normal controls

^f it may sometimes possible to measure CT perfusion on patients with normal brain

^g for K^{trans}

There are currently no realistic QA phantoms for T_1 w-DCE, although some workers have used renal dialysis cartridges. Patients with tumours are unlikely to be stable, although short term studies can be made within- or even between-centres.

There have been few studies of T_1 w-DCE variation, largely because of ethical problems around administering repeated doses of contrast agent[25-27].

In the future, the use of a pre-bolus technique [28,29], where a small dose (typically 0.1 of the standard dose) is given to determine the AIF, is likely to be adopted. The accuracy of the AIF estimation is improved

(since the dynamic range of the signal is less, and inflow effects can be avoided by using an appropriate sequence), and its reproducibility can be determined.

5.3 T_1 mapping.

T_1 w-DCE when used quantitatively is inherently a dynamic T_1 determination, and thus the factors which control T_1 mapping accuracy are also influential in T_1 w-DCE. In addition, the tumour T_1 before injection of Gd (i.e. T_{10}) must be measured. A convenient way to establish that the T_1 w sequence is behaving as expected is to also collect a PD weighted image (with reduced flip angle), estimate normal white matter T_1 from the ratio of these images[30], and compare to published values. The T_1 sensitivity of the spoiled gradient echo sequence is dependent on flip angle; thus any B_1 errors can make the T_{10} determination inaccurate (unless a B_1 map is made[31]), and B_1 errors will also affect the amplitude of the post-Gd signal.

Published values of T_1 in normal human white matter show some between-centre variation (probably because of B_1 effects, and ROI placement), and there are few large studies of normal variation.

Table 2: normal range of T_1 values in white matter

		CV ^d (%)	n ^a	mean (ms)	SD (ms)
Stevenson[32]	2000	5	40	666	36 ^b
Rutgers[33]	2002	6	15	681	40
Ethofer[34]	2003	4	8	770 ^c	30

^a sample size

^b estimated from boxplot in figure

^c used spectroscopic technique; probably some CSF or grey matter contamination

^d Coefficient of variation = SD/mean

The measured variation (see table 2) is quite small (CV=4-6%), and the intrinsic biological variation may be much smaller (since diffusion and MTR have even smaller measured CV's – see tables 3,4 below). At 3T, white matter values[35,36] are about 1050-1080 ms. Given the vulnerability to B_1 errors (which can easily be different in phantoms and human brain), then human brain QA is advised for T_1 .

Phantoms for T_1 are well established[2]; these can be aqueous solutions of paramagnetic ions, made in-house, or else purchased from commercial sources such as the Eurospin set (from Diagnostic Sonar, Livingstone, UK).

Multi-centre studies on T_1 are rare. Deoni[37] measured a mean value in normal white matter at 1.5T of 662 ms (at 3 centres; SD=44 ms; CV=7%); the between-centre variation was comparable to the within-centre variation.

Interest in T_1 measurement methods may increase, both because of its contribution to DCE, and as a surrogate for water content; if so, then more standardised methodology will evolve (including B_1 correction, particularly for 3T).

5.4 T_2 weighted DSC for blood flow (perfusion) and volume

The sources of variation are very similar to those encountered in T_1 w DCE (see section 5.2). Relative measurements (i.e. ratio to contralateral normal-appearing tissue) are often more reliable than absolute measurements. There is very little literature on DSC QA or multicentre studies[38].

5.5 Diffusion

Diffusion measurements are potentially quite reliable, because they are insensitive to B_1 errors. Gradient values are usually accurate to within 0.5% (in order to give correct object dimensions); thus ADC values should in principle be accurate to within 1%[39]. The implementation of the gradient scheme, in which a range of b-values are produced, in a range of directions, is often provided by the manufacturer. Artefacts can cause problems, depending on the sequence. These may arise from subject movement, from susceptibility induced signal dropout in the EPI sequence, or from the scanner itself (for example if the gradients cannot be switched accurately enough). In a situation where intrinsic ADC values are accurate (as demonstrated in large regions of liquid or normal brain), there may still be large variations when lesion or tumour ADC values are measured (caused by variations in the ROI generation procedure[40]).

Mean diffusivity can be conveniently validated using normal white matter, which has measured values in the range 0.69-0.93 $10^{-9} \text{ m}^2 \text{ s}^{-1}$ [41-48]. The measured value depends on the b-value, the diffusion time Δ [49,50], and the sizes of the ROI and voxel (large ROI's or voxels may produce more CSF or grey matter contamination). There is a small increase with age[51]. In white matter, low normal ranges (3-5%) for measured values have been reported (table 3), and the intrinsic normal biological variation is almost certainly below this. For within subject variation measured by repeated scans, CV's of 2.5%[52] and 2.6%[53] have been reported.

Table 3: normal range of mean diffusivity values in white matter

		CV (%)	n	mean ($10^{-9} \text{ m}^2 \text{ s}^{-1}$)	SD
Cercignani[54]	2001	5	20	0.93 ^a	0.04
Emmer[55]	2006	4	12	0.84	0.03
Zhang[56]	2007	5 ^b	29	0.69	0.04
Welsh[57]	2007	3	21	0.73	0.02

^a some CSF contamination

^b CV=2% for whole brain

Phantom measurements can be made with alkanes[21,58,59], or other organic liquids[59], which are available with diffusion coefficient (i.e. ADC) values in the range of brain tissue. Alternative liquids include sucrose solution[60,61] or iced water. At room temperature water has an ADC value[59,62,63] three times that of normal white matter, so signal is

considerably lower. Gels may be nonuniform and unstable.

Validation of Fractional Anisotropy (FA) or full tensor measurements is much harder. In humans, the corpus callosum has anisotropic diffusion (FA=0.7[64,65]) and is suitable for an approximate comparison. However the measured FA value will depend on a variety of factors, including the voxel dimension[66] (larger voxels can average out some of the anisotropy, if fibres are not exactly parallel) , the amount of image noise[67], and the precise size and location of the Region of Interest (since partial volume effects are quite strong); large within-centre variations have been reported[68] . Some anisotropic phantoms are under development[69,70], although these are currently quite complex to manufacture and are quite small (up to about 2 cm in diameter).

Two multi-centre studies of normal brain tissue[71,72] found differences of 4-9% and 2-6%, and considerable within-site variation.

In the future, the use of liquid phantoms or normal white matter will become routine, and anisotropic phantoms will probably become commercially available. Most scanner faults can probably be identified using liquids, so the added value of using an isotropic phantom may be small.

5.6 Magnetisation Transfer Ratio (MTR)

The largest sources of variation in measuring MTR values are sequence and pulse differences[73], and B₁ factors[74].

MTR values in normal white matter are in the range 30-60 pu (percent units), depending crucially on the sequence used[75-78]. Thus a common sequence must first be chosen before any multi-centre comparisons can be made. The normal range is low (below 2%, perhaps partly related to the fact that white and grey matter have similar values of MTR) – see table 4.

Table 4: normal range of MTR values in white matter

		CV (%)	n	mean (pu)	SD (pu)
Silver[79]	1997	1.9	41	39.5	0.76 ^a
Davies[80]	2005	1.0	19	38.4	0.4
Tofts[81]	2006	1.6	10	37.3 ^b	0.6

^a SEM=0.17 pu; 4 samples each n=20 or 21; estimated SD=0.76 pu

^b peak location values in white matter histograms

A phantom with a realistically high value of MTR can be made from Bovine Serum Albumin[82] (agarose gel does not have enough bound protons)[2]. Azide should be added as a preservative.

In a multicentre study, by implementing the same pulse sequence at several different centres with different manufacturers, a common sequence (the ‘EuroMT sequence’) gave almost identical MTR values in normal white matter using transmit/receive head coils[83]. A more recent two-centre study of MTR histograms in

normal brain (using two different manufacturers) showed that by controlling the pulse sequence, B₁ factors (by using body coil excitation) and the image segmentation procedure, the between-centre variation could be completely eliminated[84].

If manufacturers move to providing more choice in setting the values of the pulse parameters in MTR sequences, then centres can harmonise their data collection procedures. The MT pulse shape, amplitude, offset frequency and repetition time all have to be controlled. With the flexibility to acquire image at several values of amplitude and offset frequency, a more quantitative MT acquisition procedure is possible, where the concentration of bound protons can be measured[85-87]. More details are given in the section on MT in the multi-author chapter on techniques.

5.7 Spectroscopy

¹H Magnetic resonance spectroscopy (¹H MRS) has proven useful in the grading and assessment of therapies in brain tumours[88]. It is also increasingly used in the guidance of radiotherapy treatments[89]. Sources of variation include the pulse sequence and the procedures for shimming, for setting B₁ over the volume of collection, and for water suppression (and the resulting efficiency of each process).

Normal values for absolute metabolite concentrations (e.g. NAA) are available[90], although often ‘institutional units’ are used, which contain systematic centre effects (such as T₂ dependence); metabolite ratios are often more reliable[91].

To establish a multi-centre trial it is essential to develop a number of QA procedures to include phantoms, measurement protocols and post-processing software. Several publications have detailed MRS phantom designs which all have a common design template[92]. This consists of a larger outer volume containing a smaller internal volume; the containers are normally manufactured using Perspex (acrylic or Plexiglas). The two volumes hold different chemical solutions to enable the discrimination of signal sources under different measurement conditions. MRS localized measurements are normally performed on these phantoms to establish the following; localization accuracy, efficiency of localization, degree of contamination, linearity and magnitude of artefacts (MRS line shape distortions). Additional measurements include assessments of water line-widths following B₀ optimisation (shimming) in various phantom positions and water suppression efficiency[93,94]. MRS measurement sequences used for these tests are available on all of the major vendor platforms. Typically MRS measurements are performed with the standard head coil using single voxel PRESS measurements with an echo time in the order of 30 ms; alternatively single voxel STEAM measurements with an echo time of 20 ms are used. Similar measurements can be performed using multi-voxel chemical shift imaging measurements although there are more variations in the vendor

implementation of these measurement techniques, which may make direct comparisons more difficult.

Having established a measurement QA protocol it is important to perform the QA measurements routinely and following any hardware or software upgrades. Following phantom measurements it is important to acquire sample volunteer MRS spectra to enable expert spectroscopists to evaluate the data before beginning the trial. It is common practice in multi-centre studies to establish a single centre for the evaluation of data; this is particularly true with MRS data as it is still a relatively new measurement technique. It is important to ensure that MRS data are evaluated shortly after data acquisition by appropriate personnel, using post-processing software which is common across all the participating sites.

Considerable multi-national efforts have been made to establish multi-centre trials of MRS for the evaluation and classification of brain tumours[95]. Results in normal tissue have been relatively disappointing for spectroscopy[96,97], although within centre variation can be good (about 4%) [91,98,99]

Currently there are differences in the vendors' post processing tools for MRS data; to establish common software platform for analysis at each site would require the installation of an accepted standard software package such as MRUI[100] or LCModel [101]. Currently there is an ongoing international development to establish automatic pattern recognition tools for classification brain MRS data[102]; future multi-centre trials may be able to both utilize and support this activity.

5.8 Tumour volume

There is an increasing interest in measuring tumour volume[103,104] (rather than just making a one-dimensional measurement, such RECIST[105,106]). Our (unpublished) results on FLAIR[107] images (5 mm 2D slices) of gliomas show that good accuracy can usually be obtained, and that reproducibility is limited by how well the outline of the tumour can be delineated.

Moving patients between different scanners is generally not practicable; however the precision of the tumour segmentation process can be studied by repeated analysis at the same or different sites. In an unpublished study by one of the authors (PT), clinical images could be analysed with a precision of $SD=3.8$ ml ($CV=3.4\%$). Some tumours had indistinct boundaries which limited precision. A simple phantom was made using a set of bottles of water doped to give realistic values of T_1 [2]. A variety of volumes was used, to cover the range of tumour volumes expected (typically 40-200 ml), and the volume of water was simply determined by weighing. By scanning in oblique planes (to give realistic partial volume effects[108]), and by adding noise to the images, a set of realistic images was produced, from which accuracy was estimated. Absolute volume (in ml) could be measured to within 3%; analysis precision was $SD=0.64$ ml ($CV=0.48\%$) and overall measurement precision was 1.4 ml (1.3%).

Much work has been published on measuring total lesion volume in multiple sclerosis[6,109,110]. By standardising the imaging parameters within a range of values, and by agreeing rules on the lesion segmentation process, then within centre variation was reduced to a level that is insignificant compared to the natural variation in the disease process.

In the future there will be more clarification of when volume measurements provide added clinical value over one-dimensional measurements, both in research and in clinical environments. As manufacturers provide better techniques for volume measurement, this balance may shift.

5.9 Cerebral Blood Flow (CBF) measured using Arterial Spin Labelling (ASL).

a) ASL is a quantitative technique for CBF measurement; however sources of variation are large. Numerous acquisition methods and analysis models exist, producing a large range of published CBF values. In order to produce quantitative CBF maps, the acquisition sequence needs to take into account corrections for large vessel flow, arrival time delays, and must also provide a measurement of the equilibrium magnetisation of arterial blood[111]. Various different approaches are provided for these three issues. Firstly, arrival time delays may be corrected by using a multi-inversion-time sequence and fitting for arrival time in the analysis model[112]. Alternatively, simply waiting for a longer delay time to allow labelled spins to fully enter the imaging region can reduce the sensitivity to arrival time[113]; the Q2TIPS technique further 'cuts-off' the tail end of the perfusing bolus to enhance this effect[114]. Large vessel contamination can be avoided by the addition of dipolar diffusion gradients to diphase the high flow signal in large vessels[115]; others simply increase the delay time to allow signal in large vessels to exit. Finally, the equilibrium magnetisation of arterial blood can be measured from the equilibrium tissue magnetisation (either whole brain[116], white matter[117], or from CSF[118]), and corrected for by an appropriate blood: tissue partition coefficient.

A range of analysis models also exist: single tissue and blood compartment models and two-compartment models[119]. The choice of a particular model will depend on the acquisition technique. For example if a short delay time between labelling and acquisition is chosen a single blood-compartment may be appropriate, whereas a longer delay time may need a two-compartment model as some of the labelled spins begin to cross the capillary wall[120].

At present there is little consensus concerning which of the different acquisition approaches and analysis models are superior. Each approach will undoubtedly give slightly different CBF values, and hence adoption of the same acquisition and analysis approach for multi-centre studies is important. This is complicated by the fact that scanners produced by different manufacturers may not have the equivalent ASL sequences available. It

may be that the best approach in terms of standardisation is to adopt a simple sequence such as FAIR, to match acquisition parameters and then use the same analysis model.

At present there are no realistic perfusion phantoms, whilst normal values show considerable natural within-subject variation (according to the physiological state of the subject)[121]. These two factors limit how well the between-centre performance can be measured.

The first large multi-centre study used centres with identical scanners. The study involved 199 participants in 22 centres using a Phillips 3 T system[122]. This showed reasonable reproducibility with a coefficient of variation of 13% between repeated scans.

In the future the provision of hardware, imaging sequences and analysis software by the manufacturers may converge, and a realistic phantom may become available.

5.10 CT perfusion.

Multi Detector CT (MDCT) systems are capable of performing contrast enhanced dynamic CT (d-CT)[123,124]. Establishing a multi-centre study using d-CT will require the usual definition of a standardized imaging protocol and contrast delivery which can be implemented across all vendor platforms with the added requirement of ensuring that the total radiation dose will not become unacceptable if the subject is scanned several times. Particular attention needs to be given to the reduction of skin dose and eye lens during d-CT[125,126]. This will require the support of an experienced medical physicist capable of making this determination on all of the scanners utilized in the trial. d-CT protocols normally image a few slices with high temporal resolution (1s) during the initial first pass of the contrast bolus (50-60s) and then acquire data at a lower temporal resolution (10-15s) for a further 2-3 minutes.

Quality assurance procedures will require the use of a multi-compartmental iodine phantom to establish the linearity of the Hounsfield number with iodine concentration for the resultant d-CT measurement parameters in addition to the routine vendor specific QA procedures. Quality assurance measurements should be made following all software and hardware changes in addition to the routine daily and weekly procedures.

All equipment vendors now provide post-processing software each utilizing different pharmacokinetic models for the analysis of d-CT data. However in several papers a lack of concordance in the results obtained from post-processing the same patient data with different software indicate that only one choice of post-processing software should be used, ideally in the single centre responsible for the evaluation of data for the trial[127]. Site specific patient data processing should be performed immediately after data acquisition using available software to ensure that studies are of sufficient quality for further evaluation.

Despite the widespread availability MDCT systems there appears to be no documented multi-centre study in

a neuro-oncological setting. There are however numerous examples of multi-centre CT studies in other radiological settings.

6. Discussion and conclusions

One of the first quantities that clinicians attempted to measure in an MRI multi-centre trial was the lesion load (i.e. total visible lesion volume) in multiple sclerosis. This was carried out by the MAGNIMS (MAGNetic resonance In Multiple Sclerosis) group, which was originally funded by the European Union [6,128,129]. The inter-centre effects were initially large; by bringing together experienced neurologists from several centres to report the same images at the same time in the same room, the sources of discrepancy were identified. An agreed set of rules for equivocal cases was agreed. The within-subject variation in lesion load is relatively large (it varies by 5-10% over time, as the disease produces relapse and remission), and so variations arising from between-centre and other effects are relatively unimportant provided they are less than this.

A second study[130]by the MAGNIMS group into the much more subtle parameter MTR showed that inter-centre variation could be enormous compared with the relatively subtle effects caused by disease. The major sources of variation were the pulse sequence and MT pulse shape and size, and these varied considerably between MRI manufacturers. Through detailed study of the sources of variation, a EuroMT pulse sequence was produced [131]with which the inter-centre variation could be reduced to relatively small amounts, of the order of 3 pu. The residual difference was attributed to B_1 error and nonuniformity. By correcting for B_1 variations the inter-site difference in mean MTR value was made insignificant [132]. A recent detailed analysis and refinement of a procedure for measuring brain MTR histograms resulted in a method which gave identical histograms at two different sites, even though the imagers came from different manufacturers, and this probably represents the ultimate example of how inter-centre differences can be eliminated. [133]

Thus in any attempt to minimise inter-centre differences, the initial effort should be focused on matching the sequence parameters and image analysis procedure as far as possible, and this will be reasonably successful. However it is likely that only by addressing B_1 effects, which vary from machine to machine (through RF coil design, pre-scan procedure, slice profile), can excellent multi-centre agreement be achieved. Achieving good multi-centre performance is the ultimate test of how good our quantitative techniques are. The early history of such attempts shows that inter-centre differences can often be large, and with hindsight it is now understood that without attention to the issues described in this paper, inter-centre effects are likely to be large enough to surprise many researchers.

In the future, we can expect multi-centre studies to become easier, as researchers and manufacturers become more aware of the issues involved in good quantification.

Table 5 Fifteen principles for multi-centre studies

initial design	
1	Measure <i>quantitative parameters</i> (such as T_1 , ADC or MTR value), rather than signal intensity
2	<i>Understand the instrumental factors</i> that will cause the measured values to vary (e.g. B_1 value, sequence timing, gradient strength).
3	Ideally use the <i>same MRI manufacturer</i>
4	Use the <i>same RF coil configuration</i> (ideally body-coil transmission, with receive-only head coil)
5	Use <i>sequences</i> and sequence parameters that are similar
6	Be aware that in <i>clinical trials</i> , centres are sometimes chosen by pharmaceutical companies either on the basis of collecting as many patients as possible for the trial, or on the basis of fostering relations with clinicians who will later on be in a position to prescribe the pharmaceutical under test. Thus a large number of centres may become involved, and the quality of the MRI data may become compromised by heterogeneity in the MRI centres. Selecting a subset of these, on the basis of MRI quality and homogeneity, may actually <i>increase</i> the power of the MRI study, as well as reducing the effort required to validate the centres and read their data.
initial evaluation of centres	
7	Validate by <i>measuring control subjects</i> , if appropriate, either individually at each centre, or by sending the same ones round to each centre. If the between-normal-subject variation is small, then different controls can be used at each centre, which is clearly convenient for an initial evaluation. If the normal variation is significant, then the same controls have to be sent round to each centre, which is logistically more complex and expensive. Ideally, at each institution, use the same radiographic (technical) staff.
8	Consider <i>imaging phantoms</i> (test objects), which can either be made up for each centre, or sent round to each centre. If simple and easily reproduced, such as simple geometric objects or liquids, they can be made at each centre, and provide an easy way to make an initial evaluation of the procedure. However be aware that phantoms are not always stable and realistic.
9	<i>Record</i> all relevant aspects of the data collection process, in particular those which are not automatically recorded in the image header file. (There is a case of the wrong Gd dose being given in a multi-centre study, which was only discovered by chance after the event, as there was no record in the header file).
10	In the <i>statistical analysis</i> required for validation, measure separately the effects of the same observer repeating the analysis, of different observers carrying out the analysis, the same scanner repeating data collection, and different scanners carrying out data collection.
11	If the <i>inter-observer effects</i> are large, consider sending all the data (as computer files) to one centre for analysis by a single observer (or a convergent set of observers at one site). Sending a single dataset around to the different observers may clarify the source of variation.
12	Be aware that <i>sending data between sites</i> requires expertise in reading image files (although the DICOM format is making this easier). The image headers should be read to ensure that the correct sequence parameters were used.
analysis phase	
13	<i>Standardise the creation of ROI's</i> , image segmentation, and all other aspects of the analysis. Create all ROI's for individual patient's serial trial data at one sitting[134].
14	Use <i>automatic recording</i> of the analysis procedure so that all aspects can be re-created.
15	Use <i>appropriate study design</i> and statistical analysis techniques so that small residual inter-centre effects can be accommodated without producing false positive results or reducing sensitivity.

The recent MTR histogram study indicates a successful outcome using this approach[135], although the MRI physics effort needed to achieve this was significant. Body coil excitation (used with multi-array receive coils) will give more uniform B_1 fields. At 3T and above, B_1 effects become important, and although fast B_1 measurement techniques are now available[136] to enable residual B_1 effects to be measured and corrected, 1.5T operation is likely to be more reliable. Increased demand from quantification-aware users will (hopefully) drive the manufacturers to improve their products (we can already see that provision of spectroscopy and DTI acquisition has become routine).

A summary of issues to be aware of when undertaking a multi-centre study is shown in table 5. Provided that between-centre variation has been controlled (e.g. to <5%) then the remaining variation can probably be dealt with by using appropriate study design and statistics. The power of the study is then usually limited by the within-subject instrumental variation (as determined by repeated scans).

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