



# Techno freaks: Medical writers and independent imaging review

by Claire Gillow

At the 2008 European Medical Writers Association (EMWA) conference in Barcelona, I felt like a bit of a (techno) freak. Whilst other medical writers described their jobs to nodding heads, my position as a medical writer for an imaging contract research organisation (CRO), either ignited great curiosity, or was dismissed with a confused shrug. In this article I would like to shed light on independent review and the benefits it brings to imaging analysis in clinical trials. I will describe the medical writer's role in this process, and the most important document of the independent review: The Independent Review Charter (IRC).

## History of imaging in clinical trials

The benefits of using imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) in clinical trials are well established. Imaging is non-invasive, and can yield surrogate endpoints quickly, decreasing the time and expense of drug development.

In the past, imaging-related endpoints were derived only from assessments by site radiologists directly involved with the study. As technologies improved, sponsors increasingly relied on imaging for both safety and efficacy determinations and regulatory authorities such as the Food and Drug Administration (FDA) began to question the objectivity and validity of results. At sites, there are several areas of inherent bias causing concern: when a large number of sites are involved in large-scale trials, variability in availability of up-to-date scanners and imaging acquisition capabilities exists. This can result in imaging being acquired in a non-standardised way, significantly affecting measurements and assessments made. Site knowledge of treatment arm, patient information and clinical or laboratory data may affect the objective interpretation of imaging. Reviewer methodology and assessments are not carried out in a standardised way and there is no secure method for recording assessments.

## History of independent review

In response, independent imaging CROs evolved to organise centralised reviews of imaging, to reduce areas of bias and improve the validity of imaging-based results. The feedback from authorities was positive. Current FDA thinking is; *"We recommend that Phase 3 trials include off-site image evaluations that are performed at a limited number of sites (or preferably at a centralized site). In such off-site evaluations, it is usually easier to control factors that*

*can compromise the integrity of the blinded image evaluations and to ensure that the blinded readers perform their image evaluations independently of other image evaluations"* [1]. Independent review results are more reproducible and reliable than site assessments, and independent review may yield unexpected benefits to the public: independent reviewers have reported that due to the exposure and training they receive, their ability to identify and interpret imaging disease characteristics has been enhanced [2].

## Imaging standardisation and site qualification

Imaging CROs develop study-specific Imaging Acquisition Guidelines (IAGs), and send them to sites. IAGs describe the imaging and imaging parameters required, and adherence to IAGs standardises imaging acquisition across multiple investigator sites. Sites must complete a site survey which captures the number and type of scanners, desired mode of image transmittal, image storage capability and the ability of sites to follow the study-specific IAGs. Sites then carry out a dummy run or test transfer, using a 'phantom' or simulated patient. The results of the site survey and test transfer determine whether sites qualify for study participation.

## Quality control

Imaging received at the independent imaging CRO passes through a rigorous quality control system to ensure that imaging parameters, modalities and anatomy are correct. When deviations are found, timely feedback to sites enables errors to be corrected, and future problems avoided.

## Blinding of imaging

Following quality control, imaging is prepared by the imaging CRO for independent review. This may require 'blinding', involving the masking/removal of information which could bias the reviewers, e.g. demographic patient identifiers, site markings, dates of the imaging and indicators of treatment arm. Conversion to the required imaging format, e.g. laser digitisation, may be carried out. The imaging is then ready for independent review.

## Independent reviewers

Imaging CROs have a large pool of reviewers who are experts in their field, and are usually board-certified or equivalent. The reviewers are 'independent' because they have no vested interest in the outcome of the trial, are

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## >>> Techno freaks: Medical writers and independent imaging review

unconnected with the sponsor, and the data they review has been masked of factors described above, which may bias the outcome. The FDA states they are “*readers that are completely unaware of findings of other readers (including findings of other blinded readers and onsite investigators*” [1].

### Independent review sequence, methodology, and assessments

The sequence, methodology and assessments of each review are highly study-specific and will be prospectively discussed between the sponsor and medical writer and detailed in the IRC. For pivotal trials, typically each case will be reviewed initially by two primary radiologists, independently of each other. When one or more overall timepoint assessment(s) differ between the two primary radiologists, assessment by a third radiologist, the adjudicator, is triggered. The adjudicator will agree with all of the timepoint assessments of only one of the primary radiologists. This ‘double read with adjudication’ process improves the validity of results. Primary radiologists are carefully selected, well trained, and tested on simulated cases before the review begins, but discrepancies do occur. It’s the adjudicator’s job to come to an agreement with one of the primary radiologists. The adjudicator does not provide a third assessment as this would defeat the purpose of a double review, reducing the review once again to that of a single reviewer.

During the initial timepoint review, the radiologists are blinded to imaging dates so won’t know which scans were unscheduled. This reduces bias as unscheduled scans are often acquired for suspected progression. The radiologists are also blinded to pending timepoints as seeing how a case develops could bias their interpretation of earlier timepoints. However, following the initial blinded review, a retrospective, global review is now recommended: radiologists will have read-only access to all of their initial assessments, may view helpful clinical information such as cytology results, and can update any of their previous assessments. More detailed clinical and laboratory data may then be presented to an independent oncologist, who will review all of the imaging assessments, see the imaging dates, and may review the imaging. The oncologist will provide the final independent review assessment by providing date of progression, date of first response, date of first complete response and last date of stable disease. This is known as ‘progressive unblinding’ and helps address the need for a comprehensive global review of all information whilst maintaining the objectivity of the initial, blinded radiology review.

In pivotal studies, quality-assurance secondary reviews are carried out, the results of which can be used in calculations of reviewer variability. There are two types of variability tested:

- Intra-reviewer variability tests the variability in a single reviewer’s assessment over time. It is tested by the re-insertion of cases already reviewed into a reviewer’s queue, to observe if they record the same assessments again.
- Inter-reviewer variability is tested by ensuring all participating reviewers read a percentage of the same cases, to compare their assessments. However, there are no published figures for an acceptable range of variability, which can vary significantly depending on the type of review and indication.

### The application / electronic analysis system

The application used by reviewers to record results is built specifically for the study according to International Conference on Harmonization (ICH) guidelines. Reviewers cannot access pending timepoints until they have reviewed and signed off on the present one. This ‘locks’ their assessments so neither they nor others can change them. Various soft and hard edit checks are built-in to ensure that gross or accidental reviewer error is minimised, while providing the reviewer with the freedom to record the assessments they want.

### Investigator meetings

Project managers and the medical owner (usually a radiologist) from the imaging CRO will meet with site investigators and site radiologists to describe how imaging should be acquired and how independent reviewers will carry out their assessments. This helps minimise discrepancy between assessments made at sites and the independent reviewers.

### Medical writers and the IRC

The most important role of the medical writer is to write the IRC, the ‘protocol of imaging’. The IRC is the legal documentation of the review, and should be completed and signed before the first patient comes on study. The FDA state that “*An IRC can minimize bias in radiographic interpretation of the radiological findings and independent adjudication of assessments*” [3]. The IRC is the ‘contract’ between sponsor and imaging CRO as to how the review will be conducted. The independent reviewers are trained according to IRC content, and regulatory authorities will review the IRC in studies for submission. When a special protocol assessment (SPA) is planned prior to the beginning of a study, the FDA recommend that the IRC is submitted for review along with the protocol and statistical analysis plan.

The medical writer will begin by extracting information regarding imaging schedule, assessments and criteria from the protocol. Potential problems regarding image acquisition and analysis may be discovered at this stage and lead to a protocol update. The writer will hold an IRC meeting with the sponsor to discuss how the independent review will be carried out. Following this, medical writers may meet with several imaging CRO departments; medical, operational, application development and quality. This ensures the needs of the client are met within Good Clinical Practice (GCP) ICH guidelines and current FDA recommendations for imaging analysis.

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The IRC is a 40-50 page document written in three drafts, each reviewed by the imaging CRO team and the sponsor. On average it takes 2-3 months to write, but timelines can vary considerably depending on the complexity and urgency of the study. Accelerated timelines are often required when an SPA is planned, or when independent confirmation of screening criteria is required for sponsor patient eligibility decisions.

Similar to clinical study protocols, there is no published guideline on required IRC content and lay-out. However, a meeting between the FDA, sponsor, and imaging CRO representatives at the Drug Information Association Harmonization Initiative last year, yielded an initial, suggested IRC framework.

A typical content of most IRCs is outlined in a poster prepared by my colleagues at Perceptive Informatics for an oral presentation (see Box, [4]).

Once the IRC is signed, medical writers may be involved in writing user requirements, the first step in the building of the application. This document, also signed by the sponsor, describes the analysis form that will be used during the central review of imaging, the data collected, and rules that will be implemented on the form. Once the application is built, medical writers are involved in testing it and will take screenshots for the reviewer manual: a handbook written by medical writers containing step-by-step instructions for the reviewers on how to record their assessments in the application.

At Perceptive Informatics, medical writers work across all fields; oncology, neurology, cardiology and musculoskeletal studies, exposing them to a large array of criteria, methodologies and assessments. They have an important coordinating role between medical, operations, quality, and application development departments. Because of this mul-

tidimensional perspective and range of experience, they are called on to write company stances and standard operating procedures, and are invaluable team members.

### The future of imaging

As the recent surge in early phase imaging shows, new and improved technologies are developing all the time. This will not only improve safety but may flag early indicators of efficacy. With sites recruited globally and India and China developing rapidly, standardisation of imaging acquisition and interpretation is vital. Imaging CROs are experts at ensuring these standards are met. Independent imaging reviews are increasing in their complexity and the need for a well-written IRC is central to success, reflected in the increased recruitment of medical writers by imaging CROs.

With this in mind, perhaps at the next EMWA conference, I won't be the only (techno) freak!

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#### References:

1. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) June 2004 Clinical Medical, Guidance for Industry, Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies.
2. Perceptive Informatics, European Medical Imaging Independent Reviewer Survey, 2007.
3. U.S. Department of Health and Human Services Food and Drug Administration, CDER, CBER, Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.
4. KH Williams, SL Chica, BA Chandler, JM Hicks, The independent Review Charter (IRC): Purpose, Essential Features and Development, poster presented at 6<sup>th</sup> Annual DIA Workshop for Medical/Technical Writing and Document Preparation, October 23-25, 2005 Washington, DC.

Necessary Components of the IRC		
<p><b>SEQUENCE OF INDEPENDENT REVIEW</b></p> <ul style="list-style-type: none"> <li>• When will image be reviewed</li> <li>• Order of reviewers (i.e. radiology followed by oncology)</li> </ul> <p><b>REQUIRED INDEPENDENT REVIEWER INTERPRETATIONS</b></p> <ul style="list-style-type: none"> <li>• Type and description of assessments to be provided by the reviewer</li> <li>• Comparisons to be made between time points, if applicable</li> <li>• Information to be recorded on the analysis form</li> </ul> <p><b>LOCKING OF INDEPENDENT ASSESSMENTS</b></p> <ul style="list-style-type: none"> <li>• How the analysis forms will be locked to prevent modifications</li> <li>• Method for handling situations not specifically addressed in the charter</li> </ul> <p><b>ASSESSMENT CRITERIA</b></p> <ul style="list-style-type: none"> <li>• Identifies the assessment criteria used by the reviewers</li> <li>• Describes any proposed modification to the data</li> <li>• Provides a rationale for the modifications</li> </ul>	<p><b>SELECTION AND QUALIFICATION OF INDEPENDENT REVIEWERS</b></p> <ul style="list-style-type: none"> <li>• How will the independent reviewers be selected and required qualifications (i.e. no financial interest, no participation in the study, no association with the sponsor)</li> <li>• Training of the independent reviewers for the purpose of reviewing images and data for the clinical study</li> </ul> <p><b>INTRODUCTION</b></p> <ul style="list-style-type: none"> <li>• Defines the IRC scope and purpose</li> <li>• Provides an overview of the purpose</li> </ul> <p><b>STUDY BACKGROUND</b></p> <ul style="list-style-type: none"> <li>• Introduces the study</li> <li>• Describes relevant objectives/endpoints</li> </ul>	<p><b>QUALITY ASSESSMENT</b></p> <ul style="list-style-type: none"> <li>• Define the quality control (QC) assessment for images and clinical data</li> </ul> <p><b>IMAGE ARCHIVE</b></p> <ul style="list-style-type: none"> <li>• Defines the types of images received at the core lab and schedule for expected images</li> </ul> <p><b>DEVIATIONS</b></p> <ul style="list-style-type: none"> <li>• Defines how deviations are captured and resolved</li> </ul> <p><b>BLINDING AND LABELING OF DATA</b></p> <ul style="list-style-type: none"> <li>• Describes what the reviewer will be blinded to (i.e. subject confidential identifiers, site interpretations)</li> <li>• Identifies what will be masked on images and clinical data</li> <li>• Defines the process for compliance with local regulatory laws</li> </ul> <p><b>METHODOLOGY FOR DATA PRESENTATION</b></p> <ul style="list-style-type: none"> <li>• Order in which images will be presented (i.e. random, sequential)</li> <li>• Format in which images will be presented (i.e. electronic, hardcopy)</li> <li>• Method for presentation of analysis forms to reviewers</li> </ul>