Molecular Imaging CRO Network

Micron's ViewPoint

Kobe Cardiovascular Core Laboratory

Introduction on the Service for Clinical Trials Using Intravascular Imaging Endpoints

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Background

In the field of cardiology, there have been innovations in intravascular treatment for decades. For example, the first drug-eluting stent (DES) was invented in the early 2000s and the technology has been advancing generation after generation ever since. These innovations stimulated clinical studies developing for approval and for other purposes.

In the clinical studies for intravascular treatment, coronary imaging such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) have been applied as assessment methods for imaging endpoints. The signal of IVUS is able to penetrate below the luminal surface, so the entire internal structure of an artery can be imaged, whereas OCT uses low-coherence light and has higher resolution detection ability. With such detective ability, IVUS and OCT are used in both qualitative analysis (e.g. classification of coronary plaque) and quantitative analysis (e.g. stent and lumen area/volume). In recent years, the IVUS and OCT have become important imaging outcome measurements in the cardiovascular clinical trials (Figure 1).

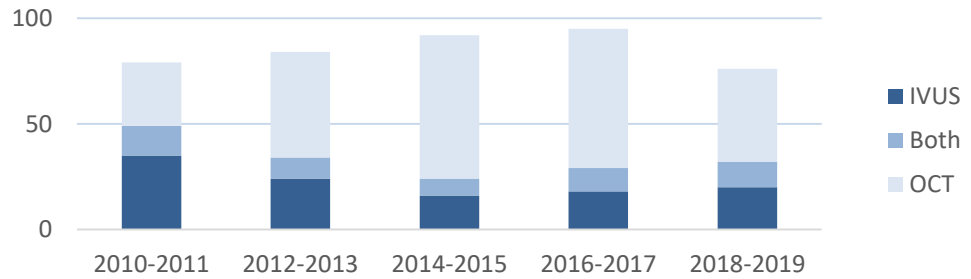

Figure 1. The number of global cardiovascular clinical trials using intravascular imaging endpoint assessed by IVUS and OCT by study starting year (Data download from clinical.gov on 19May2020)

Clinical trials using intravascular imaging endpoints have stimulated demand for independent imaging core laboratories. The cardiovascular department of Kobe University has been performing intravascular analysis academically for years. As the analysis number keeps growing, Kobe University searched for a partner to accomplish high efficiency analysis. Meanwhile, Micron, a contract research organization focusing on imaging technologies, had gained experience in serving as a core laboratory in other fields such as anti-tumor effect assessment. Based on this, Micron and the cardiology department of Kobe University started collaborating in 2012, and today, together we serve as the Kobe cardiovascular core laboratory.

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Kobe Cardiovascular Core Laboratory

Kobe cardiovascular core laboratory (KCCL) is located in Japan. Started in 2012, KCCL served as independent imaging analysis for clinical trials using intravascular imaging endpoints assessed by IVUS (intravascular ultrasound) and OCT (optical coherence tomography).

As the intravascular analysis examples (figure 2) show, KCCL can provide both quantitative and qualitative analysis results for clinical trials for approval, post-market investigation, or other purposes.

In order to maintain analysis validity and reliability as a independent core laboratory, KCCL has developed its quality control system including standardized analysis procedure. The following pages will introduce more about KCCL, including the implementation of the standardized analysis procedure, team management, achievements, and benefits of using KCCL from the point of view of a sponsor or investigator.

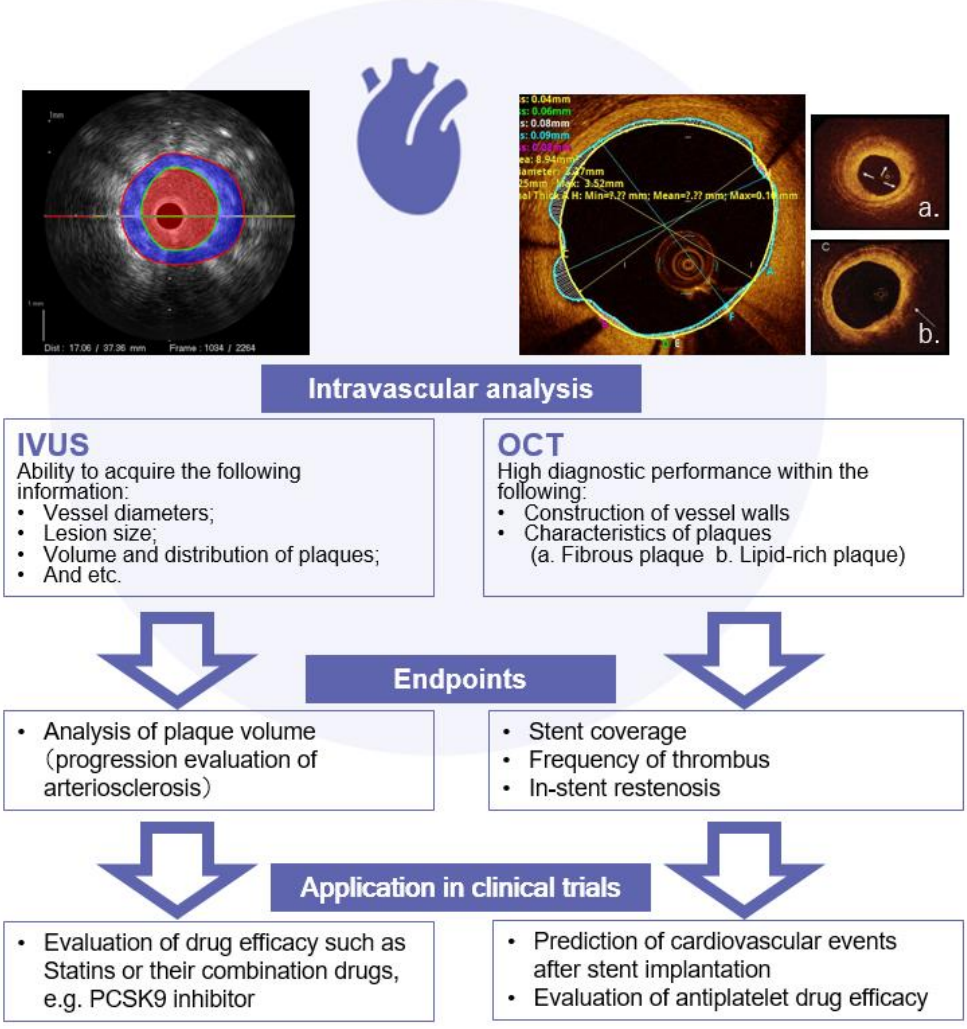

Figure 2. Analysis examples of Kobe cardiovascular core laboratory

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Implementation of the Standardized Analysis Procedure

- Procedure Based on Collaboration of Academic Research and Imaging CRO

KCCL consists of the cardiology department of Kobe University and the imaging CRO Micron. The cardiology researchers of Kobe University have provided Micron with cutting-edge information in cardiovascular imaging technologies and specialty support. Likewise, Micron's standard operating procedure in compliance with GCP (Good Clinical Practice) and the FDA guidance for imaging endpoints, as well as high expertise in supporting imaging clinical studies, has played an important role. Together, the cardiology researchers and Micron have developed the standardized analysis procedures and management systems as an independent intravascular core laboratory.

- Implementation in Clinical Studies

Before starting analysis for a clinical study, Micron will adjust the analysis procedure to adapt to the specific study as necessary. As the figure 3 shows, testing analysis will be conducted and the result will be checked to confirm if any feedback is necessary. Any changes to the procedure will be supervised by researchers at Kobe University. After, the modified procedures will be fixed and followed throughout the study. The analysis results of the study data will also be checked by the cardiology researchers to confirm the reliability.

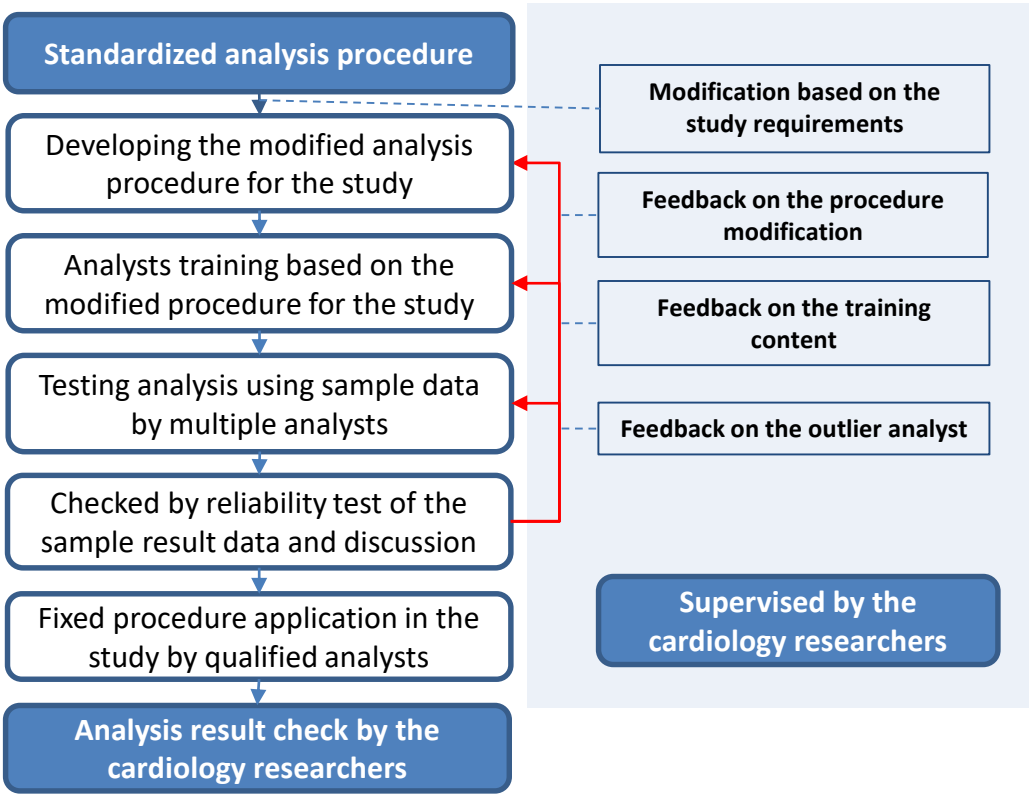

Figure 3. The simplified workflow of implementation of standardized analysis procedure of Kobe cardiovascular core laboratory

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Cardiology Team Management

In order to maintain analysis with reliability and high efficiency, KCCL has established a dedicated cardiology team in Micron with multiple experienced analysts. The team originally started by hiring staff with high-expertize in cardiology and then receiving direct training from the cardiology department of Kobe University. As their analysis experience has grown, the cardiology team has developed a set of requirements and managing methods for the team members.

- Analyst Qualification and Training

Intravascular analyst candidates are selected according to their qualifications. They will accept the training courses based on the standardized analysis procedure. After completing the training, the candidates will need to pass an operation test (challenging cases included) to acquire certification. For each study, the analysts will receive additional training on the dedicated analysis rules before starting analysis. In addition, the analysts in the team will take training courses and tests on a regular basis to maintain the analysis stability.

- Reliability Test

Before starting analysis for a new study, KCCL will conduct testing analysis using sample data as necessary. The inter-observer and intra-observer variability will be tested to be relatively low to assure the reliability of the analysis. The figure 4 below shows an example of the reliability test (by the ANOVA gauge repeatability and reproducibility analysis) result based on testing analysis by three analysts. By using the reliability test, the analyst whose result failed to meet the criteria can be identified and responded to accordingly. The analysis procedure or analyst training for the study can then be adjusted.

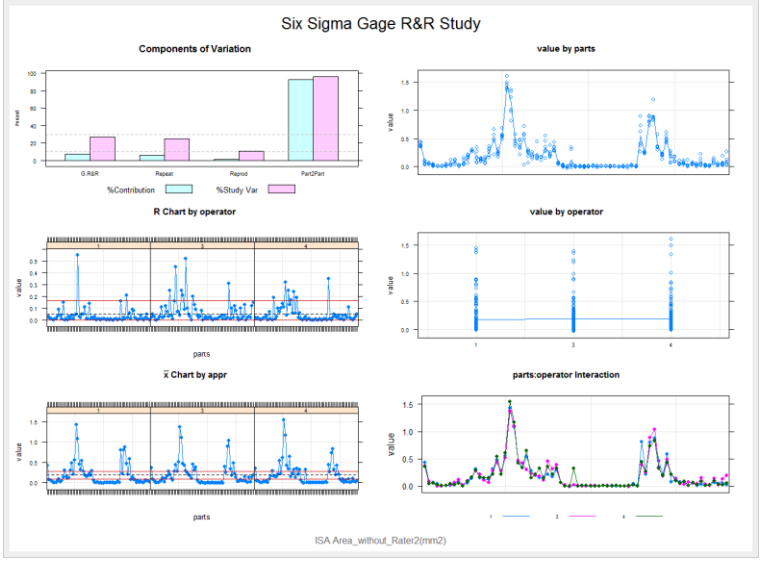

Figure 4. An example of Micron's reliability test using Six Sigma Gage R&R study of testing analysis data by three analysts

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Accomplishments

- Analysis experience in 18 clinical studies using intravascular imaging endpoints in the past 5 years
- Experience in clinical studies for approval (Stage 2 and 3 clinical trials), post-market investigation, and other purposes
- Analysis total number of over 2000 cases by the imaging modalities of IVUS and OCT in the last 5 years (Figure 5)

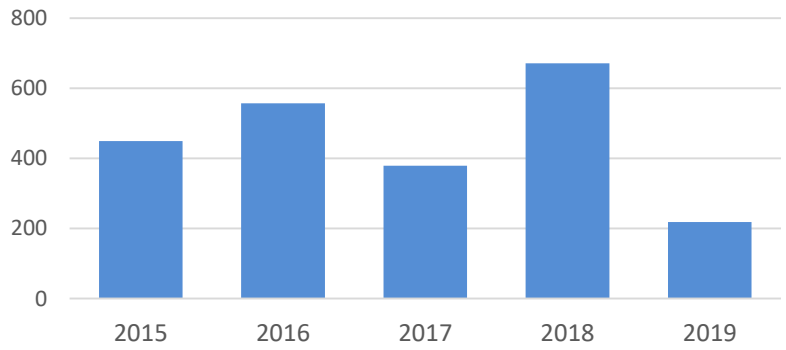

Figure 5. KCCL's analysis case number of IVUS and OCT by year

Benefits of Using KCCL

- Independent Assessment Reducing Assessment Bias and Variability

Being independent from the clinical site, the assessment bias due to the knowledge of treatment allocation (in the open label trial) or clinical symptoms can be avoided. The assessment variability from different investigators in multiple site trials can be reduced by using an central core laboratory. This is especially important when using quantitative analysis.

- High Quality Assurance

To maintain validity and reliability, KCCL's analysis follows the standardized procedure and is monitored by cardiology researchers. In addition, the analysts are managed by training courses and reliability tests.

- High-Efficiency Result Submission

KCCL is capable of conducting multiple-cases analysis with high efficiency thanks to the composition as below:

- Dedicated facilities of research room and analysis terminals / software
- Cardiology team of multiple experienced analysts
- Standardized process management specified for intravascular imaging studies

From the sponsor's point of view, by using KCCL's service, the approval application for new devices or drugs can be submitted with reliable quality and within a limited time schedule.

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Company Overview

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Business Details	1. Development support for drugs, diagnostic pharmaceuticals, and biomarkers with medical imaging techniques and know-how 2. Clinical development support (clinical study monitoring, quality control, image analysis, image data handling, image data central review) and monitoring in clinical trials for medical drugs/devices 3. Operation support for PET tracer synthesis, and PET manufacturing 4. Regulatory affairs consulting support (e.g. establishment of QA system, GMP/c-GMP for PET drugs) 5. Consulting services for drug development
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