Molecular Imaging CRO Network

Micron's ViewPoint

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

Contents

Introduction

Centralized Image Interpretation* is one of the methods to assess both the efficiency and safety of investigational drugs at once at a centralized facility, for example, as a method of interpreting medical images such as CT and MRI at a centralized facility.** Centralized Image Interpretation generally aims to minimize bias and increase precision in clinical trials. By defining the roles and objectives of Centralized Image Interpretation in each clinical trial, Centralized Image Interpretation can be performed more efficiently and effectively. When objectives and roles are well defined, each step of Centralized Image Interpretation (Figure. 1) can be designed in detail.

In this article, we are going to introduce the types of Centralized Image Interpretation and their characteristics according to their roles, which should be known when designing a Centralized Image Interpretation. We hope that this article helps pharmaceutical companies and researchers in medical institutions who are planning and preparing Centralized Image Interpretation.

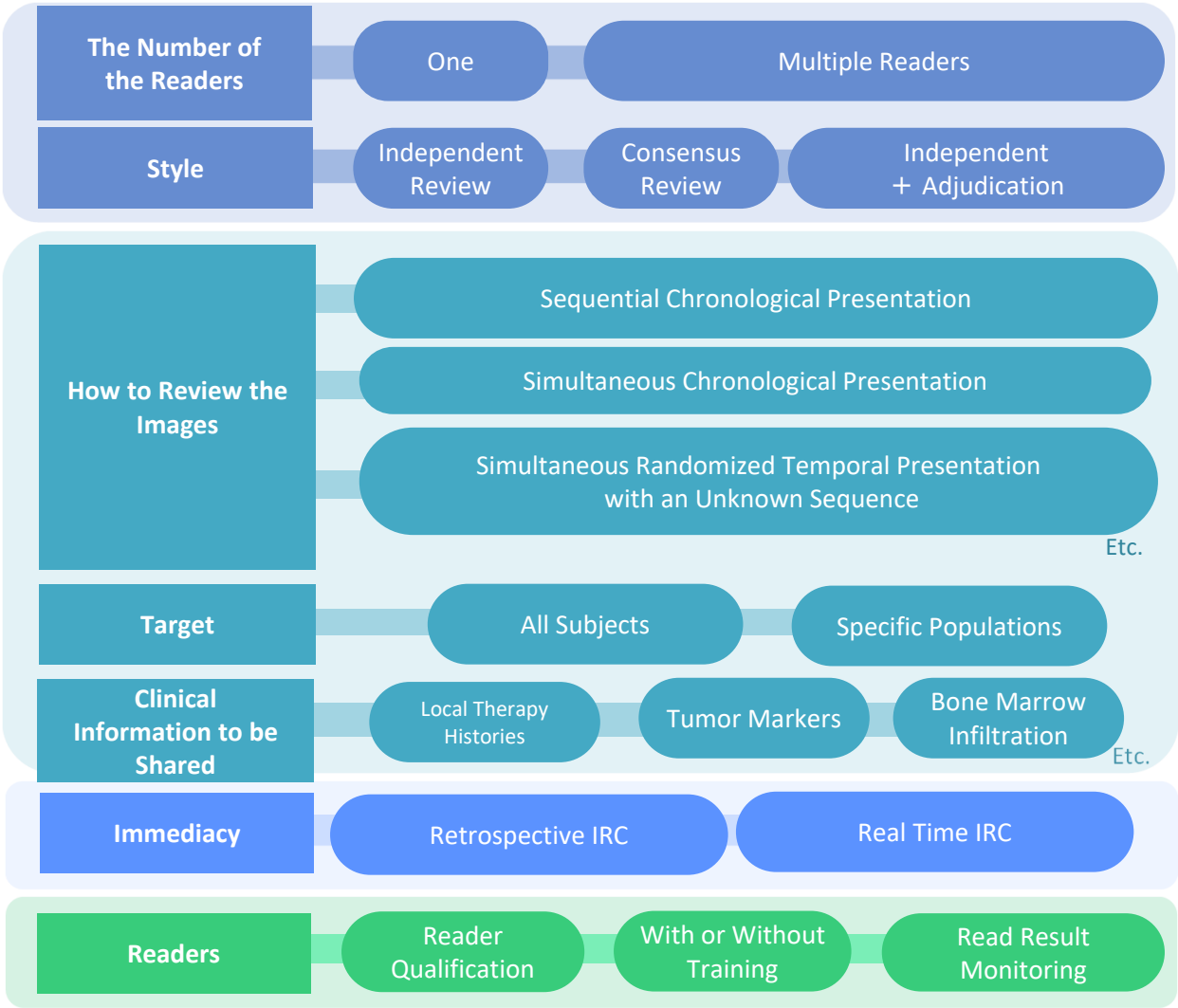


Figure. 1 Considerations of Centralized Image Interpretation

* 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.

Centralized Image Interpretation Variations

Depending on roles expected at a Centralized Image Interpretation in a clinical trial, Centralized Image Interpretation has several variations. It can be roughly classified into 4 categories:

Efficacy Assessment

A Centralized Image Interpretation to assess the response to therapy of an investigational drug is performed. Randomization will be in a blinded manner[1, 2]. It is often used to assess Objective Response Rate (ORR) and Progression-Free Survival (PFS) in clinical trials for anticancer drugs, as well as an endpoint of the cardiovascular and central nervous system fields[3]. The clinical evaluation of radiopharmaceuticals is also performed by doctors independent of the local site[4, 5].

Eligibility Assessment

Eligibility assessment performed by the blinded central readers will prevent subject inclusion errors and increase the reliability of data collected during the clinical trial [6]. Typical cases in which a Centralized Image Interpretation is used to confirm measurable lesions in RECIST 1.1, a response criteria to evaluate response of anticancer drug, clinical trials which require precise quantitative assessment for inclusion criteria (e.g., hippocampal volume measurements in Alzheimer's disease). It also has an effect of reducing excessive requests by investigators for patients to participate in trials.[7].

Confirmation of Disease Progression

Even though an investigator assesses disease progression at the investigational site, the disease progression should be assessed again at the Centralized Image Interpretation in order to confirm whether the investigational site's assessment was performed without any biases and is valid. In case disease progression is assessed at the investigational site prior to the Centralized Image Interpretation's disease progression assessment, the follow-up imaging for the subject will be cancelled. This causes the Centralized Image Interpretation will be discontinued (a censored event). If the investigational site continues the subject imaging and its imaging data reviews until the Centralized Image Interpretation assesses the disease progression to prevent the censored event, assessment bias can be avoided [8]. It is important to establish a system of rapid reading to quickly provide feedback on the results from the Centralized Image Interpretation to the investigational site.

Centralized Image Interpretation Audited Assessment

A Centralized Image Interpretation Audited Assessment is a Centralized Image Interpretation which is conducted with a group that was randomly sampled in order to detect potential biases of the investigational site's assessment. One of the characteristics of this is that not all cases are evaluated at the Centralized Image Interpretation[9, 10].

Rapid Reading

While reviewing images at an investigational site is generally conducted in a short span after imaging, there are roughly 2 types of Centralized Image Interpretation depending on their roles: Batch Reading and Rapid Reading. Batch Reading is a way to interpret images retrospectively after collecting a batch of imaging data. Although it depends on the intention of those who requested the trials, Batch Reading is commonly adopted at an efficacy assessment. On the other hand, Rapid Reading is required for an eligibility assessment, disease progression and safety evaluation of clinical trial continuation. In the case of eligibility assessment, it is necessary to transfer and review imaging data immediately and provide feedback on the assessment results to the investigational site in advance of registration and the randomization of patients. As a reading design of eligibility assessments, other than a single reading model and a 2+1 reading model, there is a method that pools several readers and assigns available readers imaging data in order to make a quick review possible[7].

In the background that a rapid reading is required at PD (progressive disease) determination, there is a problem of Informative Censoring.

Informative Censoring

The main purpose of Centralized Image Interpretation is to reduce the biases of clinical trial results and to enhance accuracy. However, when PFS becomes a primary endpoint, biases resulting from Informative Censoring could occur. If the investigational site determines PD before Centralized Image Interpretation, the patient may be excluded from the protocol remedy and the treatment method could be changed, therefore an additional imaging diagnosis cannot be expected. As a result, it would be impossible to determine PD at Centralized Image Interpretation. This case becomes Informative Censoring, which would make the survival time of the subjects with a certain treatment appear more favorable than it actually is. In the controlled trial, if PD can occur easily in the comparison group, it becomes difficult for Informative Censoring to detect the difference between the therapeutic drug group and the control drug group[8].

In order to reduce the effects of bias caused by Informative Censoring, one of the solutions is to follow the subjects until the Centralized Image Interpretation determines PD. To do so, it is necessary to send imaging data to a Centralized Image Interpretation organization after imaging without delay and feeding back the reading results of a central determination. To build this system, the staff at the investigational site's effort, secure network technology, and environmental improvement that enables doctors at Centralized Image Interpretation to conduct a rapid interpretation are required, and support from experimental and technical a Centralized Image Interpretation organization is expected.

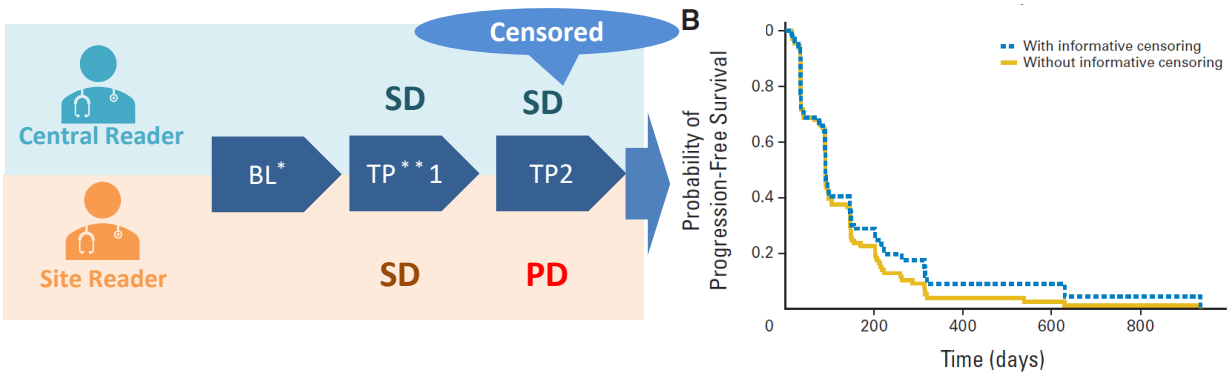


Figure.2 PFS Biases Caused by an Informative Censoring (Reference #12)

* Baseline
** Time-point

Centralized Image Interpretation Audited Assessment

It is said that biases possibly occur during an investigational site review since subjectivity is included in PFS measurement and interpretation of anticancer drugs[4]. The FDA and other regulatory agencies require Centralized Image Interpretation in clinical trials with PFS as the primary endpoint to be able to derive results under reduced bias conditions[4]. A discrepancy between the Centralized Image Interpretation and the investigational site's interpretation possibly occurs. It is reported that approximately 30% of discrepancies can occur at the subject level[11,12]. However, there was also a report that there were no differences in the results between an investigational site's interpretation and a Centralized Image Interpretation, even though the discrepancy rate at the subject level is high[8,13]. Additionally, there is an argument that it might not be necessary to conduct Centralized Image Interpretation on all subjects[14].

According to these findings, a method that conducts Centralized Image Interpretation with random sampling groups[9,10] was considered in order to detect potential biases in review results of investigational site. In this article, we call it Centralized Image Interpretation Audited Assessment. Centralized Image Interpretation Audited Assessment is a beneficial method in terms of the reduction of the sponsor's burden. If the sponsor is considering Centralized Image Interpretation Audited Assessment, they should consult regulatory authorities[4].

The phase 3 (Paloma-3) clinical trial for certification of IBRANCE ® (INN - Palbociclib) by Pfizer was a trial where Centralized Image Interpretation Audited Assessment was conducted[15, 16]. The purpose of the Centralized Image Interpretation was to assess the appropriateness of the primary endpoint (PFS by the investigational site review) analysis results and potential biases among the random sampling groups. The Centralized Image Interpretation was not for the purpose of a replacing method of final analysis, but a supplemental position of PFS. Specifically, by using a stratified random sampling method after patient registration, about 40% of patients from each level according to blind test data at the register were randomly sampled and reviewed at the Centralized Image Interpretation. It was analyzed with the National Cancer Institute (NCI) method and the Pharmaceutical Research and Manufacturers of America (PhRMA method) and it was confirmed that there were no biases in the review results by investigational sites. (For more information on analysis methods and result details, see the application documents, paper, etc.)

The NCI Method

The purpose is to guarantee that there is no major biases in the estimated value at the investigational sites.

The PhRMA Method

The discrepancy between an investigational site and Centralized Image Interpretation is reviewed using the frequency which the investigational site assesses PD prior to Centralized Image Interpretation (early discrepancy rate: EDR) and the frequency which the investigational site assesses PD after Centralized Image Interpretation (the late discrepancy rate: LDA).

		Centralized Image Interpretation	
		PD	No PD
Site's Interpretation	PD	a (a1+a2+a3)	b
	No PD	c	d

$$EDR = \frac{b + a3}{a + b}$$

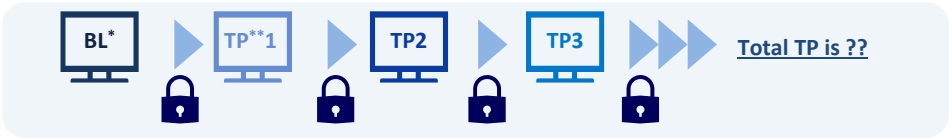
$$LDR = \frac{c + a2}{b + c + a2 + a3}$$

a1: the frequency at which Centralized Image Interpretation's PD and investigational site's PD are at the same time
a2: the frequency at which investigational site's PD is later than Centralized Image Interpretation's PD
a3: the frequency at which the investigational site's PD is earlier than Centralized Image Interpretation's PD

Imaging Presentation Procedures

The order of images to be read by the Centralized Image Interpretation and the timing of locking the evaluation results vary. [17]. Typical imaging presentation procedures are as follows (1-5). Since there are advantages such as study termination information is blinded in anticancer drug clinical trials, 1 is currently the standard method[2].

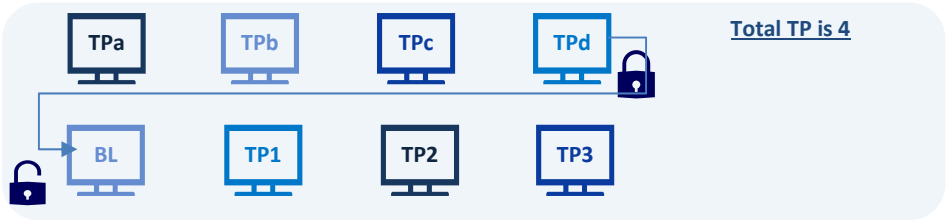
1. The reader **is not informed** of the number of time-points, but images are shown **in order of visit** (time-points). After each visit (time-point) is interpreted, the results of the interpretation are locked.



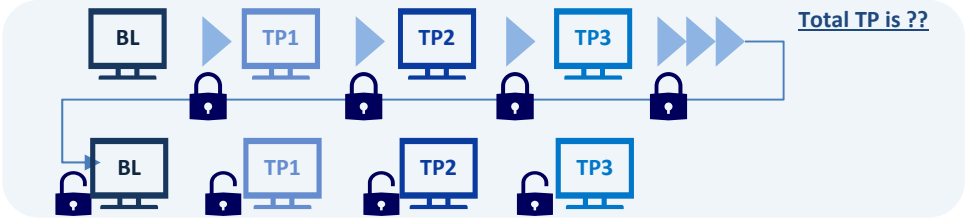
2. The reader **is informed** of the number of time-points and all of the images are shown **at the same time**.

3. The reader **is informed** of the number of time-points, but each time-point (visit number) is blinded. Images are shown **in random order**.

4. The reader is informed the images with time-point **blinded**. The images are shown **in random order**. After that, **unlock**, inform the time-point, and confirm all provided information again.



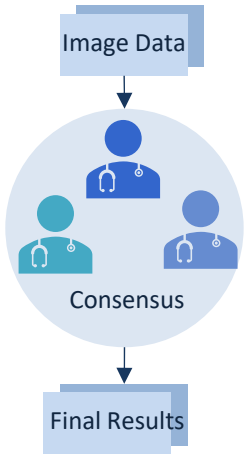
5. The reader **is not informed** of the number of time-points, but the images are shown **in order of visit** (time-point). Once each visit (time-point) is interpreted, the results of the interpretation are locked. After all visits are interpreted, **release the lock**, inform the time-point, and confirm all provided information again.



* Baseline
** Time-point

Centralized Image Interpretation's Reading Paradigm

Depending on the purpose and size of a clinical trial and the difficulty of interpretation, there are multiple ways to derive the results of Centralized Image Interpretation. The typical methods are as follows[2, 8].

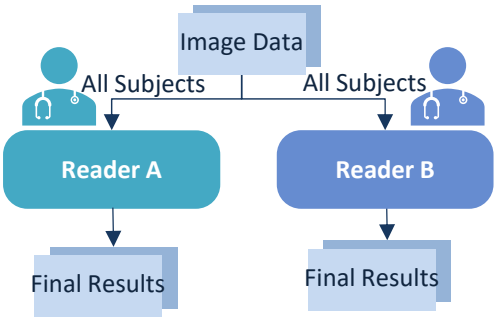


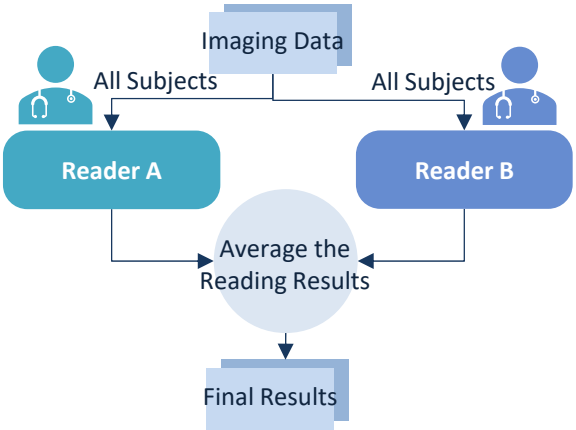
Consensus Read

The readers discuss and achieve a consensus on the reading result for every time point for each subject. While there's no adjudication and no ambiguity, consensus read is applicable to rare diseases, complicated oncological diseases, and small scale researches. On the other hand, there is a disadvantage that is logically difficult to discuss for 3 or more readers. If there is an outspoken person among readers, the result is easily biased by his/her opinion, and it could be practically the same result as that of a single interpretation by one person. Besides, especially when there are a lot of subjects, it is not preferred in large scale trials because the time scheduling of readers is difficult.

Paired Read with No Adjudication

Reader A and reader B interpret all imaging data independently. Neither of them know the other's result and two sets of reading results are derived. This method is often used when results of both the investigational site's and Centralized Image Interpretation are reported. Although it is efficient and the cost performance is good, there is a possibility of confusion in the results if the discrepancy rate is high.





Paired Read with No Adjudication (Average Results)

Reader A and reader B interpret all imaging data independently. If a discrepancy occurs between the two reading results, the results are averaged and consolidated into one single reading result. The advantages are efficiency and cost-effectiveness. On the other hand, it is not possible to determine the causes of deviations (e.g. erroneous input, incorrect interpretation, true deviation due to difficulty in discriminating, etc.), and another drawback is that the audit trail does not show a single image that corresponds to the final data. There are disadvantages of this style.

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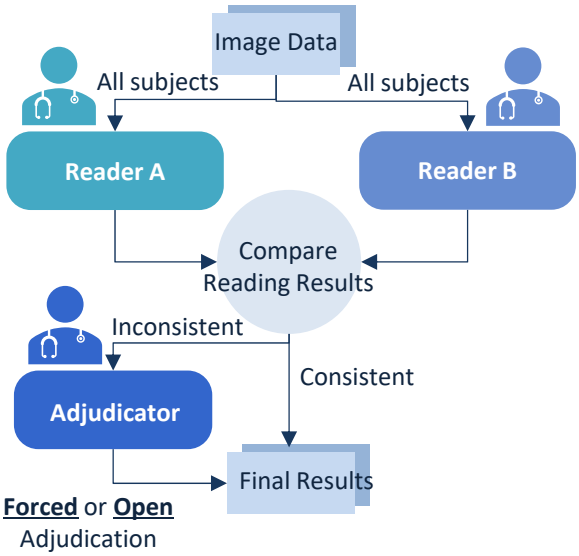
Centralized Image Interpretation's Reading Paradigm



Paired Read with Forced/Open Adjudication (2+1 Reading Model)

Reader A and reader B interpret all subjects independently. If deviations occur between two readers' results:

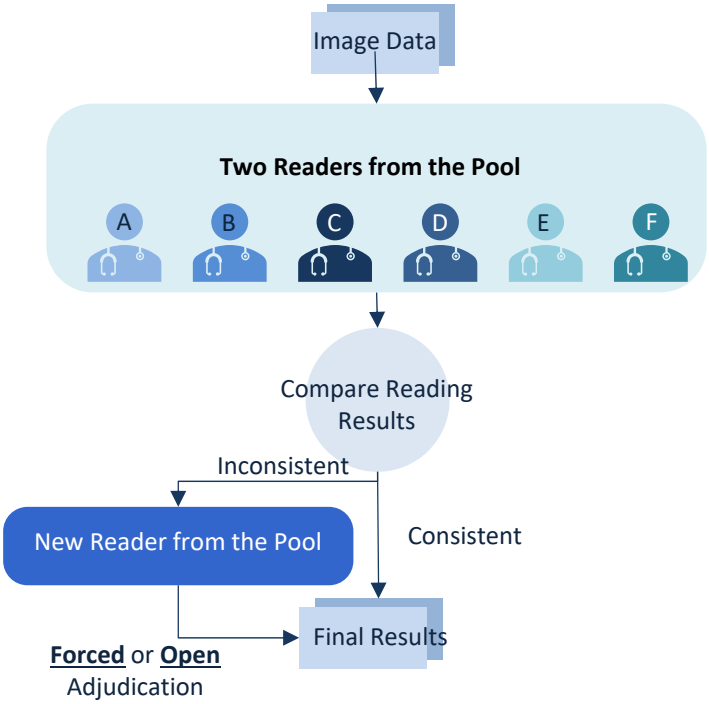
1. Forced Adjudication
An adjudicator will choose the appropriate result of reader A or reader B. All data are ensured as determined by 2 or more readers.

2. Open Adjudication
An adjudicator will choose either reader A or reader B or make reading result by him/herself.

This method is called the 2+1 reading model and it is the most common reading paradigm in phase III trials of anticancer drugs.

Pseudo-Paired Read and Adjudication

Multiple readers are pooled, and two of them who are available at the moment read the images. The combination of readers is not consistent. When deviation occurs among reading results, a reader who has not read the images will determine the reading result as an adjudicator. This method is useful in large-scale trials, for example, when a reading paradigm such as 2+1 reading model is impractical. The disadvantage of this style is the variability dispersion among readers becomes similar to that of the investigational site's reader's and the advantage of Centralized Image Interpretation becomes smaller.



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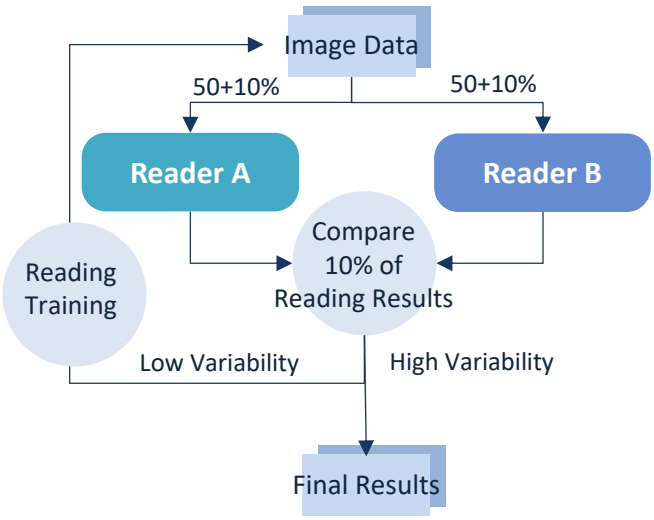
Centralized Image Interpretation's Reading Paradigm



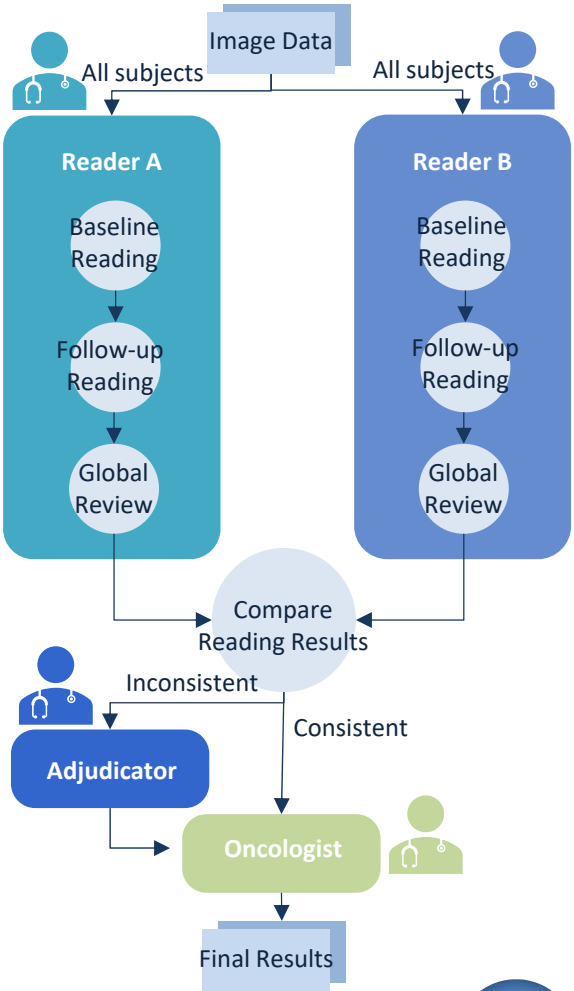
10% Re-reading

Reader A interprets half of the image data and reader B interprets the other half. Each reader also interprets 10% of the image data which was interpreted by the other reader. The readers are not informed that some particular image data was interpreted by the other reader. With this reading paradigm intra and inter reader variabilities can be evaluated. If the variability is small, a measure such as training for readers will be taken.

Global Reading

Global reading is an interpretation design which allows reviewing all images and results and changing reading results.

Firstly, following the 2+1 reading model, reader A and reader B interpret the Baseline and the Follow Up, and then interpret again with chronological order information as global review. At this point, they're not allowed to re-choose target lesions and non-target lesions, but allowed to change the time-point response at each visit. Global review allows for re-evaluations that were mistakenly determined as new target lesions and unequivocal progression of non-target lesions due to a timing of contrast agent administration and partial volume. After the global review, a review result will be determined according to 2+1 reading model.



Conclusion

Due of the development of new imaging technologies, new treatments, and the establishment of new response criteria, the process of Centralized Image Interpretation is becoming more complicated. An appropriate Centralized Image Interpretation design should be selected according to the role that is relevant for the role expected of the Centralized Image Interpretation in the planned clinical trial.

In order to establish Centralized Image Interpretation design, it is necessary to understand every step of an imaging study, such as imaging acquisition, image data transfer, interpretation and image data storage, and standardize each of them for the respective clinical trial. Study sponsors with limited experience in setting up imaging studies or without resources for Centralized Image Interpretation are recommended to ask imaging CROs with expertise to consult and manage the Centralized Image Interpretation design.

As an imaging CRO, Micron supports pharmaceuticals, medical device manufacturers and researchers at medical sites who plan and set up Centralized Image Interpretation and propose the best solution for Centralized Image Interpretation difficulties.

For inquiries of consultations and training for Centralized Image Interpretation, please contact us at the following address.

Company Overview

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