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A procedural framework for good imaging practice in pharmacological fMRI studies applied to drug development #1: processes and requirements

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There is increasing interest in the application of quantitative magnetic resonance imaging (MRI) methods to drug development, but as yet little standardization or best practice guidelines for its use in this context. Pharmaceutical trials are subject to regulatory constraints and sponsor company processes, including site qualification and expectations around study oversight, blinding, quality assurance and quality control (QA/QC), analysis and reporting of results. In this article, we review the processes on the sponsor side and also the procedures involved in data acquisition at the imaging site. We then propose summary recommendations to help guide appropriate imaging site qualification, as part of a framework of 'good imaging practice' for functional (f)MRI studies applied to drug development.

Introduction

As the field of functional neuroimaging matures, there is increasing interest in the application of functional magnetic resonance imaging (fMRI) methods to central nervous system (CNS) drug development [1–8]. These methods enable brain function to be resolved at spatial scales of a few millimeters and functional (f)MRI responses have been shown in several studies to be sensitive to modulation by pharmacological agents [9–22] and potentially predictive of treatment response [23–25]. With due caveats around its interpretation and potential confounds [26–28], the

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approach thus holds promise as a technique by which the action of both novel and approved CNS therapeutics could be more fully understood [2–4,6,7].

However, the term 'fMRI' covers a spectrum of paradigms, each of which might differ in implementation details and performance characteristics. Moreover, studies in healthy volunteers or patient populations can each bring different challenges and provide different information to the drug development process. The precise role of fMRI in drug development is thus likely to depend upon the mechanism, proposed indication and clinical phase of the compound in question, as well as the availability of stable, reproducible and validated fMRI paradigms. For example, in early clinical development (phase I/IIa studies), where the emphasis is on demonstrating safety and pharmacokinetic/pharmacodynamic (PK/PD) relationships, a role as a PD biomarker of drug effects on brain function in healthy volunteers might provide useful information confirming central pharmacological activity and potentially inform the selection of an effective dose for subsequent trials. It might also enable hypotheses around the functional effect of the drug candidate on brain structures or circuits relevant to the target or putative mechanism to be tested [11,14,18,29–31]. fMRI methods can also be used in patient populations to elucidate drug effects on CNS function in the diseased state [16,22,32–35]; in later phases of drug development [phase II–III and post marketing (phase IV)], this might be multi-site in nature.

The flexibility of the fMRI technique and the fact that no single paradigm has yet become firmly established in the industrial imaging repertoire stand in contrast to other neuroimaging techniques, such as the use of structural MRI in Alzheimer's disease. This latter method, now widely used as a biomarker in phase II/III studies, has benefitted from several multi-site initiatives [e.g. the Alzheimer's Disease Neuroimaging Initiative (ADNI) [36,37]] that have been able to promote standards relating to the specifics of image acquisition, quality assurance and analysis [37–40].

Nevertheless, application of fMRI within a drug development setting brings with it monitoring, logistic, reporting and documentation requirements. Many of these reflect sponsor processes and regulatory oversight that applies to the evaluation of new chemical entities (NCEs) in humans.[a] However, these processes typically do not reflect the specifics of the imaging technology that are crucial to a successful study. Thus, as fMRI studies become more closely integrated into the formal development of novel therapeutics, the required level of oversight will increase; however, the framework to support this properly is currently lacking. Another key factor is that multiple parties will be involved. This will, at a minimum, include one (or more) imaging site(s) and the sponsor (the biopharmaceutical company) with different functions from the sponsor company is likely to be involved. One of the imaging sites or a separate facility might serve as a 'core laboratory' with primary image analysis and/or quality assurance and quality control (QA/QC) responsibilities. As is already the case with other imaging methods, these services are likely to be increasingly offered by specialist commercial contract research organizations (CROs). Whatever the configuration for a given trial, the process requirements and multiplicity of parties require effective communication.

[a] Such trials thus differ qualitatively from investigator-initiated trials with marketed compounds.

For application to a regulated environment, it is crucial to define processes to accomplish reproducibility of practice, minimize risk of data corruption or loss and enable unbiased analyses to address the objectives of the trial. Currently, however, there are no clear guidelines as to how to control for fMRI data acquisition and analysis complexities at the process level in a systematic yet practical way amenable to effective good clinical practice in drug studies. Individual laboratories are likely to have their own methods in place to address the fMRI issues, whereas for drug studies, companies will have procedures to which the study must conform but which do not typically address important details of the imaging technique. Guidelines for best practice, drawing on the experience of both parties, will (i) help fMRI to be used robustly and consistently in a drug development context (either stand-alone clinical pharmacology studies or integrated into larger clinical trials); (ii) aid appropriate preparation and monitoring of fMRI studies to a suitable level of detail by either the biopharmaceutical company or third parties (as is currently routine for other imaging methods); (iii) minimize data loss, including incomplete or ambiguous data sets; (iv) enable objective definitions of technical failure (data exclusion criteria), including go/no-go decisions during the imaging session and (v) maximize the efficiency of the data analysis tasks and the confidence in the conclusions generated. Many of the concepts presented here draw upon over 15 years of fMRI experience with a venture-backed imaging start-up company (Descartes Therapeutics Inc.) and at the P.A.I.N. Group at Harvard, as well as pooled experience from a constructive industry – academia interaction involving three pharmaceutical companies (Eli Lilly, Merck and Sepracor) and the P.A.I.N. Group – the Imaging Consortium for Drug Development (ICD) [3,5]. The overall impetus for establishing good imaging practices (GIP) relates to defining standards for the possible future adoption of imaging in drug development by regulatory groups [i.e. US Food and Drug Administration (FDA; http://www.fda.gov) and European Medicines Agency (EMEA; http://www.emea.europa.eu)].

Here, we examine the processes involved in pharmacological fMRI studies from the viewpoint of their application to drug development. Our aim is to reflect the obligations and constraints of the pharmaceutical industry processes and equally to capture the complexities and realities of the fMRI process that must be properly understood for this technique to be most effectively applied as a biomarker. Together with the consideration of protocol-specific acquisition and analysis issues (discussed in a following paper [41]), this framework can be considered to represent GIP (Box 1). (Although we concentrate on fMRI, many of the concepts are also applicable to other quantitative MRI approaches [37,38,42–44].) Here, we summarize the processes that circumscribe clinical trials from the pharmaceutical company perspective as well as clinical studies from the perspective of the imaging site. For completeness, the fMRI scan-day process is also summarized in more detail. We then consider site selection and evaluation guidelines for pharmacological fMRI studies. The purpose of this section is to provide recommendations to aid fMRI-relevant site qualification for prospective trials.

Processes circumscribing fMRI trials of novel therapeutics

A key aspect in planning biomarker studies is to capture and reconcile accurately the time constraints and process requirements

BOX 1

High-level aims of GIP recommendations

Site capabilities

- To ensure appropriate patient and/or subject cohorts can be recruited, screened and scanned compatible with the trial protocol and timelines
- To ensure appropriate safety and clinical oversight
- To ensure compliance with all federal, state, local and institutional requirements (e.g. HIPAA and IRB)
- To enable availability of required drug formulation and dose as required by protocol
- To put appropriate imaging QA/QC procedures in place to ensure stable, reproducible imaging over the course of the trial
- To ensure appropriate data backup procedures are in place to minimize risk of data loss
- To ensure that site personnel are adequately trained and experienced with fMRI to maximize data quality
- To ensure appropriate acquisition and handling (including storage, identification and duplication) of plasma samples
- To ensure that the fMRI data can be interpreted appropriately in terms of the pharmacology of the drug being tested

Study execution

- To ensure appropriate QA/QC and documentation of MRI scanner system and coils
- To ensure appropriate QA/QC and documentation of all ancillary equipment
- To facilitate the specification of clear *a priori* criteria for acquisition-related exclusion
- To aid the specification of protocol-specific QA/QC guidelines and checklists to minimize the risk of off-protocol acquisition or technical failure
- To enable meaningful and efficient reporting of progress and diagnostic measures related to data acquisition

Analysis

- To ensure the requisite ancillary data can be collected and accurately matched with the corresponding image time series
- To enable a consistent, independent re-analysis of the study data
- To facilitate the *a priori* specification of clear (and, where possible, objective) data quality-driven exclusion criteria and diagnostic measures at defined points within the analysis pipeline
- To facilitate the clear, complete and explicit *a priori* specification of analysis steps leading to primary endpoints
- To enable rapid and efficient computation of primary endpoint measures for interim decisions and final results

of each of the parties involved. In addition to the imaging site(s) and different functions within the industrial sponsor company, these can also include CROs to whom certain clinical trial and imaging operations have been contracted. Owing to the specialist nature of imaging services, the clinical and imaging roles might be handled by two separate entities and the core imaging responsibilities might be undertaken by an academic site. At the sponsor, the process will involve required approvals, documentation and input from people who might be spread across numerous functions in a large company; at the imaging site, internal approvals, hiring or staff allocation requirements and the availability and booking of scanning slots; at the clinical CRO, subject monitoring and travel logistics; at the imaging CRO or core laboratory, turn-around time for QC or data analysis and generating data tables and reports. For patient studies, certain patient populations might be infeasible to recruit into a single-site study at acceptable rates, requiring either a broadening of the inclusion criteria or extension to a multi-site study with the additional overheads related to harmonization and QC of the fMRI procedures [45,46].

Industry-sponsored clinical trials for the purpose of drug development are planned and executed within a formal framework of distinct, sequential phases; terminology might vary but the concepts are fairly stable in the industry and, for the purposes of this article, we refer to the following:

- *Preparation*: preparatory activities, including site and CRO selection, contracting, site inspection and qualification, protocol definition and approval and regulatory approvals;
- *Execution*: implementation of the protocol, from first screening visit to final subject visit and data lock;
- *Analysis*: implementation of data analysis plan to compute prespecified endpoints;
- *Reporting*: formal report of findings, using predefined tables, figures and listings (TFLs);
- *Inspection*: regulatory inspections of all aspects should be done;

Each is associated with oversight and documentation requirements and with procedural guidelines. Transition from one phase to the next is typically associated with a key milestone and decision point that must therefore be explicitly accounted for in project planning.

The specifics of these requirements might differ depending on the company funding the study (sponsor), the geographical location and regulatory environment [47], whether the study is designed for methodological development and/or validation or if a proprietary compound is being used, and on the clinical development phase of that compound. Methodological studies with marketed, non-proprietary compounds can bring modest overheads in terms of approvals and oversight, to a large extent dependent on the processes of the industrial sponsor. However, in the case of studies with NCEs, there are substantial requirements that pertain to any human study with the compound. These can include:

- Regulatory approval for human trials with the NCE;
- Sponsor inspection and/or qualification of study sites, including the imaging site(s);
- Subject monitoring and clinical follow-up;
- Clinical safety and adverse event (AE) reporting;
- Restrictions and requirements for compound preparation.

These requirements and their logistical impact will need to be reconciled with the constraints of the fMRI facility(ies). Regulatory approval for a study [e.g. an Investigational New Drug (IND) application in the USA[b] or a Clinical Trial Authorization (CTA)

[b] IND: a package of data and documentation approved by the FDA, enabling an unapproved compound to be shipped across state lines to clinical investigators for preliminary studies in human subjects. The IND includes preclinical toxicology and pharmacology, chemical information and proposed clinical studies; http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm.

in the UK (http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/index.htm)] might be explicitly required in the Preparation phase if the imaging study is to be the first within the geographical jurisdiction of the imaging site and it is not an addendum to an existing trial. If the imaging facilities operate within a research environment, a clinical CRO might be engaged for the clinical oversight, follow-up and reporting; in this case, the logistical interface with the imaging facility needs to be clearly defined. This might include accommodating subjects in a clinical trial unit pre- and post-dosing and/or imaging to facilitate monitoring but to also ensure that any preparations (e.g. diet restrictions) are followed. The sponsor will also have processes for the inspection and qualification of sites: at the clinical [good clinical practice (GCP; http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm)] level at which a study is to be performed.

The sponsor will also have internal processes for the development of the experimental protocol, which might require input from individuals in disparate functional areas (and possibly geographies), and also processes for protocol approval (and possibly modification). These processes will impact time lines in the Preparation phase.

For trials involving other imaging methods, it is common practice for industry sponsors to engage with an imaging CRO or imaging core lab to provide some or all of the following:

- Site qualification from an imaging standpoint;
- Definition of, or input into, the imaging protocol;
- Provision of an imaging procedure manual;
- Training of site personnel on the protocol;
- Independent QA of imaging systems;
- Independent QC of imaging data;
- Analysis and report of imaging data.

These services are commercially available for anatomical and radiological imaging methods used in later-phase trials and expertise in the commercial sector is accumulating for support of more 'functional' methods, such as dynamic contrast enhanced (DCE)-MRI and [^{18}F]Fluorodeoxyglucose (FDG)-PET in oncology. In the case of fMRI, the pharmaceutical and core lab sectors are still at an early stage of building an analogous depth of experience and expertise. In particular, given the fact that fMRI remains a specialized activity where, for best results, top research sites are engaged, the fMRI site(s) and investigators themselves are likely to have a far larger input into the above tasks. However, independent assessment of site processes (qualification) at the imaging level and independent QC of the imaging data are likely to be desired or required by the sponsor and will be helpful for a broader rollout of fMRI protocols in the future.

The fMRI scan-day process

Few imaging centers are dedicated to one process and are usually very busy with multiple projects. Moreover, as primarily a research, rather than clinical, tool, fMRI might only be one part of the MR-related research activities that can involve experimentation with many aspects of the imaging system. As such, subjects need to be couriered through the system in a safe and efficient manner consistent with the scheduled booked time for the scanning and all required components of the imaging system should be in place. This relies on efficient, coordinated action of the fMRI study team, all of whom need to be present on time. This typically includes imaging technology staff (a technologist or radiographer and a physicist or engineer), additional technical staff (e.g. to control and/or monitor additional equipment, such as paradigm presentation, physiological signals and subject responses) and medical personnel (for subject preparation and setup, and monitoring after dosing, and during and after scan).

As with any MRI examination, fMRI involves image acquisition with the subject lying within the MR scanner. Standard MR exclusion criteria (including aspects relating to metal implants or fragments and claustrophobia) exist at all MR facilities and also apply to fMRI. fMRI might also require further restrictions, such as subjects with permanent retainers or other implants that, although not ferromagnetic, produce distortions of the fMRI images. Moreover, fMRI scans also involve additional equipment and typically require a degree of active participation on the part of the subject (e.g. rating a painful stimulus, button pressing to confirm compliance and assess performance in a cognitive task). Subjects who might be able to tolerate a short, passive radiological MR exam might be unable to participate satisfactorily in an fMRI trial. This can be most properly assessed by the staff at the fMRI facility and might include a session in a mock scanner, which replicates most subject-perceptible aspects of an actual scanning session in the absence of a magnetic field or any signal acquisition and can usually be customized to include the specific tasks planned for the study. Thus, an 'MR' screening visit to cover subject compatibility with fMRI process and its requirements can be useful to consider, even if a clinical CRO is responsible for initial screening.

The presence of the strong magnetic field of the scanner ($\sim 10^4$–$10^5\times$ the magnetic field of the Earth) requires MRI-compatible equipment, and strict processes to exclude from the scanner room iron-containing objects that can become lethal projectiles when attracted by the magnetic field. Hence, specialized procedures are required relating to emergency operations in the scanner room.

Before the first scanning visit, subjects have already been enrolled into the study, have signed informed consent (which implies that the details of the protocol have been thoroughly reviewed and understood) and have usually gone through some preparatory processes (e.g. pain testing or lying in a mock scanner). Following screening and recruitment, the subject's involvement with the imaging study can be broken down into five basic components: (i) off-site preparation for scan; (ii) on-site preparation; (iii) scanning; (iv) on-site post-scanning procedures and (v) off-site post-scanning follow-up. For all components, a well-defined protocol should be followed with respect to maintaining QA/QC, including appropriate documentation and reporting.

Off-site preparation for scanning

For pharmacological studies, subjects might have been informed to follow specific procedures related to the specific protocol. These can include restrictions of food or liquid intake for a specified period, as well as avoidance or limited intake of specific substances, such as caffeine, alcohol, nicotine or other drugs. If subjects are housed overnight in a clinical research facility as part of the trial, these procedures can be more strictly enforced and documented. There are likely to be specific instructions related to the subjects' medication requirements, dependent on the protocol

and if subjects are patients on chronic medications. No good guidelines exist for concurrent medication or treatments with respect to evaluating new drugs in patients who are/have been on other drugs that might have transiently or chronically altered their brain function, in addition to pharmacological interference, *per se*. Tapering subjects off existing medication is a scientifically rational approach, but there are associated issues related to human research ethics, especially when considering placebo evaluation in subchronic or chronic dosing schedules.

In addition to the preparations described above, subjects might need to attend a clinical research facility for dosing, or be admitted to a CRO the night before dosing to ensure that lifestyle guidelines are adhered to. In both cases, subjects need to be transported to the imaging facilities that not necessarily are in close proximity. A series of arrangements need to be made for subject to be transported in taxis or a suitable hospital vehicle to and from the imaging facility and be accompanied by medical personnel if warranted.

On-site preparation for scanning

Once the subject arrives, several procedures might be required before scanning. These can include basic physiological parameters (e.g. blood pressure or weight) and a urine test for drug exposure. Additionally, the protocol might prescribe questionnaires, psychophysical testing and require the placement of lines for intravenous access for blood sampling to enable comparison between the fMRI results and PK measures. A set-up for blood sampling that enables repeated, effective (volume and time taken) blood draws that do not impinge on the imaging process should be established. Before scanning, subjects will need to remove all metal objects from their bodies and, in some cases, might be asked to change into standard clothing, such as a hospital gown.

For NCEs, an fMRI study is likely to be preceded by at least a single-dose healthy volunteer study (phase 1a), which will yield important data on both safety and drug PK. Safety issues are discussed with the subject, including repeating what to do if they feel strange (e.g. nauseous); the issues of safety monitoring in the context of fMRI are discussed at greater depth elsewhere [48]. For acute dosing studies, it is likely that the compound will be administered on site. For oral formulations, dosing might occur several hours before scanning, commensurate with the PK profile of the compound; subjects will need to be monitored during this time. In addition, all blinding of drug administration should be in place. This includes at-scanner blinding but also an unblinding plan and associated facilities to obtain immediate data on the drug or placebo if there is a serious side effect. At most sites, this is available through the research pharmacy that is on-call during scan times. Importantly, on the technology side, the scanning team needs to ensure appropriate functioning of all equipment, including physiological monitors, scanning parameters and psychophysical testing measures (e.g. pain stimuli and cognitive measures).

Scanning

Any pre-scan checks and QA tests should be explicitly captured in the scanning protocol and run before the scan commencing. At research sites, this should include verification that any custom filters or connections between the scanner hardware and other electronic equipment have been removed and that the system is in its presumed state of readiness for data acquisition. The actual scanning process requires the subject to lie supine within the MRI scanner with their head restrained. Additional apparatus to apply the paradigm and record feedback from the subject during acquisition of the fMRI time series will also be present in the scanner. This might include goggles or mirrors to allow visual cues and/or feedback to be shown to the subject, a joystick, dial or button box in one hand to capture subject responses and/or a device to apply peripheral stimuli to the subject (e.g. in pain studies). The acquisition process thus involves more than just MRI scans controlled from the scanner computer; it will probably include presentation of the paradigm or stimulus, recording of the subject feedback and physiological recordings and drawing of blood samples (see below).

The subject will typically have a squeeze-ball in one hand to trigger an alarm in the case of acute need. There is a regular two-way verbal communication between the subject in the scanner and the staff in the acquisition control room; this enables the subject to voice concerns or queries while in the scanner and also enables the staff to verify the subject's comfort, give notice before the start of each scan and remind the subject of instructions for the task. The timing of the scanning session relative to compound administration will be informed by the dosing regimen and compound PK. In particular, the specific functional scans from which primary endpoints will be derived might have specific timing constraints (e.g. at or around T_{max} in the case of acute dosing studies). Blood samples might also need to be taken while the subject is in the scanner.

Considerations around the scanning process are examined in greater detail in a companion paper.

On-site post-scanning procedures

Following the scanning procedure, additional non-imaging tests and data collection (e.g. psychophysical measures and blood draws) might be required as part of the protocol. This work is usually accomplished within the same facility, close to the scanner room. The subject's status is monitored throughout the post-scanning period on site. Discharge (and follow-up as necessary) from the fMRI facility is formally managed by the responsible physician; for NCE trials, this might correspond to a handover to personnel from a CRO or the sponsor company responsible for clinical monitoring. Travel for the subject to their residence or to a clinical facility will be provided as defined in the protocol. A second, important, post-scanning procedure relates to securing all data related to the subject, the acquisition procedure, adverse events and study compliance with local regulations regarding research on human subjects. Electronic data from the experiment, including images, paradigm prompts or stimuli records, subject responses and physiological recordings, need to be checked, curated and transferred for subsequent analysis according to the trial analysis and QC procedures. Procedural data captured on the case report form (CRF) need to be filed. With respect to Human Research Protection Program (HRPP) issues, specific disclosures on any AEs need to be documented and reported to the sponsor, institutional and regulatory authorities as required. For subjects who have not completed the procedure as defined in the protocol because of a non-subject issue (e.g. scanner malfunction), retesting of the subject might be limited by the protocol and might require

explicit permission from the local human research authorization boards (e.g. HRPP).

Off-site post-scanning follow-up

For pharmacological fMRI studies, follow-up procedures should be in place for subjects to be able to contact the clinical team should they have some unexpected delayed responses. A scheduled follow-up call to the subject might be included in the protocol. Information for the subjects on how to contact study physicians or determine whether to go to an emergency room should be clearly defined. In addition, depending on the study duration, many HRPPs might require periodic subject monitoring, including specific clinical evaluations. For NCE studies, comprehensive clinical monitoring and follow-up might be contracted to a clinical CRO. In the case where the imaging study is an addendum to an existing trial, the CRO responsible for the overarching trial will typically be responsible for ongoing clinical monitoring and associated reporting.

Site requirements and qualification

For a technique as complex and demanding as fMRI, site selection is crucial. Although processes for the evaluation of sites at the clinical level are well established and applied by sponsors to all clinical trials, site evaluation and qualification based on imaging criteria is also advisable and beginning to become a part of the processes of many companies. When formalized for pharmaceutical trials, it results in a site being 'qualified' as appropriate and competent for participation in the trial. For imaging studies, the qualification exercise involves an assessment of the equipment [MRI performance and/or accreditation with the ACR (American College of Radiology), FDA approved ancillary equipment, etc.], procedures and capabilities of the site relevant to the specific imaging requirements for the trial in question. Any issues arising need to be resolved before the trial proceeding at that site. For fMRI currently, small or single-site studies are common and invariably involve academic centers; the site(s) are often chosen based on their experience in a particular area and might include an aspect of scientific collaboration in addition to the primary outcomes for the trial. The clinical assessment is also vital to ensure research center(s) can support the GCP requirements of the trial.

For early-phase trials, the emphasis on the use of imaging is typically for internal decision-making, possibly as part of a wider set of biomarker and clinical pharmacology studies. As fMRI becomes more closely integrated with other clinical activities, and oversight by the sponsor becomes more formalized, it is crucial that evaluation of actual or potential fMRI sites be based on a meaningful assessment of their capabilities in terms of the entirety of the process involved in conducting a pharmacological imaging study. This should involve consideration of logistical and operational capabilities in addition to their technical ability and the standard clinical site assessments. The development of relevant criteria will also help expand possible sites for fMRI in drug studies beyond the few highly specialized centers in which such studies are presently concentrated; this will be a key enabler for the wider application of fMRI in larger trials and different geographies.

A high-level checklist for imaging-related aspects to evaluate when selecting and qualifying imaging sites for pharmacological fMRI studies is summarized in Box 2 and considered further in the remainder of this section.

Personnel and experience

In contrast to radiological imaging sequences routinely used in clinical care, fMRI remains primarily a research tool and involves a complex combination of equipment and expertise. The fMRI site selection is often dictated or heavily influenced by technical specialty or experience of a particular facility and its staff. The experience of the site(s) in a particular methodology, therapeutic indication or type of study relevant to the trial should be assessed. Experience in a specific therapeutic area is likely to have led to substantial experience with relevant paradigms and protocol elements, constructive relationships with relevant clinics and/or clinicians and familiarity (including historical data) with recruitment strategies, potential issues and probable enrolment rates. (Note that the involvement of an experimental therapeutic can affect the recruitment rate.)

Previous site experience with pharmaceutical trials can be helpful in terms of the site being able to meet the study requirements and also provides some initial common ground as to an understanding of the sorts of processes involved. However, this need not be a hard prerequisite if there is a willingness from both the sponsor and the site to work together. An increased role for fMRI studies, especially as a part of a larger trial or clinical development plan that might constrain the options around site selection, will increase the pressure to involve a larger circle of imaging sites. In this scenario, the requirements concentrate on the technical fMRI expertise and systems and an ability and willingness to implement and resource the study competently. In a multi-center context, this might require the adoption of certain implementation details that diverge from the regular practices of the site, but which are necessary for harmonization of the protocol across the imaging sites.

Assessment of site personnel aims to document the education, technical training and specific expertise of the staff of the imaging unit as a whole. The complex nature of the fMRI acquisition process requires the coordinated action of a team of people responsible for the various aspects of data acquisition. In particular, one or more MR physicist or engineer is likely to have an important role in the study and all staff involved in the acquisition phase should be aware of the interplay between different roles in the scan day process. The assessment should also examine the experience of the personnel in coordinating and running fMRI studies, especially in formal clinical trial situations. Similarly, if data analysis is to be performed at the site, training and experience of personnel in fMRI analysis and an appreciation of the requirements of a clinical trial should be assessed (also see below).

Assessments regarding personnel responsible for clinical and laboratory practices on site, including subject interventions and sample handling, are also required but would typically be covered by standard clinical site assessment procedures. However, experience and readiness of personnel responsible for medical intervention in the magnet environment should be specifically assessed.

Imaging and data acquisition

A standard feature of the site qualification exercise involves the collection of basic information about the imaging equipment in

BOX 2

Site assessment checklist for pharmacological fMRI studies

Personnel and experience

- Experience and training
- Principal investigator:
- Documentation and duration of experience with relevant MRI techniques (e.g. curriculum vitae).

- Other imaging staff involved in running the study (e.g. radiographer and/or technologist and researchers):
- Documentation and duration of experience with relevant MRI techniques.

- Organization chart
- Training records and document controls
- Roles and responsibilities within study team
- Previous protocol-relevant experience of site
- Previous experience with pharmaceutical trials

Imaging and data acquisition

- Imaging equipment
- Scanner manufacturer, field strength and model
- Coil(s) to be used for the study
- Scanner software release

- Regular MRI QA assessment procedures
- Frequency and nature of regular scanner QA procedures (e.g. phantom scans)
- Documentation of results of same (e.g. plots of phantom SNR, drift, by week)

- Processes around upgrades and maintenance logs
- Date of last software upgrade
- Date of next scheduled software upgrade
- Frequency of preventative maintenance on scanner
- QA processes following upgrade or service intervention
- Records of QA and specification checks following upgrade or service intervention and document controls

- QA and maintenance processes for additional (non-imaging) equipment
- Stimulus presentation computer(s) and software
- Visual presentation and subject feedback equipment
- Physiological monitoring equipment

- SOPs for MRI operations

Data handling and backup

- Data routing, transfer, backup, retention and de-identification processes
- Diagram of site data flow

- Analysis pipelines and data QC procedures
- Description of study-relevant analysis procedures
- Vendor and/or product or validation records for software used for analysis
- Data and/or image QC procedures

Clinical, safety and monitoring

- Clinical support and safety evaluation, including physician requirement
- SOPs around safety monitoring and screening of study subjects

- Monitoring within the scanner environment
- Procedures for monitoring subject while in the scanner, including (as applicable):
- Two-way communication with subject
- Subject compliance with protocol (keep still and hold breath when requested)
- Physiological recordings

- Links to clinical unit and/or facilities
- Logistical interaction for smooth running of study

- Emergency procedures for subjects and/or patients in the scanner environment
- Abort procedure if subject needs to stop scan (acute and urgent discomfort)
- Procedure for medical support compatible with magnetic field

Pharmacy and pharmacology

- Research pharmacy ability to support provision of study drugs at required dose and formulation
- QA, maintenance and operating procedures for equipment related to drug delivery
- Blood sample collection, handling and controls

Site process

- IRB and internal approval process and timelines
- Subject and/or patient recruitment processes
- Scan time management and availability of imaging slots
- SOPs for imaging trials

place along with documentation on software release, upgrade schedules and frequency of preventative maintenance, providing assurance that the equipment is appropriate and adequately maintained for the purposes of the study. Procedures to document regular preventative maintenance by the manufacturer should be in place. However, these are typically not adequate to ensure acceptable scanner performance on a timescale of days to weeks and so routine site MRI QA procedures should also be assessed. These are likely to include daily, weekly and monthly measurements of scanner performance, capturing aspects related to geometric distortion, signal:noise ratio (SNR) and temporal stability. The data are acquired using a reproducible phantom and coil setup and assess the 'full chain' of components in the imaging system, including transmit – receive radiofrequency (RF) coils, gradients, electronics and image reconstruction. Although they do not probe any individual component directly, any abnormalities flagged by the QA procedure can be followed up with more specific troubleshooting. Procedures should be in place to log the regular QA output parameters, compare them with previous readings and to document the resolution of any issues that are identified. Depending on the vendor and the agreement with the imaging site,

immediate (e.g. within 24 hours) evaluation and correction of problems associated with scanners might be accomplished. In the context of multi-center studies, the fBIRN consortium has established procedures specifically designed for multi-site fMRI (https://xwiki.nbirn.org:8443/bin/view/Function-BIRN/FBIRNScannerCalibration; http://nbirn.net/research/function/fbirn_scanner_calibration.shtm).

Finally, verifying and documenting the MR system performance following software and/or hardware upgrades is especially important. In this case, a more thorough set of testing is performed involving both the manufacturer and the site; the fMRI QA must be successful before the study proceeds.

Equipment for presenting and recording the non-imaging data (e.g. stimulus and/or paradigm presentation, subject response devices and recording computers, and physiological readings) are key components of the fMRI experiment. Procedures for, and logs of, regular checks and preventative maintenance of the equipment used for these purposes should also be in place, along with standard procedures for their use and customization for an individual study. If an intravenous drug delivery pump is relevant to the study at hand, the same considerations apply. As for the scanner itself, qualifying procedures around upgrades and software releases should also be established. The site must be able to demonstrate the implementation of processes to accomplish standards of procedure and reproducibility of practice, ideally captured in standard operating procedures (SOPs) that include QA/QC.

Data handling and backup

Clear procedures for prompt raw data backup should be in place. For fMRI, this includes both imaging and ancillary data (e.g. paradigm presentation, physiology traces and subject response files). This will probably involve duplicate copies of the data, including off-site repository, and procedures for data recovery.

A second element of the data handling is effective curation, including consistency checks, routing and other procedures preparatory to subsequent analysis. This requires processes for bringing together the imaging and non-imaging data and specification of a naming convention to facilitate subsequent analysis. Details of data transfer and routing processes should ideally support local and remote analysis. Procedures able to support remote image QC independent of the acquisition site should also be considered.

A third key element is de-identification of the data before analysis or off-site transfer. When possible, it would be simpler if coded information instead of personal information were entered into the scanner database, ensuring anonymity of the participant in all imaging information. The European Union Data Protection Directive (http://ec.europa.eu/justice_home/fsj/privacy/) and the Health Insurance Portability and Accountability Act (HIPAA) mandate this. For imaging data files, this requires that image header fields containing personal identifying information be scrambled, deleted or replaced by alternative content, to be specified within an anonymization scheme for the trial. Moreover, the ancillary data files should also contain no identifying information. Procedures should be in place at the site to ensure that this is performed in an efficient way, minimizing potential for operator error. In the case of data being transferred off-site for analysis, incorporation of the anonymization step into the data transfer operation can be a useful mechanism.

For imaging trials to be used as part of a regulatory submission in the USA, Part 11 of Title 21 of the US Code of Federal Regulations (21 CFR Part 11; http://www.21cfrpart11.com/) provides development and validation requirements that must be satisfied for the treatment of electronic data and, hence, impinges upon requirements for systems and software used for data storage and analysis [49]. These include authorized access, SOPs for use, audit trails and electronic signatures. Currently, most software used for fMRI analysis comprises specialized suites developed for research purposes within the academic environment. As such, these are typically not compliant with 21 CFR Part 11. However, for early-phase, non-regulatory studies designed primarily for internal decision-making, the use of such software can be acceptable; indeed, there is currently no reasonable alternative. However, certain sites or imaging core laboratories might have performed and documented internal validation of particular fMRI processing streams based, in part, on such algorithms. In any case, site data routing, analysis and verification procedures should be assessed.

We also note that, whereas Digital Imaging and Communications in Medicine (DICOM) is the industry standard format for storing and transferring image files, enabling the development of powerful picture archiving and communication systems (PACS) designed around this standard, much fMRI analysis currently uses the Neuroimaging Informatics Technology Initiative (NIfTI) image format (http://nifti.nimh.nih.gov/). Thus, a very early step in the data routing and analysis pipeline is usually an image data format conversion and this also represents an opportune step at which de-identification can be integrated into the data-routing procedures.

Clinical, safety and monitoring

Clinical procedures and practices at the imaging site will be assessed according to established procedures that apply to any clinical study site. However, in the case of MR studies, there are also special considerations related to subject safety in or near the strong magnet of the scanner; in the case of acute drug administration shortly before the scanning session, the imperative for careful subject monitoring in the MR environment is increased. Important considerations also include the interactions within the team, specific medical safety processes (e.g. emergency procedures for removal of subjects in magnet related incidents), appropriate training of physicians (for both magnet and medical emergencies), appropriate emergency carts and contingencies for handling and/or transporting patients from the magnet to an emergency facility [48]. For fMRI, the presence of additional equipment might require additional procedures compatible with the more complex experimental set-up. Finally, although some subjects might need to stay in hospital for observation, this would be an unusual circumstance and procedures should be in place for monitoring subjects on discharge.

Pharmacy and pharmacology

For NCE studies, provision of the study drug is the responsibility of the sponsor and good manufacturing practice (GMP) in compound preparation is a prerequisite for human dosing. Extemporaneous compound preparation can thus only occur at approved facilities that might be distinct from the imaging site(s). As an alternative, the compound could be prepared by the sponsor

company and delivered to the dosing site(s) for use in the study. In these cases, the preparation, packaging, transport, receipt, storage, encapsulation and dispensing of the compound (along with the requisite unblinding information and procedures) will be an important part of the trial logistics. The institutional research pharmacy will maintain accountability for the compound at the imaging site. The capabilities of the pharmacy and its experience working with the logistics of the imaging facility will be a key determinant of how the compound delivery and dosing are managed and, hence, an important element of the site assessment. This is especially relevant if study drug dosing is to be performed at the imaging site (e.g. for acute exposure studies).

Serial blood samples from subjects will typically be required to quantify systemic drug exposure associated with the central functional effect of the compound. This might often require blood draws during the scanning session while the subject is in the magnet, requiring procedures for sample collection compatible with the magnet room and associated sample storage. At a minimum, blood samples for drug levels should be taken at the end of the scanning session to confirm drug exposure. Each imaging center in the study should have established protocols and documented success levels. Plasma preparation and storage requirements are drug specific and appropriate procedures are usually the responsibility of the pharmaceutical company in the case of investigational compounds or available from vendors for marketed drugs. Appropriate handling (centrifuge and labeling) and storage facilities are required on site. A sponsor might select a vendor for the analysis of PK samples but a facility with which the imaging site has an established working relationship can be a useful option and so the procedures of the site for blood sample analysis should also be assessed.

Site process

Effective study planning and prosecution requires consideration of site processes and constraints that will affect study logistics and timelines, as well as of the fMRI procedure itself. As for any study, the institutional review board (IRB) process of ethics review for human subject research, including deadlines for submission relative to board meeting dates and the process for dealing with any queries arising, must be captured. In general, single-site approvals are less complicated than multi-site HRPP approvals. Additional approvals for the study might also be required by the university or institute to which the imaging site belongs, and these should be made clear. Depending on the geographical location, offices equivalent to the US Office for Human Research Protections (http://www.hhs.gov/ohrp) define and require institutional assurances of ethical research, have specific and mandated regulations and policies and manage compliance oversight. For example, in the USA, accreditation of HRPPs is now being performed by a non-governmental agency, the Association for the Accreditation of Human Research Protection Programs (AAHRPP, http://www.aahrpp.org/www.aspx). With the process of HRPP approval are several associated issues, including new HIPAA rules relating to patient privacy and also the use of blood and genetic material; thus, restrictions around the use of such non-imaging data should be reported. Another logistical consideration is that, because most fMRI facilities operate within the academic sphere, rather than in a pure fee-for-service mode, the assignment of personnel to the trial (or even hiring of required staff) might often only begin after contract signature.

Given that fMRI is primarily carried out in specialized facilities, typically research laboratories, which might or might not be affiliated or physically co-located with a hospital or clinical unit, the processes by which the imaging facility interacts with other relevant site facilities (pharmacy, hospital, etc.) should be assessed. This should include site processes and historical data on subject/patient recruitment.

Another key determinant of study duration is the availability of scanning slots and preparation facilities that determine throughput for data acquisition; for example, scanning slots might be available for such studies only on certain days of the week, or at certain times of the day. The assessment should thus report on the scheduling of scanning slots, time constraints on booking them and any penalty fees that would be incurred upon scan cancellation.

The implementation of SOPs for the logistics of imaging for a formal pharmacological trial allows for a systematic approach to the complex sequence of events from patient arrival to drug challenge to ensuring appropriate data acquisition and safe subject discharge or handover to another clinical facility. A summary flow diagram of this process is shown in Fig. 2 of Ref. [41]. Crucial scan-day logistics relate to management of the subject, the study team, equipment and MRI through implementation of a protocol checklist based on the SOPs. Efficient SOPs shape and greatly facilitate considerations around processes specific to the study (see above); any such processes in operation at the site should be assessed.

Discussion

A clear idea of the expectations and process obligations of the industrial sponsor in potential pharmaceutical collaborations or sponsored trials is important to maximize the ability of the trial to answer the question(s) that motivated it. Equally, the industrial partner needs to understand the requirements in terms of site expertise, the subtleties underlying the science and the technology, the complexities involved in running pharmacological fMRI experiments as well as process constraints at the site level. Here, we have reviewed both the processes and have proposed guidelines for site assessment and qualification, a necessary part of the process of the sponsor company but one that needs to reflect accurately the nature of the experimental activity. We focused on fMRI as a specific case, but many of the recommendations might also be useful for quantitative imaging more generally. The site assessment exercise can, and should, be constructive and beneficial to all parties and constitutes one part of what we term GIP, ensuring that the equipment, expertise and processes are in place to ensure robust study execution and data acquisition. (In [41], we discuss considerations pertaining more specifically to protocol-level details and quality control.)

To some extent, our recommendations are driven by the need to communicate and coordinate between the different parties involved; in part, by regulatory requirements, operating practices of the sponsor and clinical trial standards. However, we also emphasize that, fundamentally, the aim of GIP processes is to obtain an efficiently run study and generate robust data and trustworthy conclusions adhering to standards that apply to clinical drug development. Although this might require additional

work during the Preparation phase of the trial, the result should be workable, efficient procedures and checks that facilitate a smooth execution and rapid analysis of the data.

Resource implications are still being evaluated (including investment costs in evaluating the utility of imaging) but in the context of looking toward new technologies to help make drug development less risky. However, in a recent paper addressing costs of imaging in clinical development [50], the potential value and/or costs of fMRI to aid decision-making were evaluated in terms of potential resource implications and potential benefits.

The use of fMRI as a biomarker is relatively new to drug development and has yet to define its role in terms of real utility. Nevertheless, several pharmaceutical companies are investing substantial resources into this area. Accordingly, attempts at understanding the utility of fMRI in drug development are being undertaken through various consortia [e.g. the Imaging Consortium for Drug Development (ICD) [5] and the Innovative Medicines Initiative (IMI) NEWMEDS consortium; http://www.newmeds-europe.com], within dedicated clinical imaging facilities developed by individual companies or by means of collaborative partnerships with specific institutions. Taken together, these efforts are intended to deliver robust, validated fMRI 'assays' and should enable a deeper understanding of how the technique might best be integrated into drug development. fMRI technology is rapidly and continually improving in terms of the quality of the data, the availability of more powerful and quieter scanners, faster acquisition methods and streamlined, if not yet fully automated, data analysis. As such, it is also important that the field be able to adapt to this changing environment and modify elements of GIP in the context of advances in both the technology and its application. A mechanism to enable knowledge from the different initiatives, groups and scientists involved in these efforts to be shared and a consensus or standards agreed would be beneficial. If fMRI is to be eventually used as part of regulatory drug approval processes, this will be even more crucial. The development of the Critical Path Initiative by the FDA [51,52] provides a mechanism for the evaluation of fMRI in the context of its current use to provide biomarkers in early-phase trials and (if it proves successful) continued dialog with the regulatory authorities regarding its ongoing use in evaluation and registration of novel therapeutics.

References

1 Borsook, D. *et al.* (2007) CNS response to a thermal stressor in human volunteers and rats may predict the clinical utility of analgesics. *Drug Dev. Res.* 68, 23–41
2 Leslie, R.A. and James, M.F. (2000) Pharmacological magnetic resonance imaging: a new application for functional MRI. *Trends Pharmacol. Sci.* 21, 314–318
3 Borsook, D. *et al.* (2006) A role for fMRI in optimizing CNS drug development. *Nat. Rev. Drug Discov.* 5, 411–424
4 Schweinhardt, P. *et al.* (2006) Pharmacological FMRI in the development of new analgesic compounds. *NMR Biomed.* 19, 702–711
5 Borsook, D. *et al.* (2008) A 'BOLD' experiment in defining the utility of fMRI in drug development. *Neuroimage* 42, 461–466
6 Borsook, D. (2010) *Imaging in CNS Drug Discovery and Development: Implications for Disease and Therapy*. Springer
7 Wise, R.G. and Tracey, I. (2006) The role of fMRI in drug discovery. *J. Magn. Reson. Imaging* 23, 862–876
8 Wong, D.F. *et al.* (2009) The role of imaging in proof of concept for CNS drug discovery and development. *Neuropsychopharmacology* 34, 187–203
9 Honey, G. and Bullmore, E. (2004) Human pharmacological MRI. *Trends Pharmacol. Sci.* 25, 366–374
10 Borras, M.C. *et al.* (2004) fMRI measurement of CNS responses to naloxone infusion and subsequent mild noxious thermal stimuli in healthy volunteers. *J. Neurophysiol.* 91, 2723–2733
11 Iannetti, G.D. *et al.* (2005) Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. *Proc. Natl. Acad. Sci. U. S. A.* 102, 18195–18200
12 Rogers, R. *et al.* (2004) An investigation to dissociate the analgesic and anesthetic properties of ketamine using functional magnetic resonance imaging. *Anesthesiology* 100, 292–301
13 Takahashi, H. *et al.* (2005) Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. *Neuroimage* 27, 991–1001
14 Anderson, I.M. *et al.* (2008) Assessing human 5-HT function *in vivo* with pharmacoMRI. *Neuropharmacology* 55, 1029–1037
15 Tregellas, J.R. *et al.* (2010) Functional magnetic resonance imaging of effects of a nicotinic agonist in schizophrenia. *Neuropsychopharmacology* 35, 938–942
16 Sheline, Y.I. *et al.* (2001) Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol. Psychiatry* 50, 651–658
17 Thiel, C.M. *et al.* (2002) Scopolamine but not lorazepam modulates face repetition priming: a psychopharmacological fMRI study. *Neuropsychopharmacology* 27, 282–292
18 Wise, R.G. *et al.* (2002) Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanil. *Neuroimage* 16, 999–1014
19 Abel, K.M. *et al.* (2003) Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study. *Neuroreport* 14, 387–391
20 Wise, R.G. *et al.* (2004) Using fMRI to quantify the time dependence of remifentanil analgesia in the human brain. *Neuropsychopharmacology* 29, 626–635
21 Kalin, N.H. *et al.* (1997) Functional magnetic resonance imaging studies of emotional processing in normal and depressed patients: effects of venlafaxine. *J. Clin. Psychiatry* 58 (Suppl. 16), 32–39
22 Davidson, R.J. *et al.* (2003) The neural substrates of affective processing in depressed patients treated with venlafaxine. *Am. J. Psychiatry* 160, 64–75
23 Chen, C.H. *et al.* (2007) Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol. Psychiatry* 62, 407–414
24 Whalen, P.J. *et al.* (2008) A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. *Biol. Psychiatry* 63, 858–863
25 Nitschke, J.B. *et al.* (2009) Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *Am. J. Psychiatry* 166, 302–310
26 Iannetti, G.D. and Wise, R.G. (2007) BOLD functional MRI in disease and pharmacological studies: room for improvement? *Magn. Reson. Imaging* 25, 978–988
27 Haller, S. and Bartsch, A.J. (2009) Pitfalls in FMRI. *Eur. Radiol.* 19, 2689–2706
28 Logothetis, N.K. (2008) What we can do and what we cannot do with fMRI. *Nature* 453, 869–878
29 Leppa, M. *et al.* (2006) Acute opioid effects on human brain as revealed by functional magnetic resonance imaging. *Neuroimage* 31, 661–669
30 Becerra, L. *et al.* (2006) Functional magnetic resonance imaging measures of the effects of morphine on central nervous system circuitry in opioid-naive healthy volunteers. *Anesth. Analg.* 103, 208–216
31 Honey, G.D. *et al.* (2003) Dopaminergic drug effects on physiological connectivity in a human cortico-striato-thalamic system. *Brain* 126, 1767–1781
32 Fu, C.H. *et al.* (2004) Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch. Gen. Psychiatry* 61, 877–889
33 Fu, C.H. *et al.* (2007) Neural responses to happy facial expressions in major depression following antidepressant treatment. *Am. J. Psychiatry* 164, 599–607
34 Jensen, K.B. *et al.* (2009) Evidence of dysfunctional pain inhibition in fibromyalgia reflected in rACC during provoked pain. *Pain* 144, 95–100
35 Mainguy, Y. (2009) Functional magnetic resonance imagery (fMRI) in fibromyalgia and the response to milnacipran. *Hum. Psychopharmacol.* 24 (Suppl. 1), S19–S23
36 Mueller, S.G. *et al.* (2005) Ways toward an early diagnosis in Alzheimer's disease: the Alzheimer's Disease Neuroimaging Initiative (ADNI). *Alzheimers Dement.* 1, 55–66
37 Jack, C.R., Jr *et al.* (2010) Update on the magnetic resonance imaging core of the Alzheimer's disease neuroimaging initiative. *Alzheimers Dement.* 6, 212–220
38 Jack, C.R., Jr *et al.* (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J. Magn. Reson. Imaging* 27, 685–691

39 Clarkson, M.J. *et al.* (2009) Comparison of phantom and registration scaling corrections using the ADNI cohort. *Neuroimage* 47, 1506–1513
40 Gunter, J.L. *et al.* (2009) Measurement of MRI scanner performance with the ADNI phantom. *Med. Phys.* 36, 2193–2205
41 Schwarz, A.J. *et al.* (2011) A procedural framework for good imaging practice in pharmacological fMRI studies applied to drug development #2: protocol optimization and best practices. *Drug Discov. Today* doi:10.1016/j.drudis.2011.03.011
42 Deoni, S.C. *et al.* (2008) Standardized structural magnetic resonance imaging in multicentre studies using quantitative T1 and T2 imaging at 1.5 T. *Neuroimage* 40, 662–671
43 Saam, T. *et al.* (2005) Sample size calculation for clinical trials using magnetic resonance imaging for the quantitative assessment of carotid atherosclerosis. *J. Cardiovasc. Magn. Reson.* 7, 799–808
44 Saam, T. *et al.* (2007) Reader and platform reproducibility for quantitative assessment of carotid atherosclerotic plaque using 1.5 T Siemens Philips, and General Electric scanners. *J. Magn. Reson. Imaging* 26, 344–352
45 Potkin, S.G. and Ford, J.M. (2009) Widespread cortical dysfunction in schizophrenia: the FBIRN imaging consortium. *Schizophr. Bull.* 35, 15–18
46 Friedman, L. *et al.* (2008) Test-retest and between-site reliability in a multicenter fMRI study. *Hum. Brain Mapp.* 29, 958–972
47 Lowing, R.K. (2008) Differences in the interpretation of the GLP requirements by OECD monitoring authorities: the point of view from the pharmaceutical industry. *Ann. Ist Super. Sanita* 44, 395–402
48 George, E. *et al.* (2010) Evaluation of novel drugs using fMRI in early-phase clinical trials: safety monitoring. *Drug Discov. Today* 15, 684–689
49 Steiger, P. (2009) Use of imaging biomarkers for regulatory studies. *J. Bone Joint Surg. Am.* 91 (Suppl. 1), 132–136
50 Wise, R.G. and Preston, C. (2010) What is the value of human FMRI in CNS drug development? *Drug Discov. Today* 15, 973–980
51 Lesko, L.J. (2007) Paving the critical path: how can clinical pharmacology help achieve the vision? *Clin. Pharmacol. Ther.* 81, 170–177
52 Woodcock, J. and Woosley, R. (2008) The FDA critical path initiative and its influence on new drug development. *Annu. Rev. Med.* 59, 1–12