



# Evaluation of novel drugs using fMRI in early-phase clinical trials: safety monitoring

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**A advances in functional magnetic resonance imaging (fMRI) permit the possibility of helping with dose ranging, as well as potential drug efficacy and side-effect profiles. However there are no current guidelines or standards for fMRI that meet established standards of care. Guidelines must be adopted to be used when patients are exposed to novel drugs, in particular, when immediate access to the patient is limited. When used in initial, MRI mandates certain safety standards because subjects are positioned in the magnet thereby limiting direct observation, communication or immediate access in an emergency; in testing new drugs using fMRI, we suggest that safety guidelines merit discussion and definition. This could lead to the adoption of standards. Some of these issues are unique to the application of the technology in early-phase trials.**

## Background

### *Human subjects in drug evaluation: new strategies*

*'Due to the continuous increase in time and cost of drug development and the considerable amount of resources required by the traditional approach, companies can no longer afford to continue to late phase 3 with drugs which are unlikely to be therapeutically effective.'* [1]. The failure in translation from preclinical to clinical success in drug development has led to a more aggressive approach in the use of human volunteers and patients in early stages of clinical evaluation of drugs, with a view to reducing subsequent compound attrition rates. Use of patients or surrogate models early in clinical phase central nervous system (CNS) drug development can offer more information than animal models on the likely benefits of a drug. Such an approach should also speed up the process if information such as targeted brain regions, drug dosing, CNS measures of side-effects, and so on can be determined based on functional circuitry. Such studies yield additional information

relevant to early go-no-go decisions. Indeed, the ability to 'kill' a drug candidate based on objective information in humans is invaluable. In addition, the use of objective endpoints might also include the integration of CNS-based circuitry with pharmacokinetic and pharmacodynamic measures [2]. This approach might also be useful in the reanalysis of approved drugs to identify and establish biomarkers. Such approaches can be used in pre- and post-therapy evaluation in the clinical setting.

*'Taking responsibility for the link between research and development gives clinical pharmacology a major opportunity to assume a pivotal role in research and development of new drugs'* [1]. Such responsibility, particularly when using new technologies such as functional imaging, obviously includes standards for safety, particularly in early-phase clinical trials when the safety and tolerability profile of a new agent is less well-established. Currently, the optimal use of functional magnetic resonance imaging (fMRI) in clinical CNS drug development in early-phase trials can depend on the specific drug and the nature of the behavioral measures possible in the magnet if these are used.

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### Deployment of new technologies in early clinical drug development

In CNS drug development, the use of *in vivo* imaging has revolutionized the ability to visualize target engagement of novel drugs as a function of brain region through receptor binding using positron emission tomography [3] and, more recently, functional effects of drug action using fMRI [4,2]. As such, functional maps of a drug's effect on the brain offer new approaches to develop paradigms of objective indices for go-no-go decisions based on a drug's desired actions and/or undesired side-effects. This can help in a more rapid development of drugs and potentially limit the number of subjects required for early clinical assessment of drugs [4,5]. The potential of adopting new technologies, such as fMRI, for drug development is to improve the evaluation of agents in human subjects (volunteers, surrogate models or patients), providing insights into potential efficacy, CNS dosing and side-effects in early-phase clinical trials – before, however, substantial 'drug experience' in large numbers of patients has accrued.

The potential use of functional imaging in drug development is its ability to evaluate the direct effects of a drug on specific functional CNS circuits that underlie the 'behavioral' effects (e.g. analgesia, anxiolytic, sedative, and so on) of the pharmacological entity. These effects can be for primary CNS-acting drugs, as well as for CNS side-effects of a drug being developed for a different system. fMRI measures changes in the hemodynamic response in the brain and provides an indirect measure of neural activity [6–8]. Several recent reviews on functional imaging and drug development provide further details of the technology [9,10]. Although there is great interest in the use of fMRI in drug development, issues of sensitivity, specificity and reproducibility still require further investigation.

The pharmaceutical industry has invested appreciable resources in imaging for drug development. The types of trials involving imaging include fMRI, magnetic resonance spectroscopy and anatomical imaging. Both fMRI and magnetic resonance spectroscopy can evaluate the *de novo* immediate and early effects of a drug after acute administration and the effects of chronic administration (days to weeks).

fMRI offers the ability to detect significant changes in CNS circuits in response to the direct effects of drugs in a small number of subjects [11]. This, coupled with the accelerated approval of therapeutically novel pharmacotherapies by the Federal Drug Administration (FDA), presents additional risks to volunteers participating in research and/or clinical studies in the development of these agents [12]. Consequently, those using imaging as a technique in the evaluation of new drugs must have effective standards to address any side-effects during imaging trials, particularly when the subject is 'in the scanner'. We describe in the following sections approaches that will increase safety of our patients or healthy volunteers.

### Early-phase clinical trials

Early-phase clinical trials evaluate safety (i.e. how well a new drug is tolerated), pharmacokinetics and initial side-effect profile. Administrations of drugs in phase I have specific risks associated with the process, and these are usually conducted in facilities with specialized services (e.g. emergency medical services including

critical care). As noted in a recent review, phase I trials (or early-phase trials) can be considered as opportunities for more than safety evaluation of a drug [13]. In 1997, FDA published new guidelines on the design and terminology used in clinical trials (*Federal Register* on December 17, 1997), including early-phase clinical trials ([www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm](http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm)). In this early-phase context, imaging methods can serve as informative biomarkers, providing an early signal of target engagement or central functional activity (including functional connectivity) potentially informative of likely efficacious dose. Moreover, imaging studies might require fewer subjects to obtain a clear signal of effect from novel drugs. Thus, the use of fMRI in early-phase clinical trials would, at this time, seem to be most beneficial in the transition between phase I (first-in-man) and phase II trials.

### Clinical issues

#### *Healthy vs. patient trials: differences and difficulties*

A clinical drug trial is a carefully controlled study in which healthy volunteers or patients take a drug to determine whether it is safe and effective and the optimal dosage. Although the criteria for enrollment differ, healthy subjects or patients entering into a trial that uses imaging concomitant with drug administration are subjected to different issues that might impact patient safety. This depends on the phase of the clinical trial: phase I trials aim to establish safety and tolerability margins in single dose and sub-chronic dosing, whereas phase II trials usually seek to provide some proof of concept or efficacy signal. Biomarker studies concomitant with or closely following the phase I trials seek primarily to assess target engagement, brain penetration or functional effect to provide confidence that the drug is inducing an expected pharmacodynamic signal and to help define dose selection for efficacy (phase II) trials. If new drugs are evaluated in phase I studies of patients (as opposed to healthy volunteers), patients volunteering for a study will probably be on or have been taking medications that can potentially interact with the drug being tested or they might stop taking their medication, possibly resulting in changes in their condition.

#### *Need for standards for human protection*

In addition to the normal issues involved in informed consent for phase I trials, particularly in patients, additional factors relate to early trials in terms of informed consent. A particular concern relates to the possible expectations of benefit that the subjects might have when enrolling in such studies [14].

Institutional Review Boards (IRBs) vary but have specific federally mandated guidelines to follow [15] (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>). It is only recently that IRBs have addressed requests to perform evaluation of drugs, including anesthetics, in the scanner environment. As such, informed consents must be able to appropriately apprise participants of possible dangers to the novel treatment, as well as the nature of the study in that the study takes place in a restricted and closed environment. Although the nature of the environment in the scanner is obvious, in reality there is little data on the safety of such trials. As such, it might be appropriate to consider an FDA-type program for Imaging Drug Trials to document the cumulative experience as interest and use increases. If

imaging is going to be used in early clinical trials, then the level of uncertainty relating to the use of imaging for novel drug evaluation needs to be defined and provided to volunteers participating in the study.

#### *Patient monitoring during scanning*

Based on the above, it is apparent that protocols for safety monitoring in the scanner environment need to be clearly defined and made operational. The latter is probably the most applicable in terms of the composition of teams that work together performing such studies. Medical coverage consistent with the nature of the study should be supported. For any novel (i.e. first-in-man) drug, we would recommend a minimum of one physician present with access to supporting medical personnel. In most cases, an emergency would probably relate to an allergic reaction that might require interventions by a medical team. Thus, based on medical assessment, the number of individuals in the medical team could vary. For high-risk drugs, the inclusion of a critical care physician, appropriate emergency equipment and high-level patient support equipment immediately outside the magnet should be considered in any protocol involving drugs with potential cardiopulmonary or serious CNS side-effects.

#### *General MRI safety*

A recent review on standards for medical devices in MRI summarizes the issues around the use of these devices, as defined by two working groups that focus on MR equipment, as well as active implants with leads such as stimulators [16]. Known safety issues now have standard protection processes in place in MR imaging [17]. Issues include: biological effects of magnetic fields (i.e. potential deleterious effects to a fetus), risk of metal objects brought into the field (i.e. projectiles), auditory effects (i.e. noise of the magnet) and psychological effects (i.e. anxiety). These and other guidelines are provided at <http://www.fda.gov/cdrh/ode/primerf6.html> and the American National Standards Institute website (<http://www.ansi.org/>). The addition of pharmacological interventions adds a level of complexity to safety in the magnet and could limit the type of behavioral paradigms that can be used; however, most paradigms (sensory, visual, cognitive, and so on) currently used are of short duration (<10 min of scanning time).

#### *Standard monitoring in the scanner*

In most modern MR systems, monitoring equipment for end-tidal carbon dioxide (ETCO<sub>2</sub>), electrocardiogram (EKG), pulse oximetry, respiratory rate (RR) and blood pressure (BP) are easy to use and can be viewed via a monitor outside the magnet. All data are collected on-line for subsequent evaluation of physiological changes occurring as a result of the drug. Several systems offer methods for monitoring patients; however, not all measures (e.g. EKG) are detected with the usual standard outside the magnet or when the magnet is not operating. Other options are also available, including MRI video, which allows observers in the control room to view the subjects directly. Maintaining verbal contact with the subject during breaks in scanning acquisitions is essential for helping to define the clinical status of the subject. Basic questions relating to 'How are you doing?' should be routine (part of a defined protocol) at every break in scanning.

### **Proposed guidelines for patient safety in MRI evaluation of novel drugs**

In any study involving human subject aside from specific regulatory processes, good clinical practice should apply. Such guidelines have been defined by the FDA: 'Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible' ([www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073122.pdf)). International Conference on Harmonization for Good Clinical Practice Guidelines (<http://www.ich.org/cache/compo/276-254-1.html>) make recommendations to achieve unified standards for the conduction of investigations in human subjects for the purpose of registration. The idea is to limit the need for duplication of tests involved in the development of new drugs. In the case of the use of functional imaging in drug development, however, this is a new domain that has not yet achieved consensus in terms of applications in drug development. Nevertheless, studies are being conducted with greater frequency without pragmatic standardization of safety guidelines. As an initial step towards the establishment of specific guidelines and/or GCP related to the use of fMRI, we offer the following suggestions for standard operating procedures (SOPs) in the following domains: medical issues; teamwork; monitoring, infusion equipment; and errors and safety reports.

#### *Medical issues*

**Physician training:** There are several standards that should be applied depending on the nature of the drug infusion. When working with novel agents, it is recommended that two Advanced Cardiovascular Life Support (ACLS)-certified physicians should be present in or near the scanner. At least one physician should be proficient in the use of airway management and preferably trained in critical care (for major side-effects such as anaphylactic shock).

**Co-ordination with pharmacy:** Working with a research pharmacy has several advantages including special packaging of the drug (e.g. over-encapsulating) and protocol process (e.g. blinding). In the event of an adverse event, it is crucial that access to unblinding the drug can be done immediately. Thus, a research pharmacy with 24 h coverage is essential.

**Emergency plans, oversight and practice sessions:** From a safety point of view, the importance of this issue cannot be overstated, and details addressing plans, checklists, rehearsals and physician oversight are detailed below.

**Emergency drugs for common or expected side-effects:** A code cart with most of the emergency medications should be available and have certification of routine checks for content and drug expiration dates. A summary of the medications, dosage and use is noted in Table 1.

**Anesthesia machine:** The American Society for Anesthesia has established specific guidelines for anesthesia outside of operating room (<http://www.asahq.org/publicationsAndServices/standards>). Ideally, an MRI-compatible anesthesia machine should be immediately available. Although not necessary, there is an added safety factor in having an MRI-compatible machine because it can be

TABLE 1

**Evaluation and response of side-effects during scanning**

Adverse reaction	Diagnosis	In-magnet response	Treatment
<b>Gastrointestinal</b>			
Nausea	Subjective	Halt infusion as required	As required to include extraction
Vomiting	Objective	Emergency extraction	Anti-nausea Rx
<b>Respiratory</b>			
Hypoventilation	↓ RR, ↓ O <sub>2</sub> Sat, Δ HR↑ ETCO <sub>2</sub> , ↓ MS, Δ EKG	Encourage deep breathing, cough	As required, to include immediate extraction
<b>Allergic response</b>			
Anaphylactic	↓ BP, ↑ HR, Δ MS, Δ EKG	Extract	Emergency responses: ABC, ACLS, antihistamine, epinephrine, IV fluids and steroids
<b>CNS</b>			
Drowsiness	↓ RR, ↑ ETCO <sub>2</sub>	Stimulate	Extract/Support → ABCs
Seizures	Δ RR, Δ EKG	Extract	ABCs, benzodiazepines, propofol, volatile anesthetics
Anxiety	↑ HR, ↑ RR	Discussion/abort	IV fluids, caloric intake, establish calm environment
Psychosis	↑ RR, ↑ HR, Movement	Extract	As appropriate, Haldol
<b>Cardiovascular</b>			
Hypotension	↓ BP, ↑ HR	Fluids	Monitor → Extract ABC
Hypertension	↑ BP, ± HR Δ	Cease	IV medication, PCP
Arrhythmias	Var HR	Fluid balance	EKG, eval in ED

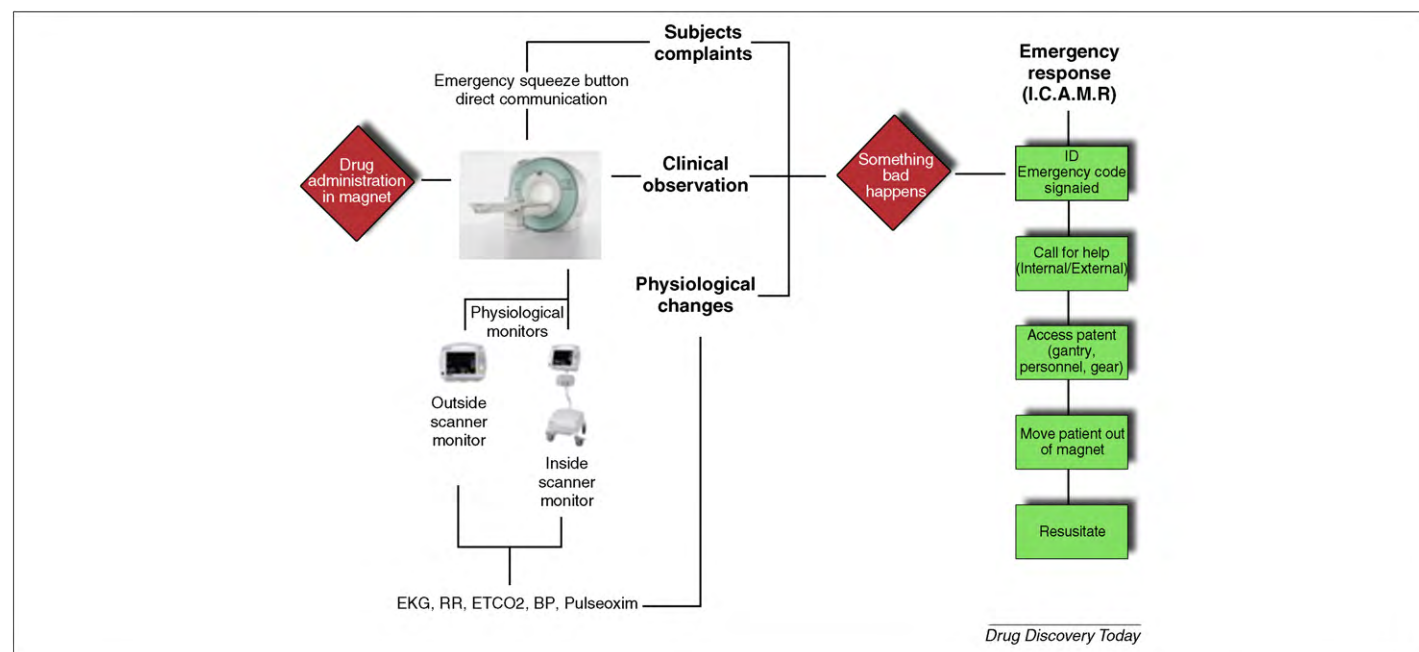
brought directly into the magnet room in urgent and/or acute situations.

**Location of magnet and study:** This is a serious consideration if magnets are located off-site (i.e. not on the clinical premises) or at institutions that do not have specialized emergency care facilities (e.g. code teams). In such cases, it is essential to ensure that the appropriate equipment (including an anesthesia machine or ventilator) is present at the imaging site. In addition, a process to call emergency services (e.g. 911 for Emergency Medical Service) must be in place.

**IRB approval:** All human studies require IRB approval. Given that the risks for new drugs are greater than drugs for which a greater

clinical experience has been accrued, it is important to define clear processes that relate to subject protection. For example, it is essential that the principal investigator or designated physician on the study discusses the protocol with the subject and that appropriate consent process is implemented.

**Response to a medical emergency in the scanner:** Convention requires that any clinical emergency arising in the scanner room might necessitate removing the patient from the magnet and out of the magnet room before initiating any required resuscitation or care (Figure 1). Typical issues can involve respiratory or cardiac compromise and might often occur as a result of an allergic reaction to the medication. Anaphylactic consequences can come



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FIGURE 1

Emergency deployment.



on within minutes of exposure to the drug. Crucial to any emergency situation is reliance upon a standardized approach to medical emergencies (viz. ACLS). In preparing the scanning team, it is imperative that procedures and roles are understood by all (see 'teamwork', above) and regular rehearsals are conducted in and around the scanning facility. Figure 1 demonstrates a standardized approach to managing resuscitation. It is also vital that appropriate emergency equipment and medications (to include oxygen), usually mandated by hospital policies, be verified as immediately available before initiating any scan. Thus, appropriate GCP that applies to MRI operating and safety procedures should be implemented.

As noted in Figure 1, an adverse clinical event is noted. This can be demonstrated as an unexpected change in vital signs or initiated by a subject's complaint. Priorities include patient rescue, call for assistance and initiation of resuscitation. It is imperative that while ascertaining the nature of the issue, the subject is extracted from the magnet room, placed on an appropriate (magnet-compatible) stretcher and brought to a pre-designated area where further emergency treatment can be provided.

**Adverse Drug Event documentation:** For new drugs, the FDA has specific methods for documentation of Adverse Drug Events. This issue is discussed in detail in FDA-issued documents (<http://www.fda.gov/oc/ohrt/irbs/>). Events are categorized as major or minor, with specific reporting and review criteria for each.

### Teamwork

Medical Team Management training formally recognizes poor communications skills and ineffective teamwork as the primary source of many adverse medical outcomes. Teamwork is a relatively new concept in medical history [18] and has been applied in operating rooms and critical care settings in a similar manner to non-medical processes. The importance is to limit preventable errors. It is crucial that the team involved in these procedures understands the technology employed, establish and rehearse functional interpersonal processes, use proper communication procedures and practice emergency responses (e.g. appropriate

removal of subject from magnet, and so on) commonly encountered in acute clinical scenarios. Thus, the importance of SOPs that are well defined, understood and implemented are crucial to patient safety.

**Setting up the imaging team:** An appropriate team needs to be in place for MRI studies. Such a team should encompass the necessary skillsets (e.g. MRI technologist, research assistants, physicists, and so on) that have a working knowledge of the protocol and the magnet environment. Teams that work together on a regular basis are clearly preferable in this type of study. Leadership can optimize the performance of team members by ensuring good communications and risk management, delegating assignments and fostering working relationships. The essential feature is to optimize high performance management of the team in a manner similar to that implemented in more traditional medical settings, such as operating rooms and/or trauma teams [19] (Figure 2).

**Team training:** It is essential to conduct training sessions before placing any subject into the magnet for drug evaluation. Such training sessions should include SOPs for the protocol that include checklists, the individual assignment of responsibilities, rehearsing emergency procedures for extracting subjects from the magnet and movement outside the magnet room to a room with appropriate monitoring and emergency equipment, and appropriate knowledge of location and use of emergency carts support equipment.

**Communications:** In the setting of drug MR studies, some of the team will usually be inside the magnet room and communications might rely either on non-verbal means or the use of a writing board. Specific signals for starting, stopping and emergencies should be defined and understood by all team members. In these studies, someone needs to be responsible for all aspects of the study, most notably for subject safety and protection.

**Checklists:** Checklists enable several important processes to take place, including standardization of procedure; optimization of safety (e.g. checking the infusion system, drug volume or dose); definition of roles; definition of appropriate sign off for specific processes (e.g. drug administration); and provision of a detailed

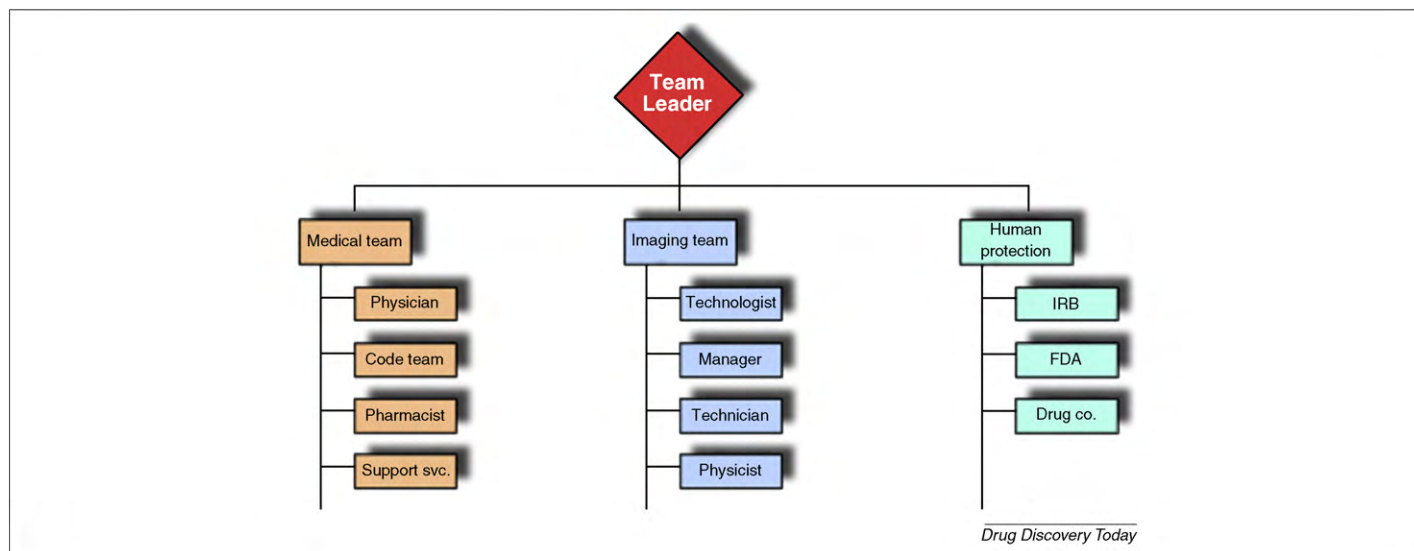


FIGURE 2

Team responsibilities.

log of events for each session. Several studies have indicated improved clinical safety and quality improvement with appropriate checklists [20].

**Test protocols:** Given that imaging procedures are demanding, even in the absence of drug administration, it is imperative to have a program of 'sham runs' of all aspects of a protocol before implementation in subjects or even to consider one or two placebo tests. This allows individuals to implement their specific roles for the team, to function appropriately and to define areas that might need improvement.

### Monitoring, infusion equipment

Standard oversight of equipment service and use is normally carried out by the imaging center under the guidance of the Biomedical Engineering group. Thus, monitoring equipment or infusion equipment should be regularly checked and serviced for optimal operation. SOPs should be implemented that include such things as a maintenance schedule to assure proper function of the equipment.

### Errors and safety reports

The importance of defining and reporting errors via the appropriate channels (e.g. the IRB, FDA or QA) is essential. Analysis of medical errors in this new environment must be collated at a central repository that should provide, upon analysis, an opportunity to enhance the practice of drug evaluation employing this technology. Such systems have been deployed for medication errors [21–23]. Thus, critical event monitoring and reporting to

the appropriate agencies is very important for improving the program of MR in drug development.

### Concluding remarks

As new technologies offer novel and improved approaches to understanding drug effects on CNS systems, developing appropriate safety procedures to ensure subject care in the event of an emergency remains a challenge. In the case of fMRI, the magnet environment offers unique challenges, and systems (e.g. GCP, SOPs) should be in place so as not to compromise appropriate and proper safety oversight and emergency procedures. As this new approach is adopted into clinical trials, there is no doubt that this oversight will need to improve to an agreed upon set of standards. We hope that this 'white paper' puts forward an initial approach that can be built upon by further data experience and additional specialist input. Although the FDA might be interested in the evaluation of smarter approaches to drug development, using smaller populations and, therefore, diminishing the overall risk, the need to apply and adapt human protection standards to meet the challenges of this new technology is obvious. This will become even more important if these approaches are properly validated and perhaps adopted by regulatory agencies. This paper hopes to encourage consensus statements on the issue that should help with IRB standards for safety in testing novel drugs using fMRI.

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