Molecular Imaging CRO Network

Micron's ViewPoint

The Methodology of Centralized Image Interpretation and Roles of an Imaging CRO: An Overview

Contents

Introduction

Centralized image interpretation* is one method to assess both the efficiency and safety of drugs undergoing clinical trials at a centralized facility, for example, interpreting medical images such as CT and MRI at a central location**. The main objective of using centralized image interpretation in clinical trials is to reduce the bias of results and increase their precision by having them evaluated by a central reader independent of the clinical trial sponsor and the medical institution conducting the trial. Depending on the design of the clinical trial, the target disease, the phase of the clinical trial, and the endpoints amongst other factors. With the recent diversification of imaging techniques and the establishment of new efficacy criteria, the best centralized image interpretation style for each clinical trial is desirable. However, this must be balanced against issues of cost and speed in implementing centralized image interpretation.

The number of clinical trials[1] planning to utilize central review is increasing every year (Figure 1). The percentage of new drugs approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for each disease category for which centralized image interpretation is used is reported to be the highest in the oncology area[2]. This suggests that centralized image interpretation is often used by pharmaceutical companies or researchers for the purpose of evaluating the efficacy of antineoplastic drugs. In addition to oncology, image-based centralized image interpretation is also widely used in neurological disease, cardiovascular disease, orthopedics, and other disease areas[2].

Pharmaceutical companies and researchers from medical institutions who plan and design centralized image interpretation should work with the Imaging CROs as needed to design the optimal centralized image interpretation. This paper outlines the environment surrounding centralized image interpretation. Although this paper focuses mostly on the field of oncology, we hope it will be helpful for centralized image interpretation in other areas as well.

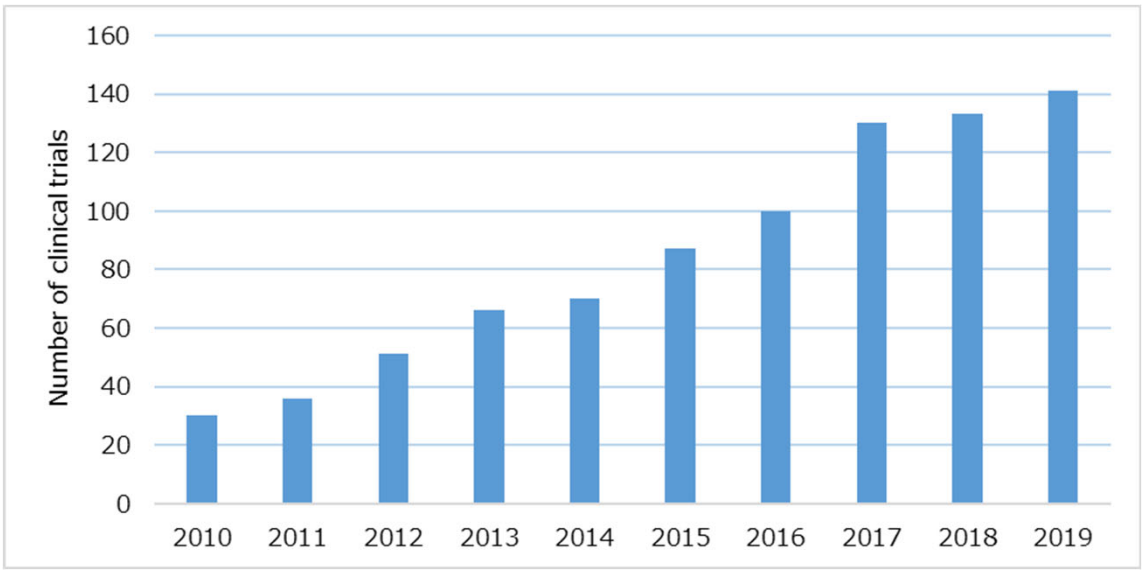

Figure 1. The number of clinical trials with centralized image interpretation

* There are several names such as Central read, Independent Review Committee (IRC) and Blinded Independent Central Review (BICR), but we will consistently use "Centralized Image Interpretation" here.

** In this article, Centralized Image Interpretation is defined as a Centralized Image Interpretation at which efficacy and safety are evaluated by using images.

The Use of Centralized Image Interpretation in Antineoplastic Drug Clinical Trials

From October 2018 to September 2019, there were 32 antineoplastic drugs approved by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, 25 of which underwent clinical trials[3]. Of those, 15 have undergone centralized image interpretation to evaluate efficacy (Figure 2). Although it depends on the phase and design of the clinical trial, there is evidence that central image interpretation was used in many of the clinical trials conducted for approval purposes.

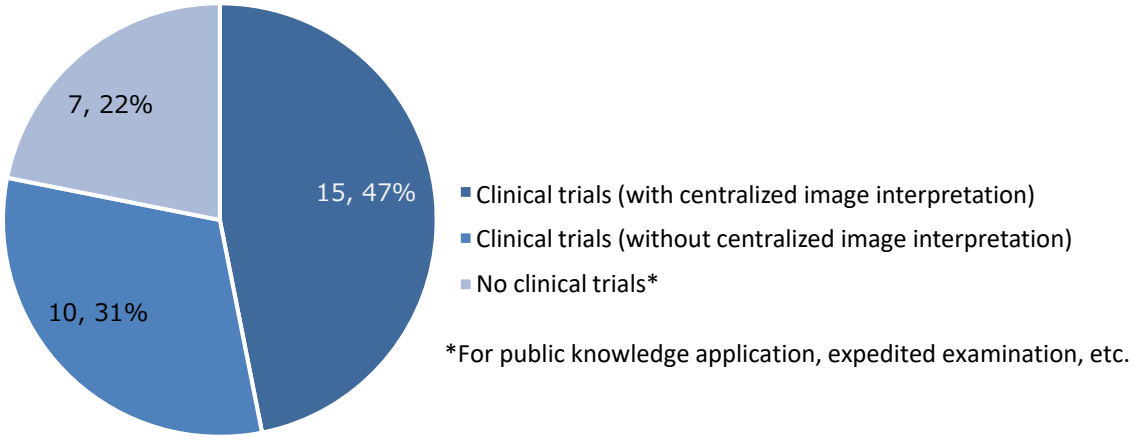

Figure 2. Antineoplastic drugs approved by PMDA from October 2018 to September 2019

The following is an example of the use of a centralized interpretation in a typical antineoplastic drug. Pembrolizumab, an immune checkpoint inhibitor, was the top selling drug in the Japanese prescription drug market in 2019[4]. Although Pembrolizumab was first approved by the PMDA in 2016, a number of clinical trials are currently being conducted to expand indications and for combination therapy and other purposes. A breakdown of the use of centralized interpretation and endpoints in Pembrolizumab clinical trials is shown in Figures 3 and 4[1]. In Phase II trials, the objective response rate (ORR) measures tumor shrinkage, and in Phase III trials, the survival period, such as progression-free survival (PFS) and event-free survival (EFS), are often used as endpoints. It can be inferred that the centralized image interpretation is used in a wide variety of clinical trial situations.

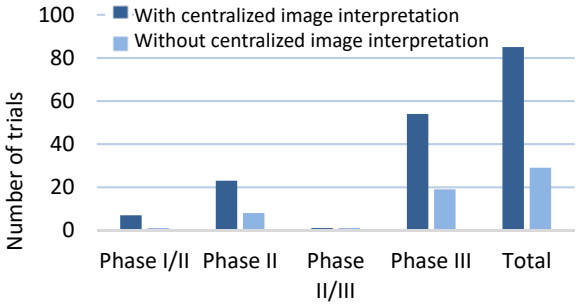

Figure 3. Use of centralized image interpretation in Pembrolizumab clinical trials

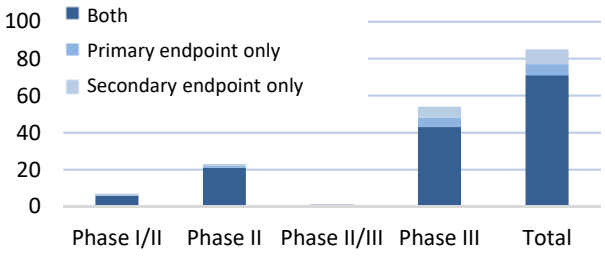

Figure 4. Breakdown of endpoints using centralized image interpretation in Pembrolizumab clinical trials

Perspectives of the Regulatory Agency on Centralize Image Interpretation

In the Guidance for Industry, the FDA recommends the use of centralized image interpretation for clinical trials considering it a necessary process for drug approval, depending on the disease and endpoint (Table 1). The FDA's guidance on clinical trials for the development of antineoplastic and imaging agents also mentions the need for centralized image interpretation. RECIST 1.1 is a guideline for the response evaluation criteria in solid tumors, it also mentions the importance of centralized image interpretation.

Guidance/Guidelines	Descriptions of the Centralized Image Interpretation (Extracts)
Clinical Trial Imaging Endpoint Process Standards[5]	The usefulness of a centralized image interpretation process is determined by the role, variability, and susceptibility to bias of imaging within the trial as well as modality-specific image quality considerations and overall trial design features. Efficacy of the centralized image interpretation is increased for some clinical trials, such as those that might be subject to bias and cannot be blinded, those that use imaging modalities vulnerable to image quality problems, and those that use specialized imaging measures.
Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics[6]	When the primary study endpoint is based on tumor measurements (e.g., PFS or ORR), tumor assessments generally should be verified by central reviewers blinded to study treatments to ascertain lack of assessment bias. Alternatively, a random sample-based blinded central review auditing approach could be used with a detailed auditing plan pre-specified including a strategy to detect potential assessment bias.
Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies[7]	We recommend that Phase 3 trials include offsite image evaluations that are performed at a limited number of sites (or preferably at a centralized site). In such offsite 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.
New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)[8]	Centralized blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome.

Table 1. Description of centralized image interpretation in various guidance and guidelines

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The Purpose of Centralized Image Interpretation

Outcomes of clinical trials should be with minimal bias and maximum precision[9] (Figure 5). However, there are many situations which it is difficult to ensure bias and accuracy, for example, in investigational site's assessments in open-label or multicenter trials. The use of centralized image interpretation assists in achieving clinical trial outcomes with low bias and high accuracy[9].

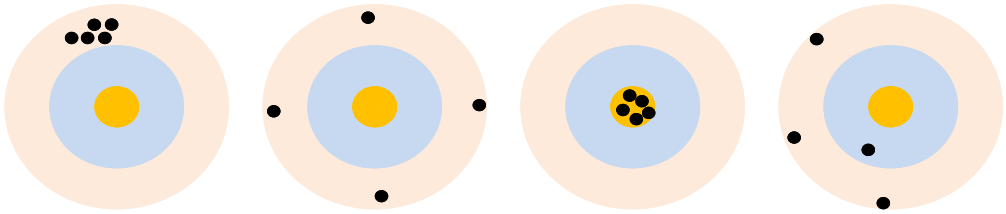

Figure 5. Accuracy and bias

The centralized imaging interpretation methods that minimize bias and maximize accuracy are listed below (Table 2).

	Items	Examples
Bias Minimization	Blinding of allocation information	Blinding of allocation information between study and control groups in randomized controlled trials[9]
	Elimination of information bias	Blinding of clinical information such as adverse events
Accuracy Maximization	Training of readers	Provision of formalized training to reduce discrepancies between readers[10]
	Metrics management of readers	Statistical control methods to manage the performance of the readers, which can be used for training and qualification[11]
	Qualification of readers	Accuracy can be improved by qualifying appropriate specialists for interpretation[12]

Table 2. Minimizing bias and maximizing accuracy in centralized image interpretation

Minimizing bias and maximizing precision not only produces results that are closer to the true value, but also allows for a small sample size to prove the efficacy of the test drug with statistical significance. Because the cost of conducting centralized image interpretation is significantly less than the cost of subject enrollment, some reports suggest that the use of centralized image interpretation can reduce the cost of clinical trials[13].

In clinical trials with centralized image interpretation, the discrepancy between the results of centralized imaging interpretation and investigational site's assessment is often a topic of discussion[14]. Factors that may cause discrepancies in results include differences in interpretation of effectiveness criteria and lesions going undetected. In the case of clinical trials in which only the investigational site's assessment is performed, it is difficult to manage each reader, but with centralized image interpretation, the burden of management is reduced. Another advantage is that it is easier to interpret potential bias in the investigational site's assessment by conducting both the investigational site's and centralized image interpretation[6]. A method of auditing the bias of the investigational site's image interpretation involves having a randomly selected sample of these cases also read by centralized image interpretation[15]. This approach is characterized by the fact that not all cases are read, which may lead to a reduction in the cost of implementing the centralized image interpretation.

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Reading Schemes for Centralized Image Interpretation in Antineoplastic Drug Clinical Trials

When planning and formulating a centralized imaging interpretation, the reading scheme that establishes the results of the evaluation is one of the most important factors to consider. The most common centralized image interpretation reading scheme in antineoplastic drug clinical trials is a reading design known as the "2+1 scheme" (Two Readers and Adjudicator Paradigm) [16, 17]. The 2+1 scheme is a scheme in which two primary readers, who are independent from the investigational site's evaluation and clinical information, each read all the cases, and if there is a discrepancy in the evaluation results, a third reader (adjudicator) makes a decision on the evaluation results (Figure 6). There are two methods of adjudication, and the method of adjudication is selected according to the characteristics of the study.

Forced adjudication:
Adjudicator selects one of the primary reader's reading results.

Open adjudication:
The adjudicator may adopt their own reading results other than the primary reader's reading results.

The 2+1 scheme, in which multiple readers independently read the same case, is an approach that ensures the reliability of the results of clinical trials. The rate at which the primary reader's reading results diverge is called the adjudication rate, and is one measure of the reliability of the reading results. In the RECIST1.1 study, factors such as the timing of the detection of new lesions, the timing of progression of non-target lesions, and measurement errors in target lesions were considered to be factors contributing to the discrepancy in interpretation results[17]. Adjudication rates can be reduced by adequate training, selection of appropriate readers, and management of reader metrics.

In addition to the "2+1 scheme" introduced in this article, there are various other reading schemes, such as "five-session read design," which will be described in detail in the next issue of Micron's ViewPoint.

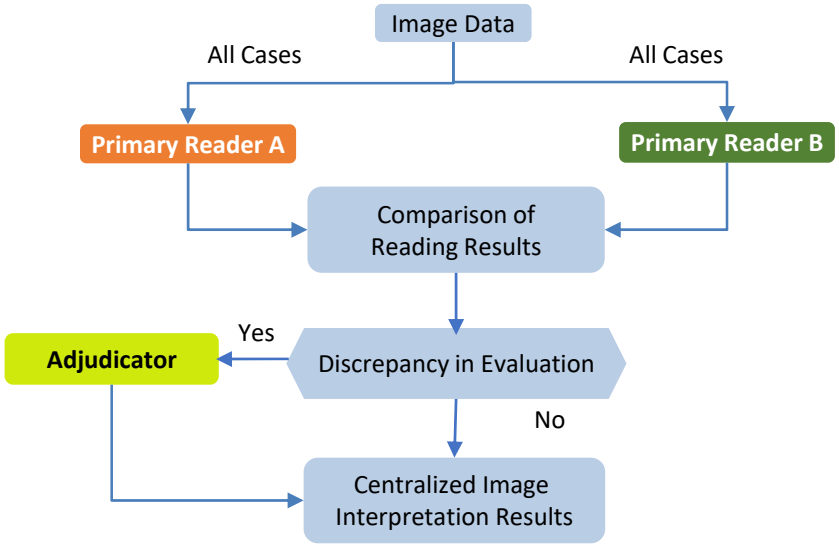

Figure 6. Example of a centralized image interpretation reading scheme in an antineoplastic drug clinical trials

Variation of Centralized Image Interpretation

Figure 7 below shows what should be considered when implementing centralized image interpretation. The items to be considered include the number of readers, the method of deriving results, the method of presenting images and cases, the immediacy of the centralized imaging interpretation, and the readers. Although these considerations depend on the study phase, target disease area, and efficacy criteria, it is important to construct a flexible centralized imaging interpretation design considering feasibility, regulatory strategy, and other factors.

In the next issue of Micron's ViewPoint, we will provide details on the centralized imaging interpretation considerations listed below.

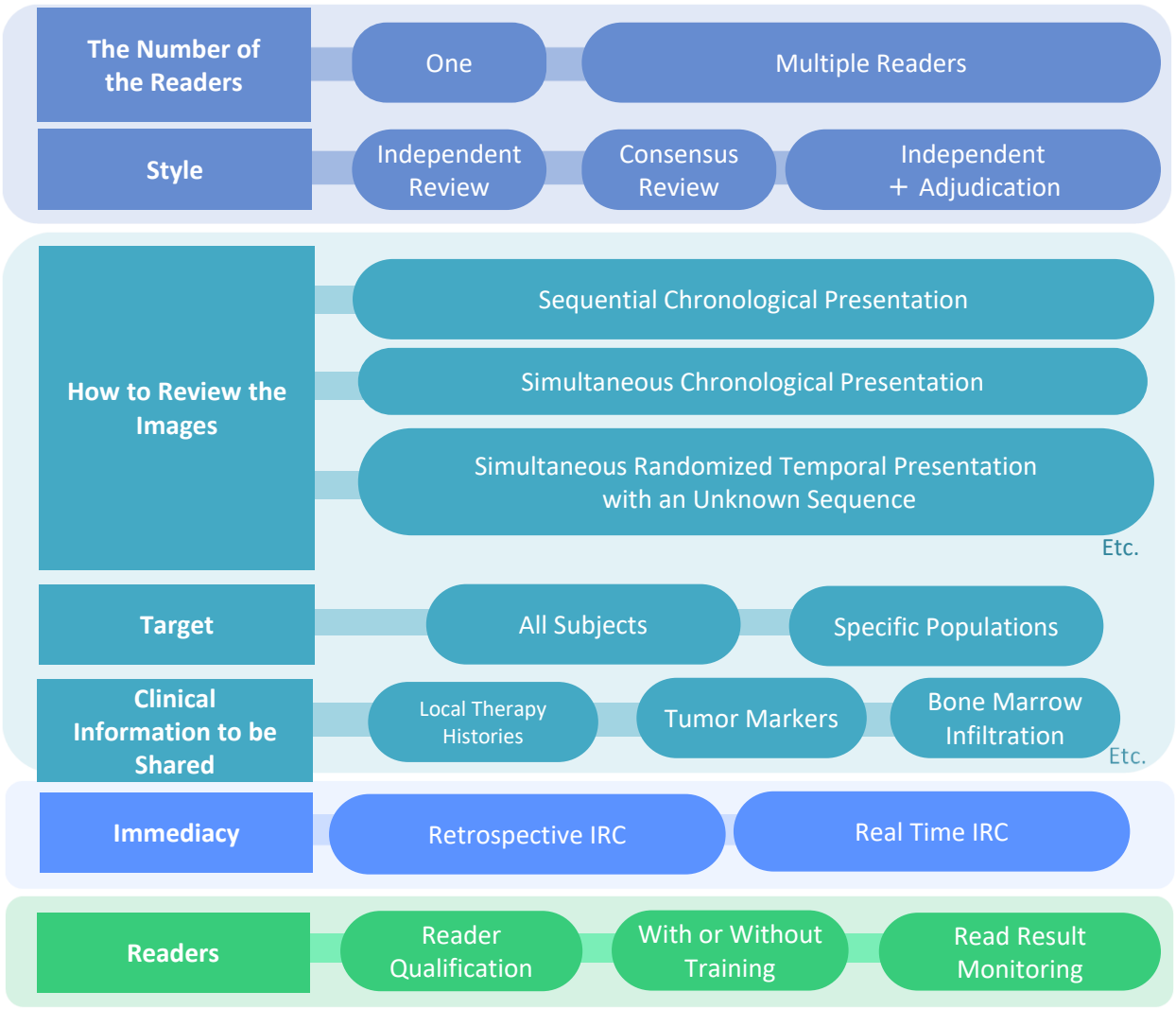

Figure 7. Considerations of centralized image interpretation

Conclusion

With the development of new imaging techniques, therapies, and efficacy criteria, the process of centralized image interpretation is becoming more complex. It is important to consider the centralized image interpretation design in detail at the beginning of a clinical trial in order to obtain reliable and reproducible centralized image interpretation results, to keep trial costs down, and to avoid long study times. In order to develop a centralized image interpretation design, each imaging procedure, from imaging to image transfer, reading, and storage, must be well understood and standardized for each clinical trial. Trial sponsors that lack experience in setting up imaging trials or lack the resources for centralized image interpretation are encouraged to seek consultation and management of a centralized image interpretation design from an imaging CRO with expertise in this area.

As a centralized image interpretation support organization for clinical trials, Micron supports pharmaceutical companies, medical device manufacturers, and facility researchers who plan and conduct centralized image interpretation, and proposes optimal solutions for centralized image interpretation issues.

For consultation and advice on centralized image interpretation, or for training inquiries, please contact us via the contact information below.

Company Overview

Headquarters (Tokyo)	3-13-16 Mita, Minato-ku, Tokyo, 108-0073, Japan Phone: +81-3-6631-3691
Osaka Branch	4-5-36 Miyahara, Yodogawa, Osaka Phone: +81-6-6399-0007
Nagoya Office	7-430 Morioka-cho, Obu, Aichi Phone: +81-562-46-2105
Business Details	1. Development support for drugs, diagnostic pharmaceuticals, and biomarkers with medical imaging techniques and know-how 2. Clinical development support (monitoring, quality control, imaging core-lab, image analysis, support for central review) 3. Support for and PET manufacturing in accordance with GMP 4. Consulting services for clinical development
Website	https://micron-kobe.com
Linkedin	https://www.linkedin.com/company/micron-imaging/
Email	imagingbiomarker@micron-kobe.com

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