EUROPEAN JOURNAL OF CANCER 45 (2009) 268–274

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Lessons learned from independent central review

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ARTICLE INFO

Article history:
Received 17 October 2008
Accepted 29 October 2008

Keywords:
Independent central review
Central review
Imaging core laboratory
Radiology review
Central independent review

ABSTRACT

Independent central review (ICR) is advocated by regulatory authorities as a means of independent verification of clinical trial end-points dependent on medical imaging, when the data from the trials may be submitted for licensing applications [Food and Drug Administration. United States food and drug administration guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Rockville, MD: US Department of Health and Human Services; 2007; Committee for Medicinal Products for Human Use. European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) guideline on the evaluation of anticancer medicinal products in man. London, UK: European Medicines Agency; 2006; United States Food and Drug Administration Center for Drug Evaluation and Research. Approval package for application number NDA 21-492 (oxaliplatin). Rockville, MD: US Department of Health and Human Services; 2002; United States Food and Drug Administration Center for Drug Evaluation and Research. Approval package for application number NDA 21-923 (sorafenib tosylate). Rockville, MD: US Department of Health and Human Services; 2005; United States Food and Drug Administration Center for Drug Evaluation and Research. Approval package for application number NDA 22-065 (ixabepilone). Rockville, MD: US Department of Health and Human Services; 2007; United States Food and Drug Administration Center for Drug Evaluation and Research. Approval package for application number NDA 22-059 (lapatinib ditosylate). Rockville, MD: US Department of Health and Human Services; 2007; United States Food and Drug Administration Center for Biologics Evaluation and Research. Approval package for BLA numbers 97-0260 and BLA Number 97-0244 (rituximab). Rockville, MD: US Department of Health and Human Services; 1997; United States Food and Drug Administration. FDA clinical review of BLA 98-0369 (Herceptin® trastuzumab (rhuMAb HER2)). FDA Center for Biologics Evaluation and Research; 1998; United States Food and Drug Administration. FDA Briefing Document Oncology Drugs Advisory Committee meeting NDA 21801 (satraplatin). Rockville, MD: US Department of Health and Human Services; 2007; Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *JCO* 2007(November):5210–7]. In addition, clinical trial sponsors have

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doi:10.1016/j.ejca.2008.10.031

used ICR in Phase I–II studies to assist in critical pathway decisions including in-licensing of compounds [Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *JCO* 2007(November):5180–6; Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *JCO* 2007(August):3407–14; Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *JCO* 2007(June):2171–7; Ghassan KA, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *JCO* 2006(September):4293–300; Boué F, Gabarre J, GaBarre J, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *JCO* 2006(September):4123–8; Chen HX, Mooney M, Boron M, et al. Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: an NCI Treatment Referral Center Trial TRC-0301. *JCO* 2006(July):3354–60; Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *JCO* 2006(June):2502–12; Jaffer AA, Lee FC, Singh DA, et al. Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. *JCO* 2006(February):663–7; Bouché O, Raoul JL, Bonnetain F, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Fédération Francophone de Cancérologie Digestive Group Study—FFCD 9803. *JCO* 2004(November):4319–28]. This article will focus on the definition and purpose of ICR and the issues and lessons learned in the ICR setting primarily in Phase II and III oncology studies. This will include a discussion on discordance between local and central interpretations, consequences of ICR, reader discordance during the ICR, operational considerations and the need for specific imaging requirements as part of the study protocol.

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1. Introduction

Independent central review (ICR) is advocated by regulatory authorities as a means of independent verification of clinical trial end-points dependent on medical imaging, when the data from the trials may be submitted for licensing applications.[1–10] In addition, clinical trial sponsors have used ICR in Phase I–II studies to assist in critical pathway decisions including in-licensing of compounds.[11–19] This article will focus on the lessons learned in the ICR setting, primarily in Phase II and III oncology studies.

2. What is ICR?

ICR is the process by which all radiologic exams and selected clinical data acquired as part of a clinical protocol are submitted to a central location and reviewed by independent physicians who are not involved in the treatment of the patients. The independent physician reviewers (radiologists and clinicians) who may be centrally located or peripherally distributed are blinded to various components of the data depending on the purpose of the review. Blinding may include the treatment arm (or any data that might un-blind the treatment arm); patient demographics; assessments made by the investigator; situational specific descriptions of the scans including whether scans are confirmatory or end of treatment; the total number of exams for a patient (to exclude progression bias); the results or assessments of other reviewers participating in the review process (except during adjudication) and any clinical data that may influence the independent reviewers. In certain review paradigms, the reviewers may also be blinded to the date of the exam, even though this is not the typical approach in oncology since the chronologic sequence of the exams is important to the assessment. To eliminate potential exposure to biasing information, independent reviewers may be restricted from communicating with investigative sites and should not read cases from their parent institution. In addition, they should have no financial interest in the outcome of the trial. In the United States (US), this means being compliant with 21 CFR 54 of the Code of Federal Regulations.[21]

3. Purpose of ICR

ICR can be used prospectively or retrospectively to assess whether patients meet eligibility criteria, such as having progressed on prior therapy or having measurable disease at baseline. It has been reported that even though eligibility requires measurable disease at baseline, up to 9% of enrolled patients do not have measurable disease as determined by the ICR.[5]

The results from an ICR should be used by the sponsor for the statistical analysis and quality control of sites, but should

not be distributed directly to the sites to use for standard of care treatment decisions as medico-legal and, in some instances, regulatory considerations prohibit interaction between the reviewers and the sites with respect to the efficacy assessments. All clinical images should always be interpreted according to geographically established medico-legal standards, and all final treatment decisions should be made by the patient and the physician who has an established patient–physician relationship.

4. Discordance between local and central interpretations

There is a distinct difference in the workflow of image interpretation performed as part of clinical care compared with an ICR. The workflow during ICR is specifically intended to produce greater consistency in image interpretation. However, not all ICR workflows and processes are the same. The differences are based on the group (e.g. academic, cooperative, commercial and independent research centre) performing the review and the reason for the review. As an example, in a commercial Imaging Core Laboratory, there are a limited number of radiologist reviewers dedicated to a specific clinical trial. Each reviewer has received training on the protocol, the protocol specific independent review charter (IRC), and the database conventions for that particular protocol. In addition, each reviewer has analysed test cases to be qualified as a reader. Each reader uses the same image analysis tools and interprets all exams for a particular patient. The most common review paradigm used by a commercial Imaging Core Laboratory for the industry-sponsored Phase II and III oncology studies is to have two primary radiologists independently reviewing each patient's images and invoking a third adjudicating radiologist, if the results from the two primary radiologist reviewers are discordant. The adjudicator's role is to pick the assessment thought to be more accurate, or in some instances, re-read the case if he/she does not agree with the two prior reviewers. In addition, there are generally edit checks and derivation procedures programmed into the database to ensure that response criteria (and the modifications) are consistently followed for all cases. There is also oversight by quality assurance that the read process was conducted according to a quality plan. The advantages of ICR are the uniform application of a structured review process, elimination of some forms of bias and the compilation of the images and image analysis data in one structured format to facilitate regulatory review if required. However, as stated previously, not all independent central review processes are the same, and process adjustments are made dictated by the group performing the review and the purpose of the review.

In addition to the differences in the workflow, there are differences in the datasets used for the review. For example, there is usually limited availability of non-radiographic clinical information for the ICR, compared to the clinical data available at the local site and despite due diligence, for a variety of reasons there may be some imaging studies that are not available for the ICR. Given the differences in the review process as well as differences in the datasets used for the review, discordance between local and central reviews (site/central discordance) is inevitable. Other factors that may lead to site/central discordance are illustrated in Table 1 and include reader variability, failure to compare all prior studies including the nadir evaluation as well as differences in the following categories: selection of target lesions, date conventions, conventions for handling missing data, protocol training and application and understanding of the response criteria.

Outcome differences between the ICR and the local investigator site assessments have been reported in the medical literature and discussed at United States Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) meetings.[5,6,20,22,23,26–28] This is summarized in Table 2. These reports indicate a consistent decrease in the response rate compared with the local investigator site with a variable effect on the time to progression (TTP) end-point. Patient-level concordance results were not detailed in those reviews. Reported rates of discordance at the patient level for progression status between the ICR and the local investigator site assessments have been reported in various US FDA summary basis of approvals to be between 24% and 29%.[6,26]

Some suggestions by these authors to help minimize site/central discordance are for the sponsors to contract directly with the local radiologists that are scanning the patients to ensure that there will be oversight that the scans are performed according to the protocol criteria. In addition, a single radiologist should read all the exams on a single clinical trial patient or, in small trials, all the exams for that particular protocol. Additional site support would come from including more detailed scanning and response-related criteria in the clinical trial protocol. Investigators should try to optimize the communication pathways and working relationship with the radiology departments being used by discussing the clinical protocols on which they are enrolling patients. Radiologists should become more familiar with the response criteria, dating conventions and conventions for handling missing data that are being used for that particular trial. These efforts would encourage the radiologists to provide

Table 1 – Causes of site/central discordance.

Factors influencing site/central discordance
Workflow differences
Limited amount of non-radiographic clinical information
Treatment bias
Lesion selection for evaluation
Missing data and conventions for handling missing data
Inter- reader and intra-reader variability
Date conventions
Variability in protocol training
Understanding of and application of response criteria
Failure to compare all prior studies
Perception of new lesions
Subjective assessment of non-target disease
Tumour type
Drug efficacy
Precision of the response criteria
Complexity of the response assessment

Table 2 – Effects of ICR on response rate and PFS/TTP.

Reference	Response rate (INV) or (ICR)	Effect on median PFS or median TTP
22	25.8% (INV) 15.2% (ICR)	N/A
20	19.1% (C)–30.2 (T) (INV) 9.1% (C)–19.8% (T) 9 (ICR)	ICR data not reported 4.17M (C)–4.86M (T)
23	2.6% LV5FU2–3.2% Ox–13.8% FOLFOX4 (INV) 0% LV5FU2–1.3% Ox–9.9% FOLFOX4 (ICR)	1.9M LV5FU2–1.4M Ox–4.0M FOLFOX4 (INV) 2.7M LV5FU2–1.6 M Ox–4.6M FOLFOX4 (ICR)
26	6.8% (C)–11.7% (T) (INV) 3.6% (C)–6.7% (T) (ICR)	N/A
28	18.7% (C)–34.8% (T) (INV) 11.1% (C)–24.3% (T) (ICR)	N/A
6	17% (C)–32% (T) (INV) 14% (C)–24% (T) (ICR)	18.3W (C)–23.9W (T)(INV) 17.9W (C)–27.1W (T) (ICR)
5	22.5% (C)–41.3% (T) (INV) 14.3% (C)–34.7% (T) (ICR)	3.81M (C)–5.26M (T) (INV) 4.17M (C)–5.85M (T) (ICR)
5	18.3% (INV) 12.4% (ICR)	N/A
27	N/A	6.1M (C)–10.9M (T) (INV) 5.8M (C)–11.4M (T) (INV)

INV, investigator assessment; ICR, independent central review; W, weeks; M, months; C, control arm; T, treatment arm; LV5FU2, bolus and infusional fluorouracil and leucovorin; OX, oxaliplatin; FOLFOX4, bolus and infusional fluorouracil, oxaliplatin and leucovorin; PFS, progression-free survival.

more consistent data to the investigators in a timely, reliable manner for investigator completion of the case report form (CRF).

5. Consequences of using an ICR

Understanding there will be site/central discordance when an ICR is utilized leads to additional considerations relevant to the statistical analysis plan for the protocol. For example, when using independent central eligibility review to determine if the requirements for enrollment have been fulfilled (e.g. if the patients have measurable disease at baseline, if they meet certain disease-specific characteristics required for enrollment, or if they have progressed on prior therapy), it is expected that some enrolled patients will not be eligible based on the subsequent independent review. In this instance, it would be beneficial to adjust the trial's power and sample size to account for an expected lack of eligibility. In addition, it should not be surprising that there will be differences in the number of progression events reported between the local investigator site and an Imaging Core Laboratory. If time to progression (or more generally any imaging-related event driven end-point) is used, this difference should be considered when powering studies, timing interim analyses and/or terminating enrollment, if ICR data is considered the definitive analysis. In addition, there are censoring issues that need to be considered. For example, in a case where the investigator concludes the patient has progressive disease (PD) and therefore removes the patient from the study without performing additional scans, but PD is not identified by the Imaging Core Laboratory, there will be an Imaging Core Laboratory/local investigator site discordance in that PD event. In the statistical analysis based on the ICR, this patient is then censored at the time of the last negative evaluation by the Imaging Core Laboratory. Informative censoring and censoring that is unbalanced across study arms can be problematic and lead to the biased estimates of the end-points as has been described by Dodd et al.[29] For this reason, in that paper the authors recommended that the investigator-based progression-free survival (PFS) end-point be used for the primary analysis of a clinical trial, and the PFS end-point determined by ICR should be used as the basis for an audit, to assure the lack of meaningful bias according to the investigator-based PFS end-point. However, this is an area of continuing discussion and debate as the use of independent review evolves. Suggestions to minimize informative censoring include rapid, real-time confirmation of PD by the central reviewers or requiring objective confirmation of progression by sites prior to a subject being taken off study. It is understood that performing real-time independent confirmation of PD does not completely eliminate informative censoring as it is always the treating physician and patient who are the final decision makers about continuing or changing therapy. Nevertheless, notwithstanding the above, in any clinical study, there should be good documentation detailing the rationale for withdrawing treatment in the absence of radiographic progression.

6. Reader discordance

As mentioned previously, there are different review paradigms that are employed based on the group performing the review, the circumstances and the purpose of the review. For industry-sponsored registration studies conducted by commercial Imaging Core Laboratories, a common practice advocated by the regulators is to involve multiple-independent radiologists evaluating each patient.[25] Other models requiring only one central reader, however, have also been approved by the FDA. One consequence of multiple radiologists functioning as independent reviewers is the potential for discordance between the independent reviewers. This source of

discordance is most commonly based on the radiologist's selection of different target or indicator lesions that each correctly considers representative of the patient's extent of disease. For example, in a patient that has multiple potential target lesions, reader one (R1) may select two lesions in the lung and a single lymph node as target lesions. Reader two (R2) may select two liver lesions and a lung lesion, all different lesions than R1. Each radiologist correctly measures the lesions and calculates the baseline sum of the target lesion dimensions (if RECIST is being used as the response criteria). At the next assessment point, the sum of the target lesions dimensions for R1 decreases by 31%, thus achieving a partial response (PR). The sum of the target lesions dimensions for R2 decreases by 29%, qualifying the patient's assessment as stable disease (SD). In this example it is likely that both the readers are correct, and the results differ because the lesions chosen by R2 change at a different rate than the lesions chosen by R1. Nonetheless, the outcome is discordant. (See Table 3 for an additional example). One method to mitigate this discordance is through the use of a third adjudicating radiologist, who reviews the work performed by both the readers and picks the accepted read as a mechanism of more closely approximating the truth. There are multiple other similar examples where adjudication is forced, by attempting to bin radiologist performance into the categorical variables of Complete Response (CR), PR, SD and PD. Additional factors that also result in reader discordance and influence the number of adjudications include the number of adjudication variables, inter-reader variability in the measurement of lesions, the perception of new lesions, the subjective assessment of non-target (non-measurable) disease, tumour type, drug efficacy, duration of treatment, the number of assessment points, the complexity of the assessment, the precision of the response criteria and the dating conventions that are followed for establishing the date of progression or response. Rates of discordance for progression status between readers at ICR have been reported in one particular study up to 38.6%.[9]

7. Operational considerations

There are operational challenges in performing ICR, with the largest being the site compliance when sending images to the central review facility. Sponsors from the pharmaceutical, biotechnology, cooperative group and academic sectors all work with investigators, who perform various clinical trial functions, including enrolling and treating patients, completing CRFs, hosting monitor visits and obtaining the scans which are sent to the Imaging Core Laboratory or radiology centre for central review. Sponsors can ensure the greatest level of site compliance and operational efficiency by linking receipt of images at the Imaging Core Laboratory to site reimbursement, similar to what some sponsors do for CRF data. In addition, educating and empowering the monitoring staff is an important consideration for the sponsors, as the monitors are regularly on-site for source document verification and can support the sponsor in ensuring that the sites comply with the imaging requirements in the protocol. Real-time image receipt and processing by the Imaging Core Laboratory is extremely important since delays in image receipt translate into missed opportunities for quality control issue remediation. Missing images have accounted for 10–13% of patients not being evaluable as reported in a summary basis of approval and an ODAC transcript.[8,24,26] Key missing exams within a single patient can have major effects on the outcome for the patient. For example, in a patient with target disease in the chest that is not assessed at a particular time point because the CT of the chest is missing, will result in an assessment of unevaluable (UE) at that particular time point, despite the fact that all other exams may be present. Missing data can also affect the number of cases censored,

Table 3 – Illustrating how the selection of different lesions at baseline may result in different response assessments.

Lesion locations		Baseline	TP1
Locations of disease and the lesion measurements			
Liver		20	15
Lung		20	10
Node		20	25
Reader 1	Target lesion #1 – liver	20	15
	Target lesion #2 – lung	20	10
	SUM	40	25
	% Change from baseline/nadir	NA	–38%
	Non-target lesion #1 – node	Present	Increased
	Response	NA	PR
Reader 2	Target lesion #1 – liver	20	15
	Target lesion #2 – node	20	25
	SUM	40	40
	% Change from baseline/nadir	NA	0%
	Non-target lesion #1 – lung	Present	Increased
	Response	NA	SD

TP1 is time-point 1. SUM is sum of target lesions dimensions. In this example, Reader 1 has chosen baseline target lesions in the liver and lung. At TP 1, the lesions have decreased in size to qualify for a PR. There has been a corresponding increase in the non-target disease; however, this was not unequivocal progression. At baseline, Reader 2 has chosen target lesions in the liver and a lymph node. At TP 1 the inclusion of the enlarging lymph node as a target lesion results in the assessment of SD.

the adjudication rate and the rate of site versus ICR concordance, therefore the amount of missing data should optimally be minimized.

8. Imaging requirements

The imaging exams required at all assessment points must be pre-specified in the protocol. It is not sufficient to survey a patient's extent of disease at screening and, at follow-up, only repeat those scans that were positive at screening. It is imperative that anatomic locations where tumours commonly metastasize are evaluated at each assessment point, as patients will progress in sites other than those that were positive for disease at screening. It should be noted the occurrence of new lesions is the most common cause of PD in the RECIST 1.1 database; accounting for approximately 50% of progression events. Exams should be performed at the specified intervals on the calendar basis, such that treatment and other types of delays do not cause imbalance in the timing of assessments across study arms. Technical parameters for the imaging studies should be listed in the protocol, and the sponsor's site selection process should ideally include an assessment of the radiology facilities' capabilities. Despite intense pressure on sponsors to operationally qualify sites to enroll patients, only sites that are able to comply with the specific technical imaging recommendations in the protocol and are willing to participate in the studies with independent review should participate in the study. The importance of site compliance in studies where imaging is a component of the primary analysis cannot be understated. As functional, molecular and more quantitative imaging techniques including volume CT are used, site compliance and phantom qualification will become more of an issue as these advanced imaging techniques are technically more demanding. This will also require medical imaging device manufacturers to develop compatible tools that can be evaluated across a variety of device platforms.

It is not unexpected that investigators may use additional imaging studies that are not required by the protocol to evaluate their patients as part of their standard of care. For example, patients with carcinoma of the lung are often followed with positron emission tomography (FDG PET) scans. This additional off-protocol imaging is entirely appropriate as part of the local physician's standard of care. The FDG PET scan results may be used by the investigator to make treatment decisions; however, the data from the FDG PET scans may not be used as part of the protocol assessment, if, for example, RECIST guidelines are being used. It would be optimal, however, if the standard of care and the clinical protocol were identical, as this would lead to less discordance between the local investigator sites and the Imaging Core Laboratory assessments. If the protocol is not reflective of the standard of care, it is important to distinguish what the investigator may use to follow the patient clinically compared to the imaging studies that may be used to determine response, as defined by the protocol. A specific example is the use of FDG PET/CT. Many sites are currently using combined FDG PET/CT scans to evaluate patients with the assumption that the FDG PET is adequate for their clinical decision making, and the CT component of the FDG PET/CT can be used for RECIST assessments. However, this is not ideal. The technical parameters of the attenuation correction CT scans that are performed for the FDG PET/CT may have lower spatial resolution and higher quantum mottle due to lower radiation dose and a larger field of view. In addition, radiology sites may not use IV or oral contrast for FDG PET/CTs as they would for a dedicated diagnostic CT scan. In general, anatomic assessments performed on attenuation correction CT scans are inferior to anatomic assessments performed on dedicated diagnostic CT scans, and the anatomically based RECIST assessments will not be as accurate when performed on attenuation correction CT scans compared to the information from a dedicated diagnostic CT. Additionally, from an analysis perspective, differences in the criteria for determining response/progression between local and central sites will increase the proportion of informative censoring as discussed previously.[29]

9. Summary

In summary, ICR is a detailed process that enables objective, reproducible (Ford, unpublished data) and independent evaluation of results when the primary study end-points are driven by medical imaging. ICR is used to minimize bias; however, it does not completely eliminate all potential sources of bias and, in some cases, may introduce bias of its own (i.e. through informative censoring). ICR facilitates review by regulatory agencies (if necessary) by accumulating all images in one location and one format. However, operational planning for the issues that exist is required. The implementation of ICR in clinical trials is a process that will continue to evolve.

Conflict of interest statement

None declared.

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