

## The workflow of evaluation of drug efficacy and safety using medical imaging information in clinical trials

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(In final form on June 11, 2016)

**Abstract :** Medical imaging in clinical trials is the essential surrogate endpoint for evaluation of drug efficacy and safety.

Imaging core laboratory builds the comprehensive process of imaging evaluation under the guideline such as Food and Drug Administration (FDA) guidance. DICOM data collection has a rule of evidence-based condition for same image quality by the medical imaging devices such as CT, MRI, PET, SPECT, and the US. DICOM de-identification for clinical trials guided by DICOM standard (The DICOM standards committee Working Group 18 (WG18) wrote Supplement 142).

Detailed DICOM masking rule is identified in this DICOM standard supplement such as de-identification, pseudonymization, and anonymization. Various criteria represented such as Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for drug efficacy and safety have introduced with recently advanced computer assisted lesion management software systems. These big data in imaging clinical trials are managed not only local PACS but also cloud imaging storage and managing with Vendor Neutral Archiving (VNA) and Quality Management Systems (QMS) system.

In this educational paper, we introduce the advanced workflow of evaluation of drug efficacy and safety with application technique of medical imaging and IT cloud solutions.

**Keywords :** Imaging Core Laboratory, lesion managing, RECIST1.1

### Introduction

The endpoint of medical imaging approach in clinical trials or clinical study between this about ten years has changed dramatically. The FDA (US Food and Drug Administration) requests the IRC (Imaging Review Charter) about imaging in clinical trials, the role of imaging becomes an important endpoint in the evaluation of various clinical treatments.

In Japan, medical imaging is the essential scientific, quantitative contents for clinical research and development. Japanese regulatory agency falling under the category of FDA is Pharmaceutical and Medical Devices Agency (PMDA). PMDA described that medical imaging considers one of essential technology and evaluation of biomarker. “Headquarters for Healthcare Policy” and “Japan Agency for Medical Research and Development (AMED)” were established as centers of research and development. The agency, as an institution that plays a central role in research and development and the environmental improvement of the medical field, this until the aggregate budget on research and development in the medical field. The agency makes the management of consistent research from the primary stage to practical application. The number of approved drugs available for the first time in Japan has significantly increased. However, still, many of basic researchers are not able to perform their research adequately reflected through translational medicine into clinical advances. The International Organization for Standardization is ahead in the process of quantitative assessment using imaging technologies of its value by the evidence to evaluate the safety and efficacy of such as an anti-cancer agent for cancer therapy and neurodegenerative disease therapeutic agent for such as, Alzheimer’s disease, multiple sclerosis.

The Clinical Trials Imaging Market expected to reach USD 981.53 Million by 2020, at a CAGR of 6.25% by MarketsandMarkets according to a new market research report” Clinical Trials Imaging Market by Modality (CT, MRI, PET, Ultrasound, Echocardiography, X-rays). Quantitative treatment response criteria using imaging biomarkers are currently an indispensable component of patient care and discovery of new agents. Response Evaluation Criteria In Solid Tumors (RECIST) is a standard published rule that defines when tumors in cancer patients improve, stable disease, or progress disease during treatment.

In recent years, lesion management system becomes an essential tool for evaluation efficacy and safety with long-term treatment of disease. On the other hand, development of infrastructure to storage and distribute the information on drug efficacy and safety is an important issue. Multicenter, due to large-scale clinical trials and international clinical trials, the case number of registrations over the thousands of cases. Image data is dramatically increasing and the risk of data pollution enough to become large-scale increases. Therefore, it is one of the efficient methods to use the DICOM cloud network system which eliminates drug lag using such as server installation and software installation secure.

In this review, to introduce the working flow of evaluation methods of response treatment and the concept of lesion management flow of clinical trial.

### 1. The role of imaging in clinical trials.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) explains guidelines two purposes of clinical trials should be distinguished : (1) assessment of the efficacy and safety of a

treatment and (2) assessment of the relative (comparative) efficacy, safety, risk/benefit relationship or utility of two treatments [1]. Imaging is the important biomarker and endpoint to assess of both two aspect efficacy and safety in clinical trials. A biomarker is a characteristic that are objectively measured as indicators of normal biological processes, pathological changes, or pharmacologic responses to a therapeutic intervention [2]. Imaging biomarker means the quantitative indexes extracted by medical imaging contents such as CT, MRI, PET, US or X-rays. The endpoints of a clinical trial include the objectives study. The endpoint is the characteristic value that reflects the patient's condition and judgment in clinical trials. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumor.

## 2. Workflow of imaging clinical trials based imaging charter

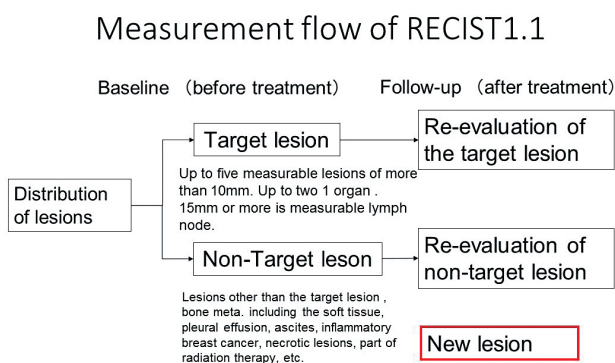
Imaging Review Charter (IRC) is a regulatory document drafted to define and describe all aspect of procedures that an imaging core lab follows when processing image data and conduction the independent read. IRC is a guideline required by FDA [3].

The workflow based on IRC is as follows :

1. Design imaging protocol referenced target disease.
2. Build study start-up team and decide expert radiologists or medical doctors specialty of the disease about clinical trials.
3. Making communication procedure between the facilities performing clinical trials and imaging core laboratory.
4. Data collection blinding of subject and site identification (DICOM masking).
5. Secure data backup and storage system using robust PACS system.
6. A plan for the “Mock” read by radiologists or specialized physicians before the start of independent reads.
7. Check consistency among readers and detailed adjudication criteria to settle discrepancies between readers.
8. Submission of a result of criteria reports and final analytic report.

### 2.1 Design imaging protocol referenced target disease.

Response Evaluation Criteria in Solid Tumors (RECIST) is the most widely accepted method to objectively assess response to the solid tumor. RECIST were modified based on data and outcomes from a variety of clinical trials [4]. Fig.1 shows the schematic flow of distribution of lesions in RECIST1.1.



**Fig.1** Distribution of lesion in RECIST1.1

RECIST 1.1 defines the size of measurable lesion of longest dimension in the plane of measurement with a minimum size of 10 mm by CT and MRI. Lymph node defines of assessment as follows :

Normal if short axis < 10 mm, “measurable” if short axis  $\geq 15$  mm, and “non-measurable” if short axis < 10 mm, “measurable” if the short axis is 10-15 mm. The size of the lesion is necessary to decide the suitable slice thickness of CT or MRI scan on RECIST. Additionally, Imaging core laboratory should create a procedure manual of image data acquisition for any criteria in clinical trials. Many scan parameters can have direct or indirect effects on identifying, the stable drawing the region of interest ROI of the lesion and measuring tumors. To reduce this potential source of variance, we effort to made to have as many of the scan parameters as possible consistent with the baseline.

The following parameter is a recommendation of parameter setting for consistency with the baseline study via image data acquisition of computed tomography by QIBA [5].

1. DICOM image header.

Image Header recordings of the key parameter values facilitate meeting and confirming the requirements to be consistent with the baseline scan. The reason checking DICOM tag is for the minimum scan duration requirement is to permit acquisition of an anatomic region in a single breath-hold, thereby preventing respiratory motion artifacts or anatomic gaps between breath-holds. This provision applies to scanning of the chest and upper abdomen, the regions subject to these artifacts and is not required for imaging of the head, neck, pelvis, spine, or extremities.

2. Total collimation width

Total Collimation Width defined as the total nominal beam width, NxT, for example,  $64 \times 1.25$ mm. Wider collimation widths can increase coverage and shorten acquisition but can introduce cone beam artifacts which may degrade image quality. Imaging protocols will seek to strike a balance to preserve image quality while providing sufficient coverage to keep acquisition times short.

3. Nominal Tomographic Section Thickness (T)

The term preferred by the IEC is sometimes also called the Single Collimation Width. It affects the spatial resolution along the subject z-axis.

4. Pitch

The pitch is a term used in helical CT. It has two terminologies depending on whether single slice or multislice CT scanners are used The pitch is a term used in helical CT.

5. FOV

Scan field of view is an actual area of interested by the CT scanner.

Display field of view is the reconstruction field of view. Reconstruction Field of View affects reconstructed pixel size because the fixed image matrix size of most reconstruction algorithms is  $512 \times 512$ . If it is necessary to expand the field of view to encompass more anatomy, the resulting larger pixels may be insufficient to achieve the claim. A targeted reconstruction with a smaller field of view may be necessary, but a reconstruction of that field of view would need to be performed for every time point. Pixel size directly affects voxel size along the subject x-axis and y-axis [5].

6. Parameters influenced to the stability of pixel values.

The balance of HU between time points and its effect on pixel measurements is necessary for consistency with all follow-up. The parameter index influenced HU value are tube voltage, tube current, reconstruction kernel type, the injection timing of contrast media and so on.

## 2.2 Designing of the independent review board.

Building study start-up team for the central reading committee is essential for precision evaluation of drug efficacy and safety in clinical trials. The most common read design focuses on efficacy when the progression of response as captured objectively in an imaging read is a primary or secondary endpoint and usually, includes the following sessions [3].

1. Baseline/Screening lesion selection and measurement
2. Sequential lesion measurement and incremental radiological response assessment in follow-ups
3. Approving final selection and measurement of lesions.

Fig.2 shows the 2+1 reader allocation model. If there is disagreement on the main points of assessment, a third reader reviews the first readers' responses and selects the assessment with which is in greatest agreement.

## 2.3 Data collection blinding of subject and site identification (DICOM masking).

DICOM masking rules, in the past, IRB (Institutional Review Board: Review Board) is often determined the state of DICOM masking based on HIPAA (Health Insurance Portability and Accountability Act: Accountability Act and the Health Insurance). However, the anonymization of DICOM has not completed yet. This fact sometimes lead to fatal errors of privacy and a major obstacle of Clinical Trials. DICOM rules experts, so do masking service with sufficient explanation and training satisfying requests from pharmaceutical companies. Radiological Society of North America (RSNA) recommended

international standard DICOM Editor and CTP (Clinical Trial Processor) for masking for clinical trials. DICOM masking rule describes in Digital Imaging and Communications in Medicine (DICOM) Supplement 142: Clinical Trial De-Identification Profiles [6].

Typical Characteristics of DICOM image masking software for clinical trials have functioned as follows:

- Series/Images level masking can generate both masked and masking its copy of the original image (s)
- All UID is editable and changes ID.
- Events that occur during the anonymization process records as audit trail function.
- Go and return between both De-identification and Re-identification.

Fig.3 shows the tool for DICOM both de-identification and re-identification for clinical trial (DICOM Anonymizer PRO, Neologica, Montenotte, Italy).

## 2.4 Regulatory compliance of imaging evaluation tool and network system.

Following the receipt of DICOM image on archiving media, an imaging core lab will quality control (QC) this data for protocol compliance and prepare the data for the independent read. In the United States, HIPAA, known as the Administrative Simplification (AS) provisions, requires the establishment of national standards for electronic health care transactions and national identifiers for providers, health insurance plans, and employers. As an example of the global trend towards strengthening privacy laws, extensive amendments were introduced to Japan's data protection law, "The Act on the Protection of Personal Information" ("APPI"), on September 3, 2015. The APPI will become active within the next two years. While the details on the manner of its implementation remain unclear, the following are some noteworthy amendments to the law [7]. This rule will apply to PACS (Picture Archiving and Communication Systems) for the cross-border transfer of

## Assessment flow of reader allocation for oncology trials

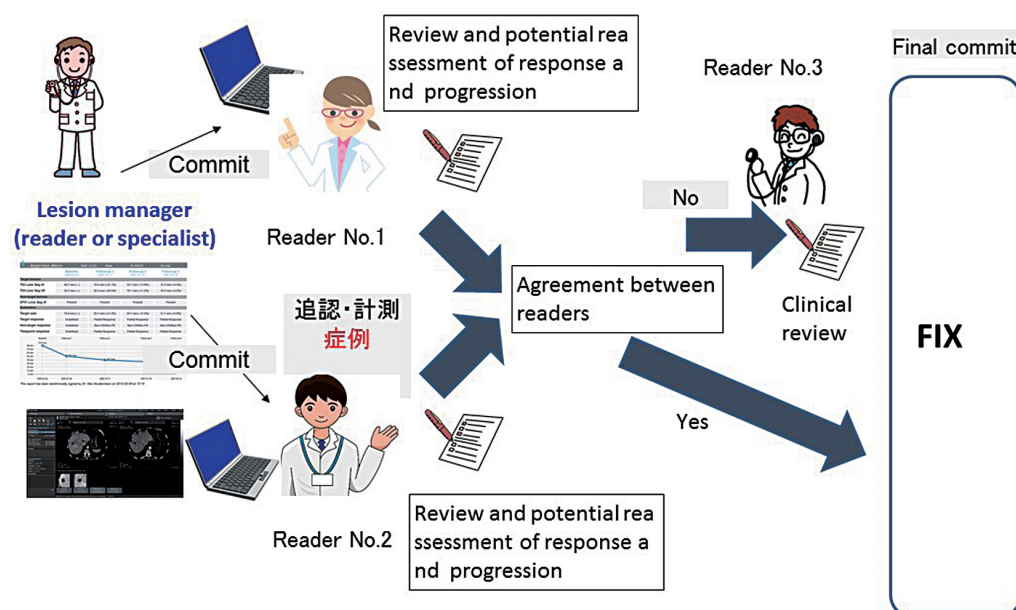
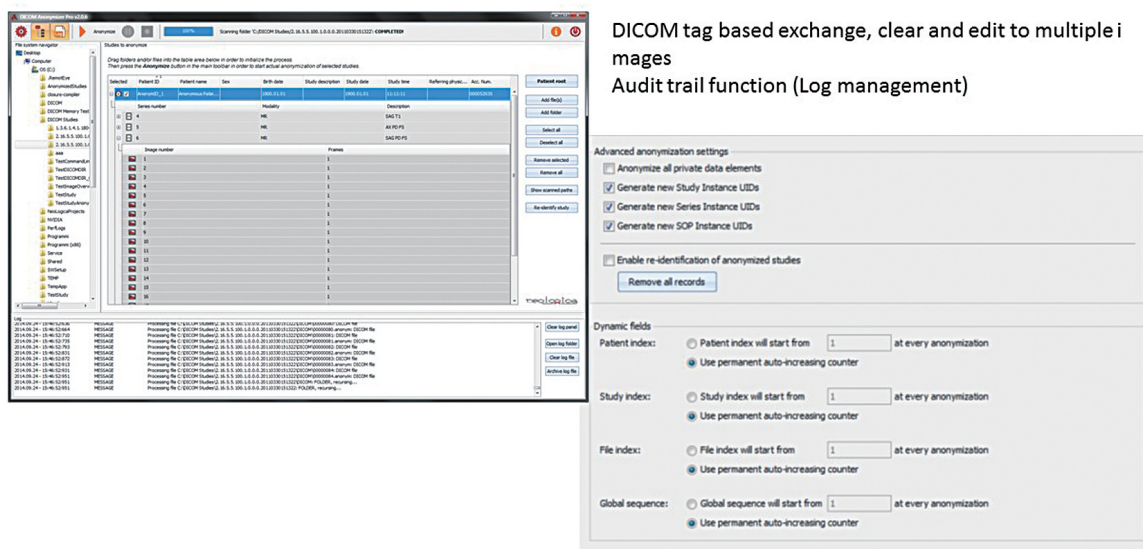


Fig.2 2+1 reader allocation model for an example of oncology trials.

## DICOM Masking tool (De-identification and Re-identification)



**Fig.3** DICOM Masking tool (DICOM Anonymizer PRO developed by Neologica, MONTENOTTE (SV), Italy)

personal data. The amended APPI provides that personal data may be moved to a foreign country only when the country has a legal system that is deemed equivalent to the Japanese personal data protection system, or to a third party which undertakes adequate precautionary measures for the protection of personal data, as specified by the Committee.

Additionally, supporting internal database audit is a need in clinical trials. According to the recent cloud storage and management produce the electronic signature and record.

21 CFR Part 11 (Part 11), the United States FDA: as the Federal Law 21, Section 11 of Article (Food and Drug Administration Food and Drug Administration) is promulgated March 1997, came into effect the same year in August [8]. It is that electronic records and electronic signatures can not be tampered with, has requested and that the change of the history remains. The Imaging Chater should consider the following issues regarding electronic records for the independent read to be in compliance with 21 CFR Part 11(3):

- Security controls and system access
- Audit trail

- Protection of records for a given retention period
- Ability to supply copies of documents during an inspection
- Developer and user qualifications
- System documentation control
- Controls over information transmitted over an open network.

Software for criteria evaluation and measure support is different from general 3D/4D DICOM Viewer Workstations.

Fig.4 show the differentiation between 3/4D DICOM Workstation and Lesion Management Workstation. Most of the function of RECIST1.1 or other criteria in 3D/4D DICOM Viewer Workstation is a one of plugin application that can time series recode and measurement. However, there are not compliance with 21 CFR part 11 overall response and the best overall response export function compatible CDISC or SAS file in most of the general 3D/4D DICOM workstation.

On the other hand, clinical trials use workstation compliant with GCP is build for the just purpose for evaluation of drug efficacy and safety. There is a reasonable function of clinical trials.

### Differentiation between 3/4D DICOM Workstation and Lesion Management Workstation

#### 3D/4D DICOM Workstation



- DICOM Audit Trail
- DICOM Database Conformance
- One study DICOM View Core
- Real Time Volume Rendering
- Segmentation for rendering
- Plugin into DICOM Viewer
- DICOM-SR

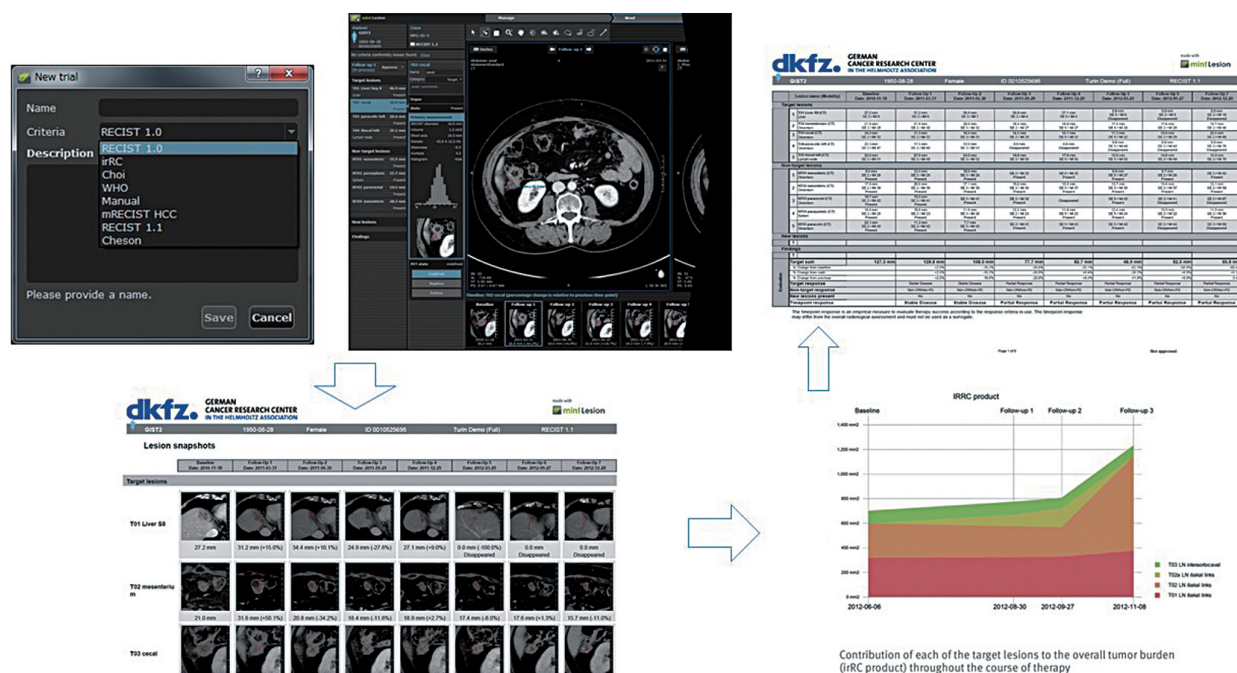
#### Lesion Management Workstation for Clinical Trial



- CSV-GCP applied to Clinical Trials
- Clinical Trials Database Conformance
- Time series lesion manage core
- DICOM Measure based Axial DICOM
- Segmentation for measurement
- Plugin of Additional Variable Criteria
- 21 CFR part 11 DICOM-SR

**Fig.4** Differentiation between 3/4D DICOM Workstation and Lesion Management Workstation





**Fig.5** Example of design and workflow figure of lesion management workstation for clinical trials. (mint Lesion, Mint Medical GmbH, Dossenheim, Germany)

Fig.5 shows the example of design and workflow of lesion management workstation for clinical trials.

Typical standard criteria on lesion management workstation is as follows :

- WHO Criteria (In 1981, the first tumor response criteria as a standard for assessing treatment response [9])
- RECIST Criteria (In 2000, the new guideline after WHO Criteria to evaluate the response to treatment in solid tumors [10])
- RECIST Version 1.1 (In 2009, including the assessment of lymph nodes and the use of newer imaging technologies such as multidetector CT and magnetic resonance (MR) imaging [4])
- Choi Criteria (In 2007, Choi *et al* developed new criteria for gastrointestinal stromal tumors (GIST), which assess change in size or a change in density of target lesions [11])
- Modified RECIST (In 2005, a panel of experts on HCC convened by the European Association for the Study of the Liver proposed that estimation of the viable tumor with contrast-enhanced imaging should be the optimal method for assessing treatment response. The new criteria, referred to as mRECIST, were subsequently endorsed by the American Association for the Study of Liver Diseases [12])
- PERCIST (In 2009, metabolic response as a leading indicator of tumor response may be even more predictive of outcome than morphologic criteria using PET, PERCIST criteria were proposed in 2009 to refine and validate quantitative approaches to monitoring PET tumor response [13])
- Cheson Response Criteria (In 1997 and 2007, Lymphoma is another disease in which there has been the development of specific tumor assessment criteria. Again, this is due to disease-specific complexity, wherein the basic assessment of interval change in size alone may not accurately reflect disease status[14, 15].)
- Immune-related Response Criteria (In 2009, conventional

response criteria may not allow adequate assessment of the activity of immunotherapeutic agents [16].)

- Immune-related Response Criteria based of RECIST1.1 (irRECIST based on RECIST1.1, irRC [17].)
- RANO criteria (In 2010, assess response to first-line treatment of glioblastoma [18])

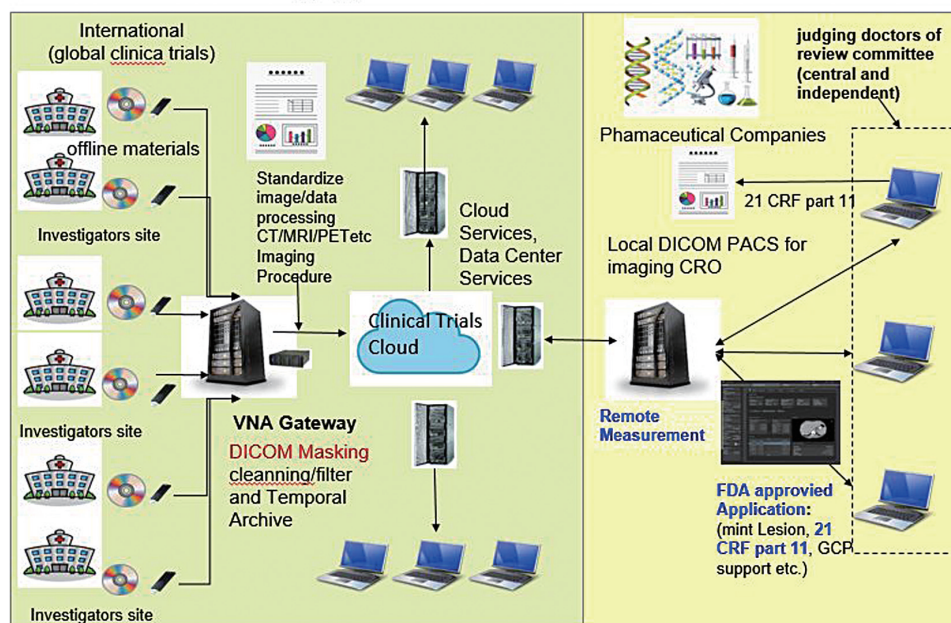
They are the commonly selected criteria in a different type of cancer disease. The number of criteria increases and will revise fitting with flexible diagnostic devices. Manual input work for calculating overall response using, for example, Excel is no more accurate evaluation method. Software for lesion management is essential for the accurate assessment and converting multiple criteria comparison.

Fig.6 show the example schematic network for image and document delivery system for clinical trials. Recent cloud storage and application introduce the support service of clinical trials. Advanced fast and large scale cloud network is tolerable of international clinical trials. DICOM cloud is also convenient for data communication among investigators site, sponsor site, and imaging core laboratory with compliant such as HIPPA and 21 CFR part 11.

### 3. Conclusion

The evaluation of medical imaging in clinical trials has standardized and developed in the recent years to build a growing industry like imaging CROs or imaging core laboratories. Priority of drug efficacy and safety evaluation by imaging in the pharmaceutical industry in Japan become higher year after year. To know the standard workflow of criteria, computer system validation rule, GCP based guideline action, and secure network believes in contributing to the development of medical care greatly.

## Cloud Imaging Communication in Clinical Trials



**Fig.6** Example schematic network for image and document delivery system for clinical trials

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