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Review article

PROspectiVe imaging research DEsign and coNducT (PROVIDENT): Considerations for clinical trials and studies using imaging (Part II)

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ABSTRACT

Objectives: Imaging is used in a wide range of contexts in clinical research projects, but adds complexity to the design, conduct and analysis. This paper is the second of two in which we use a consensus approach to combine multidisciplinary perspectives on the challenges in conducting prospective clinical trials and other research studies involving imaging. Here we consider challenges in image interpretation and quantification, quality assurance and quality control (QA/QC); scanner imaging acquisition, data flow and storage, health economics (HE) decision modelling, costings for running a trial; and commercialisation.

Key findings: Availability of scanners and staff can impact deliverability. Pre-specification of key procedures, roles and responsibilities via appropriate documentation is important; ensuring compatibility across different sites and machines is challenging and requires advance input from multiple stakeholders. Testing critical procedures, including the flow of images and derived data between participating sites and/or external legal entities, can avoid delays. Effective QA/QC is conducted at regular intervals; relevant staff should be involved at the planning stage. Identifying appropriately qualified readers and arranging for image hosting takes time; this should be done prior to image acquisition. Testing image interpretation burden informs feasibility and costings. Cost estimates for research involving imaging and HE modelling of imaging interventions can be complex due to the interplay between local and national policies, and the extent to which the research imaging is integrated with standard care.

Conclusion: These considerations derived from a multidisciplinary team will be useful for funding applications, protocol design, trial implementation, conduct and commercialisation and uptake of new imaging techniques.

Implications for practice: Many prospective imaging studies could be improved by the upfront awareness of potential challenges and understanding of real-world examples these considerations provide.

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Introduction

There are specific challenges associated with the design, conduct and analysis of prospective clinical research studies that incorporate imaging as an integral component.[1,2] In the first part of this article, PROVIDENT Part I,[3] we presented the background and methodology of a consensus project aiming to bring together multidisciplinary perspectives to identify and provide considerations for addressing these challenges; we also summarised recommendations on five identified domains following our consensus meetings. Here we continue with the considerations on seven further domains. Four are key to generating robust image-derived data for the study: imaging acquisition and processing; quality assurance/quality control (QA/QC); image interpretation and quantification; and data flow and storage. The last three domains focus on the economic issues: health economic decision models within a prospective clinical trial; costing a trial; and commercialisation. We present these domains structured under the key subdomains identified in the consensus workshops (Table 2) and provide real-world examples that illustrate potential pitfalls or highlight best practice. As in part I, throughout we have used 'trial' and 'study' interchangeably.

Domains and considerations

Table 1 shows how the 12 domains are split between PROVIDENT Parts I & II; Table 2 summarises all 12 domains.

Imaging acquisition and processing

The accessibility of and sources of variability in image acquisition need consideration during study design, including multicentre, multi-vendor, and multi-operator differences.[4–6] We highlight some of these below.

Availability of scanners and staff

Availability of scanners and staff responsible for acquiring, processing and/or interpreting images for research needs consideration at study design, particularly where imaging research capacity may be limited to particular time slots or expert centres.[7,8] Scientific integrity should be balanced against Ionising Radiation (Medical Exposure) Regulations (IR(ME)R)[9] considerations e.g., consider wide screening windows for baseline scans, and where possible use standard of care scans as baseline measurements. Mapping of the participant pathway from recruitment or referring centres is essential to ensure continuity of clinical patient care pathways and to reduce barriers to participation caused by research imaging logistics.[10] To future-proof a study, consider the potential impact of software updates or changes of hardware. Reproducibility across software updates, calibrations and scanners should be documented.

Table 1
Split of domains between PROVIDENT Parts I & II.

Part I	Part II
Ethics, participant information & consent	Imaging acquisition and processing
Recruitment	QA/QC
Trial and site set-up	Image interpretation and quantification
Training	Data flow & storage
Trial or study conduct	HE decision model within prospective clinical trial
	Commercialisation

Abbreviation: HE, Health economic; QA/QC, Quality assurance/quality control.

Scanner calibration, imaging protocols and manuals

The variation in make, model and age of scanners used should be minimised, if possible, where appropriate to the research question. Scanner calibration and consistency with acquisition protocols (e.g. same sequences and participant position in scanner) are important in reducing variation; however, where research aims to use imaging in the context of real-world practice, more flexibility in acquisition protocols may be appropriate.

Imaging protocol development requires input from physicists, radiographers, and radiologists/clinicians to ensure the validity, reproducibility, and feasibility of the research. To ensure quality, adherence to protocol and completeness of imaging data, trial-specific quality assurance and quality control (QA/QC) processes at participating centres are important (see section 'QA/QC').

Imaging manuals or protocols are important to define:

- Image storage formats (e.g. Digital Imaging and Communications in Medicine (DICOM)[11] and Neuroimaging Informatics Technology Initiative (NIfTI)[12]), and data organisation/naming conventions (e.g. Brain Imaging Data Structure (BIDS)[13]);
- image and image-derived data flow, and instructions for using image hosting platforms (note that image and data flow for all centres will need to be tested; see 'Data flow & storage');
- interpretation workflow, including use of scoring manuals and scoring/analysis software; and
- the methods via which image-based data will be derived.

The need to pre-specify the imaging acquisition protocol in a prospective clinical study depends on the purpose of the imaging within the study, e.g. imaging for routine clinical management versus research, developing novel imaging interventions or quantitative biomarkers, assessing technical improvements of imaging processes, or integrating image-derived artificial intelligence (AI) algorithms into clinical pathways.[14,15]

If the research imaging incurs additional radiation exposure, the study lead must determine the dose constraints and communicate these to the ethics board and approving authority at the submission stage. Doses incurred during the trial must then be monitored to ensure these limits are not exceeded; documentation should describe roles, responsibilities and procedures for this process.[9,16,17]

Procedures for de-identifying images

Image de-identification can be complex; in some cases, the images themselves may be identifiable e.g. images of the head require details of the face and ears to be removed.[18] De-identification procedures need to be regulated across study centres.[19,20] Image metadata can include identifying information or conversely may include important clinical information; the extent to which these are present prior to, or are removed during, de-identification can vary between centres which can risk confidentiality breaches or data loss.[21] Everyone handling images and derived data should be made aware of the difference between anonymisation and pseudonymisation (i.e. the latter allows

Table 2
Domains, subdomains and items to consider for design and conduct of prospective imaging trials.

PROVIDENT PART I	
Subdomain	**Items to consider**
Ethics, participant information & consent	
Ethics	Explaining the purpose, risks and uncertainties of imaging; communicating potential future out-of-scope use of images or data; careful wording in participant-facing documents around diagnoses; potential for imaging eligibility and processes to affect fairness & representativeness.
Participant information	Provision of adequate information regarding imaging to participants, including: Sufficient detail around what will happen during imaging visits; why the imaging is being performed; the potential risks; the potential benefits; what will happen to images and derived data.
Consent	Transparency around levels of de-identification and image/data storage locations; consent to archive/share images and data; processes and responsibilities regarding withdrawal of consent for storage of images and derived data; consent for future use, follow-up, AI applications, commercial access.
Recruitment	
Communication between clinicalt eams	Recruitment can be challenging as participant contact and trial processes can be split between clinical and imaging teams; effective communication and co-ordination is key, particularly with local radiology departments to ensure efficient scheduling.
Reducing barriers for participants	PPI involvement is essential to help anticipate and understand patient needs. Measures to improve accessibility and attractiveness of research include: Providing adequate information; reducing clinic visits, limiting scan durations, offering flexible scanning schedules, remuneration, consideration of mobility issues, caring responsibilities and work commitments, continuity of care.
Trial and site set-up	
Site selection and accreditation	Run feasibility site surveys to understand local settings; establish what imaging equipment they have and their capabilities, and how they will be able to implement trial procedures. How to ascertain whether sites meet a certain threshold of knowledge.
Establishing the right team	Identify key imaging personnel for your study and document in a delegation log, defining responsible personnel for each element.
Site initiation	Engage site imaging personnel involved and summarise key trial documents, including imaging manual and data flow. In addition to QA/QC processes to set-up/approve a site, test locally all stages of acquisition, processing and transferring of images and imaging data.
Training	
Clinical staff	Any specialist training for the clinical staff is required e.g., annual MR safety training and MR knowledge to answer patient questions.
Imaging technology	Training re imaging technology (e.g. how to acquire new scanning sequences). Consider training encompassing different responsibilities of the site team.
Safety	Research team members may require imaging-modality-specific safety training, both for their own safety and participants'' safety.
Image interpretation	Training required for scoring, analysing or reporting of images for the trial and whether standard/certified training is available or an ad-hoc training for the trial needs to be devised.
Data capture	Training on (electronic) data capture systems or CRFs that capture imaging data (e.g. clear guidance to readers/scorers on how to complete scoring sheets, conventions (i.e. 0 if none, avoid blank data fields).
Readers	How to train/qualify new readers during study i.e. whether baseline treatment is enough or whether training should be targeted to achieve good agreement with ongoing readers, and consider inter-reader reliability.
Trial or study conduct	
Engagement	Establish clear responsibilities for trial imaging components, linked to specific team members. Ensure communication in advance any changes to imaging and data acquisition to key team members, including statisticians.
Monitoring processes	Anticipate problems early by site visits and monitoring of imaging protocol compliance. Build into protocol and establish ongoing real-time transfer of scans into imaging repository during recruitment. Consider plan to ensure timeliness of trial reporting, if the trial radiologists are not available.
Monitoring data	Imaging data should be subject to the same level of scrutiny as clinical data. Off-protocol imaging and its impact on patient management. Compatibility with existing data when changes to scanning and imaging acquisition processes are made.
Safety	Which adverse events are to be deemed relevant to the trial; whether adverse event rates can be affected by participant information about possible diagnoses; procedures to allow images and/or derived data for specific participants to be released to and reviewed by the clinical team early, either due to incidental findings or participant emergency care needs.
PROVIDENT PART II	
Subdomain	**Items to consider**
Imaging acquisition & processing	
Availability of scanners and staff	Whether there is sufficient site capacity to accommodate additional research scans. The potential for decommissioning of specific equipment, technology or software; the need to document reproducibility with each change or update.
Scanner calibration, imaging protocols and manuals	Sources of variability that could impact the variability of acquired images, between or within study participants; the need to standardise image flow process across all sites; the degree to which imaging acquisition protocol should be prespecified.
Procedures for de-identifying images	Standards and procedures may differ across centres; different sites may treat metadata differently and leave behind identifiers or strip out important clinical information; difference between anonymisation and pseudonymisation; testing processes in advance avoids delays and risks to confidentiality; principal investigator oversight is key to ensuring these procedures are adequately resourced.

(*continued on next page*)

Table 2 (*continued*)

PROVIDENT PART I	
Subdomain	**Items to consider**
QA/QC	
QA/QC program	Consider if a QA program should be in place throughout the study and how often image QC checks should be performed and reviewed centrally. At each site, consider QA checks to identify potential artifacts and the requirements for within-site consistency checks. Define a site accreditation process required for sites to start imaging into the study.
Image interpretation and quantification	
Burden	Whether planned scoring/analysis can be completed within trial timelines, including assessment of inter- and/or intra-reader reliability; even automated methods will incur a time burden.
Personnel	Inclusion criteria for image readers; whether trial-specific training is needed; procedures for introducing new readers due to staff turnover.
Interpretation methods and procedures	The number of readers, rules around reliability; adjudication procedures; the number and ordering of reads; subjective elements of quantitative analysis; how final scores will be determined if multiple readers are planned; budget and contracts for scoring/analysis and hosting of scoring platforms.
Responsibility for quality control of images during trial	Who will determine image quality, and which criteria will be used; who specifies rules around participant recall if image quality is poor and has responsibility for recall.
Data flow & storage	
Data flow	Using flow diagrams to illustrate the transfer of images and derived data between departments, institutions, sites and external contractors; need for procedures, protocols, permissions and/or contracts, data protection impact assessments; testing the flow processes in advance; transferring in regular batches rather than at the end of the trial; early engagement with information security teams within clinical and non-clinical institutions.
Data storage	Ensuring adequate capacity, budget, access, security and archiving arrangements for storage of images and derived (meta)data; effective user acceptance testing of electronic or paper case report forms capturing imaging data; compatibility between standard care imaging forms and research protocol; compatibility between clinical and imaging forms and databases; maintenance of blinding of readers and/or clinical staff to imaging data; validation of imaging data to same high standard as clinical data.
HE decision model within prospective clinical trial	
Model costings	Establish focus of commissioner of decision model costing requirements (e.g. national or local costing). Decide cost model for standard imaging i.e. nation-wide or local costing. Identify costs for imaging not part of standard of care, including any costs for roll-out of new infrastructure and scanners for imaging. Opportunity costs for reconfiguring patient care pathways.
Model outcomes and comparisons	Consider most appropriate HE model outcomes to meet HE claims (e.g. time to diagnosis, number of tests, diagnostic accuracy etc.). Consider variation in standard of care pathways between sites, where imaging is compared to standard of care.
Costings for running a trial	
Standard costings	Costing informed by nationally-agreed reference standard costs for standard imaging.
Costs for trial delivery	Costs additional to standard care required to enable trial delivery including: New imaging scanners, sequences and methods; staff and staff training; image acquisition and processing; image interpretation and quantification; and data flow.
Commercialisation	
Access to scanners	Commercial needs including: Access to clinical care scanners; manufacturer permissions to install new commercial imaging sequence methods on imaging hardware.
Access to participant images	Commercial use conditions including: Legal agreements, permissions and conditions; image de-identification.
Regulatory needs	Regulatory pathway of new technology and intended markets (e.g. UK, EU, USA) needs to be planned in advance to ensure study design is suitable for regulatory purposes. Commercial establishment of: any potential differences between international regulators in requirements for validation of imaging biomarkers; best strategy for comparison to current practice where standard of care varies; extending use by reproducibility studies across different sites/scanners/software; post market surveillance requirements.
Clinical guideline inclusion	Company needs include: Up-front clarification of HTA approval requirements to plan evidence acquisition; plan for wider clinical utility of imaging to expand longevity; communication on statistical outcomes to avoid misperception that non-inferiority results are without benefit.
Market positioning, Innovation opportunities	Impact of local health systems including: Separate decision making creating small market place, except for e.g. National screening programmes; different processes to integrate new imaging systems to hospital PAC and electronic patient record systems.
Pathways to NHS adoption	Adoption requires consideration of barriers to clinical uptake including: Mixture of manufacturers and age of equipment within each hospital; cost of set up of new imaging and software into hospitals; difficulties to persuade staff to use novel imaging unless in clinical guidelines, due to workload pressure stifling time for innovation; lack of nationwide platform for sharing images; difficulty of reconfiguring clinical pathways and care.

linkage to a specific participant via a code), as they differ with respect to data security requirements and regulations.[22] Testing de-identification and image transfer procedures prior to the study opening is best practice to avoid delays and breaches of confidentiality. Principal investigator oversight is key to ensuring there are adequate resources for such image processing procedures, including required staffing, time, and costs, as these can often be overlooked. Example A presents some examples of issues relating to this domain.

Example A: Real-world challenges in imaging acquisition & processing, image interpretation and quantification, data flow & storage

For this example, we consider a multicentre trial of a new pharmacological treatment for inflammatory arthritis where inflammation and damage in several different joints were measured using validated semi-quantitative scoring systems to assess features visible on ultrasound, MRI and radiographs. These imaging-derived scores formed secondary trial outcomes. (This example is a synthesis of real-world issues arising from different trials with this design that the authors have worked on.)

For examples relating to QA/QC, trial and site set-up & training please refer to Example B.

Imaging acquisition & processing

The trial included novel whole-body MRI imaging. No validated whole-body scoring system was available at the time the protocol was written. Sequences collected in some joints proved to be incompatible with the scoring system that was eventually chosen.

MRI image quality, only assessed at the end of the trial, was inadequate for some body regions due to poor positioning.

The MRI scanner was decommissioned partway through the trial; MRI-derived outcomes had to be downgraded from secondary to exploratory, only collected in a subgroup of participants.

Here, defining the scoring system in advance and assessing image quality in a pilot stage, with additional QA/QC during follow-up would have avoided missing data. The team might have made continuity arrangements if the possibility of decommissioning during the lifetime of the trial had been considered in advance.

Image interpretation and quantification

As no established whole-body scoring system was available, towards the end of the trial, following discussion with expert scorers, the protocol was amended to include several different scoring systems covering distinct body regions. However, the complexity of the scoring required hosting the images on a dedicated scoring platform; arranging Sponsor approval and contracts caused delays. The planned scoring could not be completed in time to meet key trial milestones; as a result, the team had to settle for single-reader rather than consensus scoring. Furthermore, scoring could only be completed following the breaking of the trial blind (although the scorers remained blinded); this required additional approval from the trial Sponsor. In this instance, agreeing the scoring system in advance, obtaining realistic estimates of how long the images would take to score, and identifying a host platform and scoring team in advance would have improved data quality and saved time overall.

Data flow & storage

The radiographs were not requested from centres for central scoring until after the end of the trial. Unfortunately, some centres had already disposed of them. Using a flow diagram to identify routes via which images and associated data were to return to the coordinating centre, testing these in advance, and ensuring they were retrieved regularly during follow-up could have avoided this issue.

An ad-hoc spreadsheet was used to collect radiograph-derived scores for joints in the hands and feet. However, the study statistician was not given the opportunity to test the spreadsheet before it was populated. The field layout chosen was impossible to import into analysis software. A formal user acceptability testing process, involving all key personnel involved in entering, validating, processing and analysing the data, would have avoided this issue.

QA/QC

Within imaging research, most errors and sources of variability occur during scan acquisition, as there is often substantial variability between sites and scanners. Standard of care imaging does not always translate into the best imaging quality for research purposes; for instance, when investigating novel quantitative imaging biomarkers, sites may be required to adopt a study-specific research imaging protocol.[23–25] In multi-centre imaging studies, consideration should be given to including both local and central QA/QC processes to reduce variability. For all studies involving imaging, it can be helpful to consider if a QA program needs to be in place throughout, with regular image QC checks performed and reviewed, centrally in the case of multi-centre studies.[26–28] At each site, this could include QA checks to identify potential artifacts, and within-site consistency checks (i.e., use of phantoms/healthy volunteers/patient imaging). It can be difficult to implement QC retrospectively, so it is best to engage with QC staff during protocol development. For a benefit-risk approach, an integrated QC component within the data pipeline is more risk averse than a stand-alone approach. Automation could help facilitate this (e.g. an Extensible Neuroimaging Archive Toolkit (XNAT)[29] container for checking the acquisition protocol).

Example B shows how one trial conducted centralised QC of magnetic resonance imaging (MRI) and ultrasound images.

Example B: Real-world challenges in QA/QC

For this example, we consider METRIC, a multi-centre prospective cohort diagnostic accuracy study comparing magnetic resonance enterography (MRE) with ultrasonography (US) in newly diagnosed and relapsing Crohn's disease patients (ISRCTN 03982913).[41,42] Trial outcomes included diagnostic accuracy metrics, interobserver variation and diagnostic impact. MRE and US were performed by two blinded independent radiologists.

QA/QC

QA/QC oversight was considered and described, both overall and for each recruiting centre, by exploring the trial dataset or performing site visits as described in the METRIC Quality Management and Monitoring Plan (QMMP). The frequency, type and intensity of routine and triggered on-site monitoring were detailed in the QMMP, alongside procedures for review and sign-off of monitoring reports. For image acquisition, compliance with the minimal protocol data set was confirmed, but formal QA was not undertaken given that all sites were experienced in both MRE and US techniques.

MRE and US images from all sites were sent to the coordinating site to be securely uploaded and stored. For QC of MRE imaging, a quality score assessed technical quality of MRI sequences, including presence of any artefacts and their impact on imaging interpretation, and anatomical coverage to report whether all of both small bowel and colon were optimally imaged on all sequences. The radiologist performing US provided a cine clip (or static image if cine clip not possible) of the ileo caecal valve as a marker of technical adequacy of the examination which was reviewed centrally at the coordinating site.

Image interpretation and quantification

Decisions on image interpretation made at the design stage have implications for study feasibility, analysis and results.

Burden

Consideration should be given in advance to how long each imaging analysis will take.[15,25] For example, where primary or key study endpoints require one or more readers to review and score images, it is essential to ensure it will be feasible to score all the images within key study milestones such as data lock prior to unblinding. Consider that inter- and intra-reader reliability assessments, where required, will also affect burden. Even semi- or fully-automated analyses will have some associated time burden.

Personnel

Inclusion criteria for image readers, scorers and analysts should be considered, as should the potential need for additional study-specific training, particularly where interpretation methods differ from usual care (see Training). There may be staff turnover within the study, so the procedures for qualifying new staff as readers should be set out in advance.[15] Consideration should also be given to monitor the readers' performance to address any variation in performance over time.[15,30,31] This can involve mixing test images with trial images to assess proficiency and consistency; readers who fail to maintain consistency may need to be retrained and requalified, or replaced. If test images are sourced from trial images, methods should ensure that the first reading is considered final for analysis, and that sufficient time has elapsed between the test-retest reads.[15]

Interpretation methods and procedures

Many types of data can be derived from images. Some of these require human and/or machine interpretation, including measures based on scoring of visible disease features, adverse events, and other aspects. Interpretation methods, the number of readers, rules around reliability, adjudication procedures, number and ordering of reads can all impact results and should be pre-specified.[15,32] Even quantitative analysis may require human participation (e.g. to delineate a region of interest) which can introduce a source of error. Where multiple readers are planned, define how final scores are to be derived.[15] Adequate funds and contracts for scoring/analysis and hosting of scoring platforms need to be arranged in advance. Artificial intelligence approaches can introduce complexity, requiring additional resources and multidisciplinary input during set-up.

Responsibility for quality control of images during study

Trialists need to assign responsibility for determining the quality of images and identifying which criteria will be used (see QA/QC). Rules and responsibilities regarding participant recall in the event of poor image quality need to be defined[15]; recall procedures should be included in the participant information sheet (PIS).

Example A illustrates some real-world consequences of not sufficiently outlining imaging scoring procedures in advance.

Data flow & storage

Data flow

Capturing, cataloguing, storing, retrieving, de-identifying, hosting and interpreting/scoring images, and transferring image-derived data back to the research team, can be complex processes involving a wide range of internal staff members and/or external collaborators. Establishing early on how data sources will move, or how access permissions will differ, between different individuals, teams and institutions can improve efficiency.

Data flow diagrams (DFDs) illustrate these processes and can highlight points in the pathway(s) where custodianship, levels of security/de-identification and/or access permissions change[4]; see Fig. 1 for example. It is important to separate the flow of primary images from image-derived data, to distinguish direct electronic data entry from capture on paper, and to include processing stages. Indicating required retention periods for both source and data is helpful.

DFDs can help identify potential bottlenecks and areas where additional standard operating procedures, protocols, permissions, data sharing agreements and/or contracts are needed; developing them in tandem with the study protocol allows teams to highlight areas of concern. The sponsor institution's governance policy may require a data protection impact assessment (DPIA) covering cybersecurity and data transfer, and identifying data controllers and processors, which can take time to be approved; the DFD(s) can provide helpful summaries. Coordinating permissions and agreeing processes for data transfer between clinical and non-

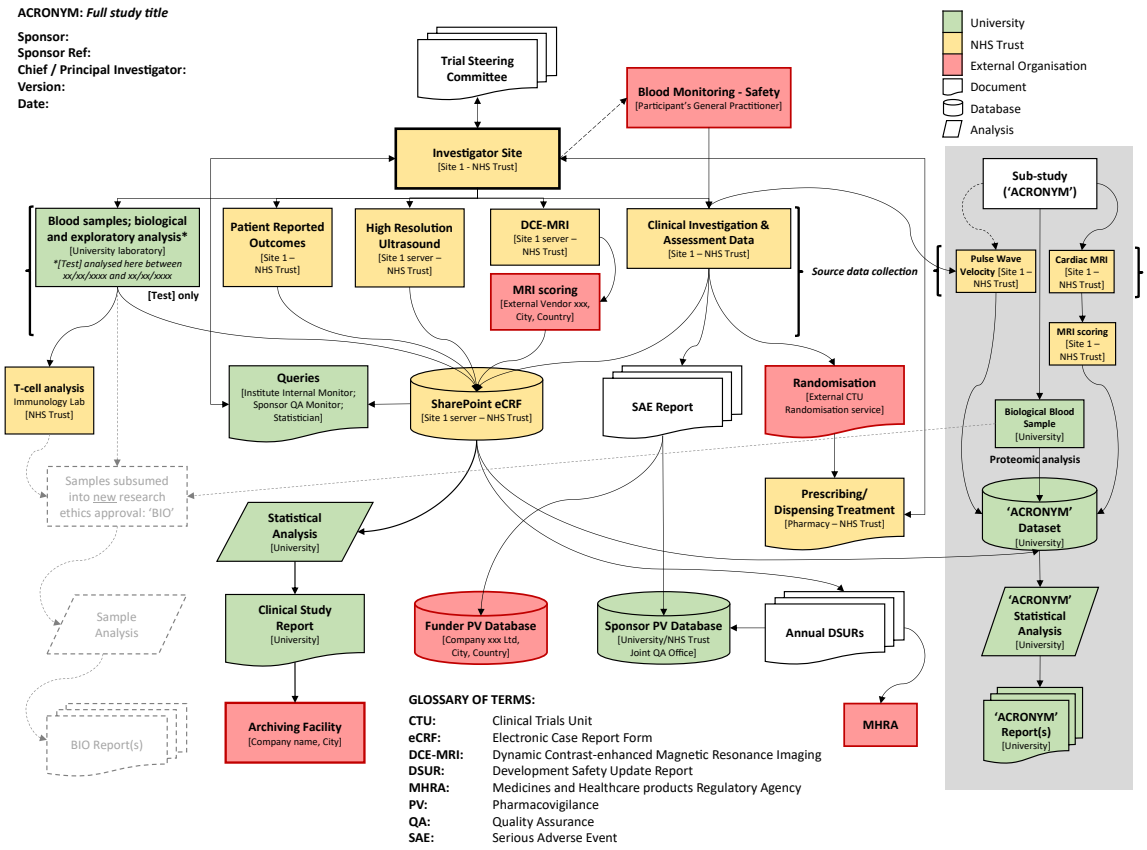

Figure 1. Data flow & storage diagram. This diagram depicts the data flow and storage in an imaging trial that collected MRI-derived data as a secondary outcome of the main trial, and included an imaging sub-study (right panel), plus optional biological sample collection (dotted lines). This was a academic-sponsored trial, with data collection in the NHS and involvement of external organisations in some trial processes; colour coding helps identify movements of data, images and/or samples between institutions. Due to an equipment issue in the Trust pathology laboratory, one blood test was analysed at a university laboratory during a discrete time period; the flow diagram was updated during the trial to indicate this (top left).

clinical institutions can be complex and time-consuming, so effective, early communication is key.

Best practice includes testing all processes around image capture, processing and data transfer before the study starts and auditing them during the study. Availability and compatibility of hardware, software and other infrastructure involved in the processing and/or transfer of images and data, and the capacity of the relevant teams are also key considerations.

Arranging for regular transfer of batches of images during the trial or study rather than waiting until the end to retrieve images from sites and/or machines supports regular QA/QC and presents less risk to data integrity.[15]

Data storage

Images

It is helpful to establish in advance where images will be stored, both at the point of collection and centrally (if relevant), and to understand access issues such as who will need access to them, and when, how this will be overseen & documented, who can grant access, should there be back-ups in case of illness or staff turnover.

Storage capacity, both physical and electronic, is an important consideration, as is funding to cover image handling, storage and hosting. It is best to highlight retention periods to relevant staff and storage providers, bearing in mind images may need to be archived as source data.

It is important to consider the level of security and de-identification required at each stage between image capture, processing/scoring and data storage. A repository platform such as XNAT may be helpful; methodology could potentially be adapted from sample management, such as image transfer forms for tracking.

Case report forms (CRFs)

Ensuring imaging CRFs, particularly participant and visit identifiers, and field headings, are compatible with clinical CRFs, supports effective data linkage.

If the study will use standard image scoring or measurement proformas, the contents should be compatible with the study protocol; if the standard forms collect more data than required for the research project, the protocol or imaging manual should specify which parts of the form constitute study data.

Leaving fields blank for anatomical sites without abnormalities does not allow missing data to be identified and can result in blank scoring sheets. If multiple areas are being scored, a prefacing question could ask whether there were any abnormalities; if there were none, the rest of the sheet can then be left blank, otherwise it is best to complete all fields.

Some staff may need to remain blind to imaging data during a study. This may require arranging timely, independent source data

verification of imaging data to ensure any issues can be resolved contemporaneously rather than risking delays and data quality problems at the end.

Image scoring forms contain source data to be retained and returned to the central site where relevant. Difficulties can be avoided if early consideration is given to how results will be extracted from CRFs and who will be responsible for data entry. An electronic (e) CRF may be preferable but may potentially introduce different logistical difficulties if images are being scored in different clinical sites, or other centres. An audit trail is important, including who entered the data, who made changes, when and why. Ad hoc spreadsheets are unlikely to offer sufficient capabilities in this regard.

Imaging data

Image-derived data is often stored in separate databases from clinical data; these may receive less user acceptance testing and data validation as a result. We would recommend considering how to store image-derived data with(in) the main study dataset.

If image-derived data are to be entered directly into an eCRF and scorers should remain blind to other study data, then their access will need to be limited to specific forms.

It is helpful if metadata, such as image quality assessments and reasons for missing data, are collected and stored with the rest of the imaging data in a suitable format, avoiding free text where possible.

If images are collected on different dates to clinical data for a given study 'visit', it is important that the database allows them to be matched up effectively.

Designing the electronic data capture system from the point of view of all users, not just the person analysing the data, can ensure it effectively supports key imaging processes. Image readers and other researchers may need to store and access information (e.g. regions of interest, other imaging metadata) which is of less relevance for analysis.

Examples A & C present real-world examples relating to this domain.

Example C: Real-world challenges in data flow & storage, image interpretation logistics, HE decision model costing and costings for running trial

STREAMLINE Lung investigated the use of Whole Body MRI (WB-MRI) to identify whether lung cancers had spread (staging for metastasis) beyond the initial tumour site, to enable better and more timely cancer treatment (ISRCTN 50436483).[43,44]

The trial compared the diagnostic staging pathways of WB-MRI (and any additional tests required to make a treatment decision) to the standard NICE guideline pathway (computed tomography plus any additional tests required), with trial outcomes including diagnostic accuracy, time to diagnosis, number of tests, cost of testing and patient experience of different pathways.

Data flow & storage and image interpretation logistics

To ensure integrity of the comparison of test accuracy between WB-MRI images and conventional imaging tests, separate radiologists completed each imaging pathway interpretation blinded to imaging data from the other pathway. Additional measures to ensure blinded image interpretation included WB-MRI images being uploaded directly into a commercial image review platform (Biotronics 3D) for interpretation, identified only by trial study numbers (pseudo-anonymised). A PC based internet gateway from each imaging site enabled automatic transfer of WB-MRI scan data and radiologist report back to the hospital Picture Archive and Communication System for ongoing patient care, at the appropriate time after trial multi-disciplinary team meetings had been completed. Using this Biotronics platform enabled anonymised image interpretation for multi-reader agreement studies.

HE decision model within prospective clinical trial: costing, comparisons

In STREAMLINE WB-MRI was considered as a pathway compared to the standard-of-care pathway consisting of a collection of tests differing at NHS hospital sites and by patient. As the trial was commissioned with a national NHS perspective, and the test comparisons were to NICE guidelines, the variation in standard of care costs was not a major issue and costings were based on standard of care tests used during the trial. Trial outcomes included diagnostic accuracy and in addition time to diagnosis and reduction of tests when WB-MRI replaces a combination of tests.

Costings for running a trial

Although WB-MRI was not used in the NHS for standard of care, because results from the WB-MRI were revealed in the study to clinicians and participants, NIHR grant funding staff required the trial to cost the imaging as treatment costs and reclaim the extra money to acquire and interpret imaging for each participant at each hospital. This was a significant barrier to the trial recruitment and running.

Table 3
Additional costings for running a prospective imaging trial.

Costing an imaging trial requires trialists to carefully think through additional costs to enable trial delivery such as:
New imaging scanners, sequences and methods sufficient for trial delivery
Training staff for image acquisition and interpretation included
Additional expertise of staff required to acquire, analyse and interpret imaging
De-identification, imaging storage and access for image interpretation included
Variations in imaging costs differ between sites
Imaging interpretation and access to specialist radiology interpretation or for out-sourcing of radiologist interpretation to companies
Companies providing mobile scanners to NHS services
Hosting for image scoring
Post-trial archiving requirements

Health economic decision model within prospective clinical trial

Costing within health economic (HE) decision models requires a clear focus on who has commissioned the model and their perspective on costs, which may have either a national, regional or local hospital focus.

Dependent on the commissioning focus, the costs may need to be estimated for imaging additional to standard of care, and may include the costs of roll-out of new infrastructure and scanners with additional staffing costs. Sometimes the opportunity cost of imaging that changes a patient pathway is considered, which requires extensive clinical input to understand how imaging fits with facilities and job roles in routine care.

Where the impact of diagnostic imaging as an intervention is the focus of the HE model, then consideration of a range of HE outcomes may be required depending on what aspect of the imaging intervention is considered important. Although in some trials diagnostic accuracy is relevant, in other imaging trials the key benefits of the imaging might come from reducing time to diagnosis, reducing invasiveness of alternative tests, reducing the number of tests or saving scarce resource such as radiologist interpretation time or fewer patient clinic visits.

For commercial trials, collecting evidence directly for the claim for a diagnostic imaging test is critical to Health Technology Assessment (HTA) approval. Ongoing research has investigated the range of outcome claims and evidence in a series of HTA organizations.[33] HTA methods guidance for HE modelling of outcomes for diagnostic imaging is sparse as this is an underdeveloped area of research.[34]

Where an imaging intervention aims to replace, triage or be an add-on to current patient pathways, it is important to evaluate the imaging pathway in comparison to standard care. Differences in standard care between hospitals can make this difficult to model and difficult to generalize the value of comparisons to commissioners.

Example C presents a real-world example.

Costings for running a trial

Costings for imaging trials and studies need to start with an understanding of how the research imaging methods and costs will be different from current standard of care.[35] National standards for costs, which can form the basis for reference costings, may not reflect local hospital costs.

Imaging trials using new imaging methods or incurring additional imaging costs have no nationally-agreed costings and will need justification. A particularly challenging area in imaging studies is that funders can classify imaging costs as treatment costs, instead of research costs covered by the trial. This is a major barrier to imaging research when imaging costs require cost reclaims at each hospital.[2]

Table 3 lists some additional costs that are often overlooked when planning an imaging trial. Example C presents an example of a trial in which unexpected costs affected recruitment.

Commercialisation

Understanding challenges for commercial partners can facilitate and enable imaging studies (Table 2).

For commercial research evaluation studies, such as those using imaging within intervention studies or discovery trials of new imaging technology, companies acquiring prospective images need to be aware of potentially long timelines for clinical trial ethical approval, agreements, set-up and trial recruitment.

Access to clinical care scanners for commercial studies requires planning including legal agreements and permissions especially where scanners are primarily for clinical care and where there may be no access outside of office hours. When new third-party software is required on scanning equipment upfront timely planning is required. For studies that use routine care systems for image sharing, anonymisation and de-anonymisation, the lack of a unified NHS image system may require different imaging access at each centre.

For commercial studies evaluating new imaging technologies requiring regulatory approval for implementation in clinical practice, there are difficulties in defining and generating sufficient evidence for regulatory or HTA approval, and multiple organisations (e.g. local and national policies, different regulatory jurisdictions) can have different evidence needs. Clarification of evidence requirements at the outset is critical to planning evaluation imaging studies, to avoid delay given the associated costs and short product life cycles of imaging technology.

A clear understanding of the role and position of the imaging technology in clinical care pathways is essential to understand the design of imaging comparison, including target condition (disease), participant characteristics, prior tests and standard-of-care comparison arms. Different regional hospitals can have different standard-of-care clinical pathways for both diagnosis and therapeutic management of patients. Proving that an imaging technology will improve patient care usually involves evaluation compared to the standard pathway, paying attention to any current or upcoming clinical guideline recommendations and consultation with key opinion leaders to ensure generalisability. Evaluation of new imaging is most straightforward in comparison to current imaging methods rather than comparison to non-imaging pathways, as clinical studies that require re-configuration of standard clinical pathways within hospitals are hard to achieve.

For a novel diagnostic imaging method, HTA approval committees may require several different performance claims relating to clinical utility prior to approval for routine use and inclusion into clinical guidelines. Evidence of performance may include diagnostic accuracy, cost-effectiveness and in addition evaluation of claims for less invasive processes for patients ease of use, health service IT integration and impact on services and staffing; these claims may need multiple studies with different designs. Cost-effectiveness for drug interventions typically do not include diagnostic costs, whereas resulting treatment costs are required in diagnostic imaging applications. The biggest challenges to commercialization include the short life-span of imaging products and their necessary integration with other healthcare systems including software (e.g. PACS) and hardware (imaging scanners) where the systems are not standardized across the country.

Enabling use of new imaging technology usually requires already busy clinicians to learn a new method or way of working, and then to integrate it into their practice. Including additional benefits for users in the imaging technology, such as time saving benefits via linking to clinical reporting is critical to uptake if a new imaging technology is not specified in clinical guidelines.

Discussion

In this two-part article, we have drawn on a multidisciplinary team to identify challenges in the design and conduct of prospective imaging studies. Imaging requires specific technical acquisition, quality assurance, processing, data derivation and data entry processes, elements which are often conducted by different team members and/or may be performed by independent contractors, separate from the team tasked with clinical data collection. As a result, imaging procedures can sometimes receive less

attention and oversight from those managing the trial, allowing problems to arise which cannot be rectified if identified too late.

Understandably, given the pace at which new imaging technologies are emerging and the financial pressures facing healthcare and academia, research teams need to move fast when designing and setting up new studies. However, due to the inherent complexity of delivering imaging-based research, '*less* haste, *more* speed' is the appropriate motto to adopt. Giving careful consideration in advance to how images and derived data will be collated, transferred and stored, predetermining and testing procedures for ensuring compatibility across centres, and making arrangements for regular quality checking are all important for study success. Including imaging in research incurs additional costs, and increases the complexity of economic calculations. The variation in equipment, expertise, procedures, costs and policies within and between countries makes it challenging to bring new technologies and methods into routine use.

We adopted a consensus approach in which all considerations suggested by workshop attendees were included, as they reflected real-world research experience. Whilst more formal approaches might have gauged the relative importance of each consideration, we did not feel this was warranted, given that no one person will have insight into all of the processes involved in delivering imaging research, and people in different roles will have different priorities.

In this project, we focused on the common operational challenges particularly pertinent to imaging and did not aim to address general methodological challenges associated with clinical trials, or challenges associated with imaging for particular purposes or indications. There are some existing publications in this area; however, they were based on the experiences of a limited number of people or roles and considered a smaller range of purposes and/or domains.[36–39] In one perspective paper, two authors considered the standardization challenges presented by quantitative MRI biomarkers in oncological clinical trials.[36] In another, three authors considered the challenges in translation of biomedical optical spectroscopy, with a particular focus on commercialisation and clinical adoption.[37] A third paper highlights the challenges involved in acting as an investigational site, based on the experiences of two investigators at one site, and provides some more detailed discussion of the complexities of setting up a new trial, training staff, and de-identifying images.[38] A mini-review of challenges in gastrointestinal imaging considered the specific challenges of obtaining viable images that are posed by different modalities in that field.[39] Although these papers may discuss specific challenges in more detail, we believe this is the first publication to provide an overview of the wider research delivery process that is not disease- or modality-specific. We believe this will alert researchers to more of the issues that may arise, that they may address these ahead of time at the design stage.

This project was instigated by members of the NIHR Statistics Group Imaging Studies Section,[40] whose remit is to encourage the adoption of best practice in imaging research. Having presented considerations for set-up and conduct in parts I & II of this article, our future work will address challenges in the statistical design and analysis of imaging studies.

Ethics approval and consent to participate

Not applicable.

Availability of data

Not applicable.

Author contributions

KB: Conceptualisation, Methodology, Visualisation, Supervision, Writing- Original Draft preparation, Writing- Reviewing and Editing, Project AdministrationNP: Conceptualisation, Methodology, Visualisation, Supervision, Writing- Original Draft preparation, Writing- Reviewing and Editing.

PC: Methodology, Visualisation, Writing- Reviewing and Editing.

SD: Methodology, Visualisation, Writing- Reviewing and Editing.

AR: Methodology, Visualisation, Writing- Reviewing and Editing.

SM: Conceptualisation, Methodology, Visualisation, Supervision, Writing- Original Draft preparation, Writing- Reviewing and Editing.

TN: Conceptualisation, Methodology, Visualisation, Supervision, Writing- Original Draft preparation, Writing- Reviewing and Editing.

EMAH: Conceptualisation, Methodology, Visualisation, Supervision, Writing- Original Draft preparation, Writing- Reviewing and Editing.

Generative AI use

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Conflict of interest statement

None.

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