Chapter 7
Evaluating and Working with an Imaging Core Laboratory

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Abstract This chapter will take you through all of the key components to evaluate selecting an imaging core laboratory for a clinical trial from the sponsor perspective. There is a corresponding checklist that will ensure none of the key components are overlooked during the selection process.

Keywords Corporate infrastructure • Regulatory experience • MCC metrics • Strategic partnership

Introduction

This chapter takes the perspective of the sponsor who is retaining an imaging core lab as part of a specific clinical trial or a clinical trial program. We make the assumption that the clinical development program is targeting regulatory approval at some point in the future and that conduct of the clinical trial will be performed consistent with good clinical practice and in a manner that will satisfy reviewing regulatory authorities. In discussing the attributes and behaviors of the imaging core lab, we will follow the traditional sequence of events that occurs during the clinical trial process and how to utilize metrics to effectively monitor trial progress and guide interventions as needed. The traditional sequence of events starts with establishing a partnership between the sponsor and the imaging core lab. This includes

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aspects related to general corporate characteristics such as number of employees, financial viability, experience, and degree of success with respect to regulatory approvals, as well as previous findings on health authority audits. Next we go through study design, study start-up, study conduct, data management and documentation, data analysis and reporting, regulatory support for health authority interactions, and project-specific attributes. In addition to these primarily technical factors, we will briefly discuss the culture of the organization that you are considering partnering with as this can become an important facet that can impact on performance between the sponsor and imaging core lab.

Corporate Infrastructure

The corporate infrastructure represents the demographics of the imaging core lab. This includes the number of employees, physical locations, financial status, and years in the imaging core lab business. Is the organization new or established? Is it growing, stable, or consolidating? What are the reasons for this? Is imaging an established core competency or a business expansion opportunity? From the sponsor perspective, one wants to ensure that the imaging core lab that we consider retaining is able to provide the necessary resources, both human and financial to the project for the entire life of the project including the period of health authority review. Therefore, the firm must be financially stable and ideally making a profit since companies losing money will for their own survival need to either remove resources or come to the sponsor for more funding to adequately resource the project. The ideal situation is a company that is stable or growing slowly. Rapidly growing organizations are associated with higher turnover at the project level which means that the sponsor team will be reorienting new team members at an above industry average over the duration of the project.

The nature of the sponsors' objective will also influence the selection of an imaging partner. Consider the example where there is a preclinical finding of heart failure in toxicology studies at doses greater than 50-fold the maximal predicted human dose. The team would like to incorporate an echocardiogram assessment at baseline and on the last day of drug administration in a phase IB study. They feel that echocardiograms performed locally in the radiology department are sufficient for their purpose. In this case having the CRO leading the study collect the echocardiogram reports may be sufficient. If there is greater concern regarding the potential for an adverse event of heart failure due to the mechanism of action of the drug or the calculated therapeutic window is only 3–5 times the predicted human dose, then a greater focus on the echo findings is warranted and an experienced imaging core lab would be desired.

The corporate structure of your imaging partner needs to mesh with that of the sponsors. The imaging partner should have a project team structure that aligns with the structure of the sponsors' team. Ready access to senior management within the imaging organization is essential for efficiently managing challenges that arise.

The imaging partner must be able to support the clinical trial in the geographic locations where the sponsor intends to recruit. This often means a requirement for a global infrastructure. It is good practice to drill down into these global requirements including the need for adequate resources to cover the volume from specific time zones.

The processes and procedures of your imaging partner will impact on the amount of sponsor resources that will be needed to successfully manage the study. Organizations that have well-established standard operating procedures that are reviewed and updated at regular intervals will benefit the sponsor. Inquire about the internal quality control measures employed by the imaging core lab. A high-level assessment can be easily obtained by requesting data from recent health authority audits that are routinely performed as part of submission reviews. For projects that merit increased scrutiny of the imaging core lab, the sponsor should request an on-site visit where they can assess the capabilities and can make a determination regarding the robustness of the imaging processes. Two additional aspects which are markers of successful partners are the current investment in R&D and their track record of successful health authority approvals. Imaging companies need to stay on top of new developments in their field. The rate of change in imaging technology is quite rapid. As a sponsor, it is imperative to know whether the guidance that will be provided is up to date from both a technical and regulatory perspective. Look for ongoing projects and relationships with the imaging hardware manufacturers and with leading institutions or companies developing new imaging standards. From a regulatory perspective, look for the presence of relationships with key imaging leaders within FDA and EMA. Look for an ongoing and consistent record of product approvals where imaging was a key component of the submission from the major health authorities.

One common mistake within study teams is that they focus on managing a specific trial and do not focus on the overall objective which is product registration. There are significant differences between successfully completing a trial and gaining timely regulatory approval. When imaging endpoints are key efficacy or safety parameters for regulatory approval, an imaging partner who has successfully navigated the approval process is a very valuable partner. This factor should be heavily weighted when deciding between imaging partners as within the pharmaceutical industry the cost of a non-approval or a deferred approval will usually be several multiples of the entire imaging contract.

Study Design

The most important milestone that should be achieved during the study design phase is to get an imaging partner on board. When the sponsor views the imaging core lab as solely an operational vendor, the imaging core lab is retained after the protocol is finalized. To date, I have yet to see a phase II/III protocol where some improvements to the protocol were not recommended by the imaging partner. I have

also observed many instances where protocol amendments were required or when decisions were made to compromise on some imaging aspects due to the desire not to amend the protocol or imaging charter due to the late engagement of an imaging partner.

Clinical trial protocols have many facets. Protocol development involves not only a thorough literature review but also dialog with those who are at the forefront of the field under investigation. Very few clinicians have had exposure or training in the principles of diagnostic imaging. Therefore, inclusion of imaging experts internal to the organization in conjunction with your imaging partner is preferred.

The powering of the study will be dependent upon several factors. These include the clinically meaningful change, the detection limit of the imaging technology, and the scan-to-scan variability within an individual subject. The scan-to-scan variability will be impacted by standardization of the acquisition procedure and by training of the investigational sites.

It is wise to involve the imaging partner in the protocol design since you may want to include in the investigational site feasibility assessment the availability of specific imaging hardware and software. The available hardware will impact the imaging sensitivity and may also impact reproducibility. Software updates are also common and may also impact key variables that will impact the power calculation. Since most-experienced imaging partners survey the investigational sites for technical and personnel information during start-up activities, early collaboration with the imaging core lab could gain efficiencies and remove duplicate efforts from the overall site feasibility and site survey processes conducted by the sponsors' team or their delegates.

Study Start-Up Activities

Following completion of the feasibility assessment and discussions on protocol design, a final protocol has been agreed upon. Due to differences in radiation exposure standards, clinical practice, hardware availability, and other considerations, specific geographic regions have been selected for participation. A single or a series of investigator meetings are being planned. Investigational sites are being identified, and study contract negotiations are underway. Investigational site qualifications need to be done together for both the imaging and other clinical aspects of the trial. Thus, the systems and personnel from both the sponsor and imaging partner need to be aligned. Informed consents need to be drafted, and the imaging partner will be asked to respond to questions or requested changes to the imaging component of the informed consent by the respective institutional review boards.

In many organizations there is a 6-month time period from final protocol to the investigator meeting. Prior to or immediately following "final" study protocol, it may be of value to the sponsor to conduct a reproducibility study. This study will involve taking patients who would be eligible for the study and imaging them

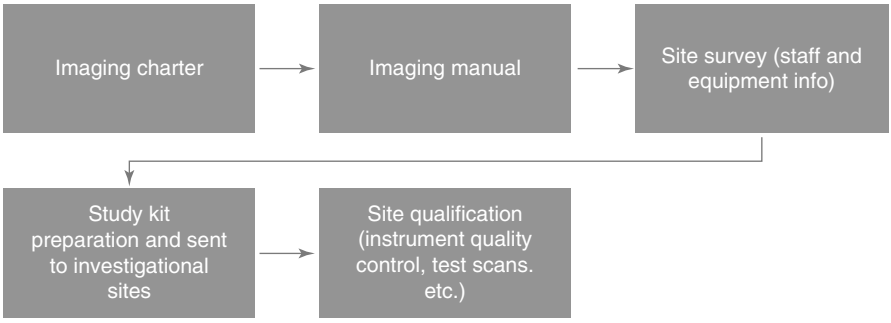

Fig. 7.1 Critical start-up points of the imaging workflow

according to proposed study guidelines. After acquisition of the image, the patient would get off of the imaging apparatus. Several minutes later the same process would be repeated. This type of study can be used both to determine the within subject variability between scans and to identify key factors involved in determining the final image read out. By identifying key variables that impact upon the final image acquisition, instructions to the study sites can be generated that specifically focuses on these areas. This will enhance the imaging investigational site training. A reduction in scan-to-scan variability has the effect of increasing the power of the study to demonstrate a statistical difference between the investigational and comparator groups.

Several tasks led by the imaging core lab with assistance from the sponsor and CRO need to occur before the first patient can be enrolled in the clinical trial. As mentioned previously, selecting and engaging your imaging core lab vendor early on in the process is key, as it will enable sufficient time to complete these start-up activities with the required quality for a successful study. A high-level flow diagram in Fig. 7.1 highlights the start-up activities from the imaging core lab perspective. All of these activities are dependent upon and driven by the clinical protocol. Therefore, it is essential that a well-developed protocol has been completed prior to study start-up activities.

The imaging core lab should be able to take the lead in generating the imaging charter. The imaging charter may be included as part of a special protocol assessment or scientific advice which will impact the timelines of development and finalization. It will include detailed information regarding image acquisition, read methodology, and data management. The importance of an imaging charter has increased with the draft FDA guidance document released in August 2011, focusing on the content and importance of the imaging charter which is explained in great detail in Chap. 4. The final protocol is imperative to ensure there is no delay in finalizing the imaging charter or the need to produce several amendments.

Imaging manual refers to the detailed instructions regarding image acquisition that is contained within the training manual developed for the investigational sites. This document must fully describe the imaging time points, the imaging modalities,

de-identification procedures, image submission procedures, source data storage regulations, query resolution process, and imaging protocol to be followed by the investigational site technologists. The imaging protocol that needs to be followed for a clinical research study differs markedly in comparison to everyday clinical practice. There is much more attention to detail and more documentation involved in performing research studies. Therefore, the technologists need to review the imaging manual document in full before scanning any subjects. We will touch upon this further when we discuss the importance of investigational site training and qualification.

The site survey will capture the investigational sites' contact information and equipment information which is necessary for ensuring the site is capable of participating in the trial as well as identifying the need for site training when personnel changes occur. Any issues identified with the investigational sites' equipment capabilities must be flagged to the sponsor and CRO to discuss options and associated risks with that investigational sites participation. In order for the imaging core lab to send the site surveys, they will need to receive a site list from the CRO containing the following required information: investigational site number, investigational site name, study coordinator name, and email address. If this required information is not included in the site list, the imaging core lab will be unable to survey the sites thus possibly causing a delay in start-up. Prioritizing investigational sites for this activity by the study initiation visit dates will be more effective.

Study kits are prepared by the imaging core lab and sent to all the participating investigational sites. A typical study kit will include an imaging binder and media (CDs, films, etc.) and mailers to submit the image data to the imaging core lab. If the imaging core lab has the ability for the investigational sites' to submit image data electronically and the investigational sites' have the capability to do so less materials/forms will have to be generated and sent to the sites via courier saving on shipping costs. Just like the site survey, the study kit must be sent to the site at the appropriate time to avoid duplicate work and unnecessary follow-up. This requires clear communication between the imaging core lab and CRO to ensure these activities take place when IRB approval is complete and the SIV is scheduled for the best response from investigational site.

Investigational site qualification refers to the process where the imaging lab certifies that the investigational site is able to successfully conduct all of the procedures required for the clinical trial as detailed in the imaging manual. While this process can increase the time required for having the investigational sites ready to acquire and submit image data, it directly improves the quality of the image data being submitted to the imaging core lab. Qualification can include test scans being submitted for review and approval, phantom scans and instrument quality control. This needs to be highlighted in the risk management plan to ensure the study team takes the appropriate actions with investigational site qualification in respect of time and the imaging modality or modalities involved in the clinical trial. Poor quality scans can have a major effect on the outcome of a trial. Therefore it is imperative that the investigational sites demonstrate proficiency not only at study initiation but throughout the study. This requires ongoing monitoring by the imaging lab.

Investigational Site Training and Qualification

The imaging manual document will need to be generated by the imaging partner. The key elements in maintaining consistency in image acquisition should be highlighted. Investigational sites should identify a primary and a backup technician who will be performing the image acquisitions. Their credentials should be reviewed by the core lab. The technicians should attend the investigator meeting, and special sessions should be devoted to review of the protocol and imaging guideline contents that are relevant. A formal assessment should be performed at the investigator meeting to determine whether the content was understood and is able to be acted upon according to the needs of the trial. Similar to the way the clinical monitor reviews the patient data from the first few subjects in detail with the study investigational sites, the imaging core lab should review the first few images being acquired in detail to ensure that they are consistent with the image standards set up for the trial. Should the image quality not meet prespecified standards, for trials where the imaging assessment is the primary endpoint there is no value in randomizing the subject as without a valid baseline assessment there is no way to generate data on change from baseline. Should there be minor issues with the investigational site these may be managed remotely. However, whenever there are significant issues, trained individuals from the imaging core lab should go to the investigational site, ideally when a patient is scheduled for imaging to assess and remedy the situation. In certain situations such as pivotal phase III trials the sponsor may wish to qualify individual investigational sites prior to permitting randomization of any subjects. This usually involves acquiring images from several patients and sending the images to the core lab for verification of image quality. Once the investigational site has demonstrated proficiency, then they are qualified to begin randomizing subjects.

Investigational site training should not be viewed as a onetime event at the investigator meeting. There will be some imaging technicians who are unable to attend the group training. There will be loss of recall regarding specific procedures over time especially at investigational sites less experienced in conducting these assessments and at slow enrolling investigational sites. A training plan should be requested from the imaging core lab that outlines all activities including investigational site remediation activities that may be required spanning the entire study interval. The training plan should detail how a need for training will be identified proactively via various quality gates established by the imaging core lab.

Study Conduct

Study conduct involves the collection and communication of data between the investigational site, imaging core lab, and study sponsor. The core lab should provide the investigational site with a secure process for transmitting the images together with subject number and core information required for interpreting the images. If the acquired image needs to meet certain criteria for study enrollment,

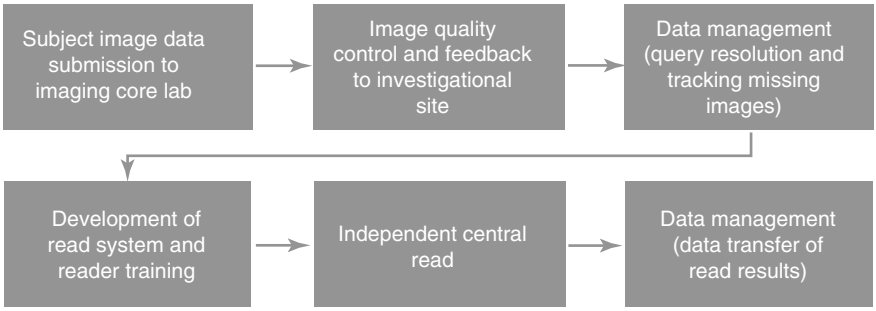

Fig. 7.2 Critical study conduct points of the imaging workflow

such as a bone mineral density for inclusion in an osteoporosis trial, then turnaround should be sufficiently rapid so as to permit good operational flow at the investigational site level. The same system that securely transmits images between the investigational site and core lab should enable transfer of the images to the blinded readers where assessments can be recorded. Queries pertaining to the data will originate within the core lab to the investigational sites. In the current era of electronic data capture, the imaging core lab should have the ability to do this electronically. The core lab should review with the sponsor the systems, procedures, and data standards that they have in place. They should be able to provide real-time reports regarding the number and type of queries and be able to drill down to the investigational site and subject level upon request. Prior to engaging a core lab, one may want to inquire regarding metrics for similar trials they have performed in the past.

Similar to the conduct of the nonimaging components of the trial, a monitoring plan should be in place for the imaging component. The core lab systems should provide a full audit trail with date and time stamped entries that identify the individual entering the data that are CFR part 11 compliant. In essence the documentation system should allow any auditor to be readily able to reconstruct the events that occurred during the trial. Successfully conducting a clinical trial requires not only technical skills but also good interpersonal communication skills and good attention to detail. As a sponsor one should insist on meeting the team members that the core lab plans to dedicate to your study. You should also inquire as to whether these team members have other significant responsibilities or are dedicated primarily to your project. You should feel comfortable that the team has sufficient experience to solve the problems that will invariably be encountered during the conduct of the trial. Finally, you should agree on a plan for project oversight from both the sponsor and imaging core lab perspective including when certain milestones are achieved such that data will be transferred to the sponsor for assessment of data integrity and analysis.

As we did with study start-up, we are going to now discuss the key tasks and associated best practices for study conduct following the flow diagram in Fig. 7.2.

The investigational site image data submission to the imaging core lab is an extremely important area that needs to be focused on. Image data must be submitted

to the imaging core lab within 3 days of acquisition to maintain high quality. The 3-day window is commonly missed. It is important to understand the process at the investigational sites in order to provide the best solution via electronic submission or simple process improvements at the investigational sites.

If the investigational sites are submitting the image data within 3 days of acquisition, the imaging core lab will have the ability to identify issues early and implement corrective actions with the investigational sites via the image quality control and feedback process. The imaging core lab will need to have highly qualified and certified modality-specific imaging technologists for the required image review per the study protocol and imaging charter. The experience of the imaging technologists is important to ensure imaging-related queries are being generated when required. Some imaging core labs will generate imaging-related queries when they are not necessary or not generate them when they are needed, which will be reflected in the independent central read.

Managing the resolution of queries and tracking down any missing image data from the investigational sites must be ongoing with close collaboration between the CRO and imaging core lab. The process for following up with the investigational sites needs to be clearly stated in the communication plan as well as the appropriate escalation paths when issues need to be escalated. Re-occurring meetings with the imaging core lab and CRO will drive the necessary communication to monitor investigational site, as well as aligning the CRO and the imaging core lab's activities. Responsiveness from investigational sites is historically poor which is understandable and should be anticipated. Sites commonly do not follow instructions regarding submitting image data as soon as possible after each time point is acquired for each subject. Instead, they send multiple time points together which is referred to as batching. The CRO and imaging core lab must be open in acknowledging these issues and should work together to develop effective solutions.

The development of the read system and reader training has to be completed in order for the central read to commence. There are numerous tasks that have to occur for these activities to be completed. Therefore, the imaging core lab must set the appropriate expectations, roles, and responsibilities to ensure each task is completed and nothing gets overlooked. If one of these tasks is overlooked, it may very well impact the ability to deliver the read results when required. Flexibility in designing a read system can easily improve the power of your data by being able to perform additional analysis. Experienced imaging core labs will bring this to your attention and involve the relevant experts when necessary. Reader training is best accomplished in a face-to-face meeting with imaging core lab, readers (radiologists, oncologists, cardiologists, etc.), sponsor and/or CRO. The ability of the imaging core lab to calibrate the readers through the initial reader training will be reflected in the adjudication rate. Adjudication rates vary per indication, and an experienced imaging core lab will be able to advise you on what is expected and what is abnormal before the independent central read begins.

Once the independent central read has begun, the imaging core lab is responsible for communicating status updates and loading all available subjects into the read systems. The rule for when a subject is to be read needs to be established well in

advance. The imaging core lab will use the read plan in order to monitor expected vs. actuals. A bell-shaped enrollment curve is desired by the imaging core lab as it prevents the need to shorten timelines or add resources for the interim and/or final data analysis like when there is a bolus of subjects enrolled at the end of the enrollment period. The time from final read to interim or final analysis needs to be looked at closely as the time necessary to complete this task will vary per read methodology, the required image data being available to be read, the selected readers' availability, and time needed to send the data transfer containing the read results.

Data transfer of read results should be a smooth process as it is the final critical point in the process when tension is at its highest point. An experienced imaging core lab will start discussions of the data transfer early and finalize the required specification document shortly after the design of the read system has been finalized. The sooner this can be done and a test transfer can be generated and approved by the recipient (sponsor, CRO, or third party), the better as it allows flexibility to review the read results earlier than expected if necessary.

Once the final data transfer is completed many imaging core labs feel that their work is done for the most part which is incorrect. An experienced imaging core lab will assist with the interpretation of the data from the images with the health authority submission. Presentation can make or break any deal in real life and this also rings true with submission. You have to put the results in context of both a clinical and therapeutic response. An imaging core lab advising the sponsor about the data significance will be a great asset to the health authority submission.

Risk Mitigation Plan

In addition to the monitoring plan, a risk mitigation plan for the imaging component is another document that will benefit the clinical trial immensely. The imaging partner should lead this process by going through deviations from the intended imaging process and should gain consensus on how to manage these deviations prior to study initiation. This should all be clearly detailed in a risk management document that focuses on the foreseeable risks specific to the clinical trial. Risks associated with investigational site start-up, investigational site training, missing images, resolution of queries, independent review progress, data transfers are all crucial to discuss at the start of the clinical trial, and this open dialog needs to continue throughout the trial. Transparency between all parties is critical to success. The experience of an imaging core lab feeds into this document and is a good test to determine if you selected an experienced imaging core lab or not.

Study Closeout, Analysis, and Communication

Study closeout is an intense time for the study team as they are under pressure to close out all queries in order to lock the clinical trial database. The imaging core lab must finalize the reads, perform internal quality checks regarding within reader and

between reader variability, as well as resolve differences between readers through the prespecified adjudication process. Since it is relatively easy for the imaging core lab to be on the critical path towards database lock, it is imperative that the sponsor work proactively with them and the investigational sites to collect all needed data and to resolve discrepancies. The amount of work to be done at this critical time is inversely related to the ongoing efforts of the study team during the trial. This is when imaging core labs with substandard processes and reporting systems or those who do not communicate openly with the sponsor will "suddenly" become the rate-limiting step for database lock. From the sponsor side, periodic data transfers followed by sufficiently in-depth analyses should alert the sponsor ahead of time to any issues that require resolution. Sufficient resources both on the sponsor and imaging core lab side should be applied to the project well in advance of the last patient completing the study.

The analysis plan should be outlined in the protocol and imaging charter. More detailed documentation of the analysis plan must be finalized in the statistical analysis plan and associated documents in advance of database lock. At times some anatomical structures are not evaluable due to previous surgery or other circumstances. This may necessitate manual coding for some subjects. Interaction between sponsor statisticians and the imaging core lab may be required. Following prespecified statistical analyses, the data must be interpreted and communicated in clinical study reports as well as submission documents to health authorities. Invariably, there will be questions that arise regarding the imaging data such as differences in study drug efficacy according to scanner type, geography, or specific patient demographic or disease variables. Individuals from the imaging core lab who have had experience with other studies can assist in the interpretation of this data. Their expertise may also be very helpful in responding to imaging-related questions from the health authorities. Certain health authorities will also want to audit the actual images from the clinical studies. However, rather than travel to the core lab, they will request that the images be sent to them. In such cases which are becoming more common, it is important that the core lab has experience with the required specification of the viewing system used by the health authority reviewers.

Metrics Champion Consortium (MCC)

When evaluating the operational effectiveness of an imaging partner, there are standardized measurements which are utilized within the industry that can serve as a useful assessment tool. The Metrics Champion Consortium (MCC) was established in 2006, focusing on improving clinical trial processes via standardized performance metrics. In January 2009, the MCC published the standardized imaging metrics for clinical trials. The metrics focus on four key elements: quality, timeliness, efficiency/cost, and cycle time. There are a total of twenty (20) standardized MCC imaging metrics, version 1.1 issued November 2011. We have compiled two tables which separate the quality metrics from the metrics that focus on timeliness, efficiency/cost, and cycle time as often different individuals are responsible for these different metrics within the sponsor's organization.

Table 7.1 MCC version 1.1 quality metrics. One additional metric which is not part of the MCC is included in this table as it is a great indicator of quality at one of the final steps in the process

MCC metric #	Metric category	Area targeted	Metric definition
10	Quality	Image QC	Percentage of suboptimal (but evaluable) images
11	Quality	Image QC	Percentage of non-evaluable images vs. total received
12	Quality	Image QC	Percentage of non-evaluable baseline images vs. total received
13	Quality	Data management	Percentages of missing imaging visits
14	Quality	Data management	Percentage of investigational site queries
19	Quality	Protocol	Number of image acquisition technique-related amendments per modality per protocol
n/a	Quality	Data transfer	Percentage of the data transfers meeting the data transfer specification document

As a sponsor it is critical to clearly communicate to both the imaging partner and CRO what quality metrics are targeted for the study. Quality can be defined as the percentage of non-evaluable images during the central read, the amount of missing imaging visits, the number of queries that are generated for images not acquired by the imaging protocol, and/or data transfers meeting the expectations of the data transfer specifications document. If quality is not discussed at the beginning of the study, it will most likely not be discussed throughout the clinical trial. By discussing quality as a team, quality will stay in the forefront of everyone's mind and result in a successful study. Once quality is defined, the team can focus on how to monitor and develop standard practices for addressing any challenges the team may face. Table 7.1 represents the MCC quality metrics as well as an additional suggested quality metric.

All of the quality metrics focusing on image quality have a direct impact on the imaging endpoint. Non-evaluable images at baseline mean that a change from baseline cannot be calculated rendering the patient as noninformative for the imaging endpoint. Non-evaluable images post-baseline will need to be imputed according to methodology agreed upon by the health authorities. These methods are deliberately conservative, meaning that the missing data will be treated in a manner that usually will reduce any treatment effect that an evaluable image would have provided. Suboptimal but evaluable images will diminish the accuracy of the reading and therefore serves to increase the scan-to-scan variability which also diminishes the ability to demonstrate a treatment effect. Missing imaging visits will also need to be imputed, thus every effort should be made to obtain the scheduled scans.

Amendments to the image acquisition technique reflect a failure to fully anticipate events occurring during the trial, may result in data collected using multiple techniques, and have several undesirable operational consequences. The number of investigational site queries involves several factors that can have opposite effects. A lack of queries may indicate that the imaging core lab is not being thorough in their review. Excess queries may indicate poor investigational site performance, or poor communication between the CRO, imaging core lab, and study site. Data transfers

Table 7.2 MCC version 1.1 timeliness, efficiency/cost, and cycle time metrics

MCC metric #	Metric category	Area targeted	Metric definition
1	Efficiency/cost	Business development	Average percentage of variance in the imaging budget
2	Cycle time	Business development	Average number of calendar days from imaging study award to contract signature
3	Timeliness	Project start-up	Percentage of investigational sites qualified vs. actual
4	Cycle time	Project start-up	Average number of calendar days from investigational site designated ready to first date of image receipt
5	Cycle time	Image acquisition and submission	Average number of calendar days from image acquisition to image receipt
6	Cycle time	Image QC	Average number of calendar days from image receipt to initial feedback to investigational site
7	Cycle time	Image processing	Average number of calendar days from image QC complete to reporting of eligibility results
8	Cycle time	Image processing	Average number of calendar days from image receipt to ready for independent review
9	Cycle time	Image processing	Average number of calendar days from when the image is designated for review to completion of the review
15	Cycle time	Data management	Average number of calendar days an imaging query is outstanding
16	Cycle time	Data transfers	Average number of calendar days from last patient reviewed to delivery of dataset
17	Timeliness	Data transfers	Average number of calendar days from original estimate to actual for export submission
18	Cycle time	Project start-up	Number of weeks to develop and write independent review charter
20	Timeliness	Protocol	Percentage of images acquired at investigational sites within agreed-upon timeframe for imaging time point (as defined by protocol)

also involve communication between the imaging core lab and the receiving organization as well as adherence to the transfer specifications. It is important to perform several transfers over the course of the trial as information technology systems may be updated, and the historical data transfer specifications may no longer function as they did previously. Close communication between all parties is the most important aspect to a successful trial. Also, close monitoring and prompt attention to these quality metrics often impacts the outcome of the trial.

Table 7.2 focuses on the timeliness, efficiency/cost, and cycle time metrics.

Timeliness, efficiency/cost, and cycle time are a direct reflection of the experience, specifically within project management, at the imaging core lab, CRO, and sponsor as well as the overall performance level of the imaging core lab. Setting the appropriate expectations and having strong communication between all parties involved greatly improve these metrics stated previously. The key to these types of metrics is to monitor on a continuous basis and have action plans established. The most difficult metrics to achieve prespecified targets typically include investigational site involvement. An agreed-upon action plan for identifying investigational sites with trending issues will lead to having predetermined corrective actions depending on the level of severity. These corrective actions should include putting the investigational site on hold to provide the proper retraining or possibly closing the investigational site to enrolling new subjects or participating in the trial. In a lot of cases, the investigational sites are not addressed appropriately and continue to impede progress of achieving the targets for these metrics and the overall quality and timeliness of the trial.

An imaging core lab should have the capabilities to track MCC metrics or a variation of the MCC metrics. Depending on the need and goal of a clinical trial, not all of the metrics listed previously may apply, but the majority usually does. The implementation of operational metrics is useful in focusing team activities towards prespecified goals. By capturing metrics on a monthly interval, it is very easy to see the areas that require additional focus or process improvements. The relationship between the imaging core lab, CRAs, and investigational sites is crucial.

The impact of not meeting the desired target for these metrics will vary depending on the indication and central read design, but the imaging core lab must be proactive and should develop solutions on how to tackle these challenges via training, communication, setting expectations correctly and early, and identify issues immediately when appropriate corrective actions can be taken. Training is a key component to ensuring that key metrics are met within the agreed-upon target. In general, the more high-quality training that can be applied at the onset of a clinical trial, the fewer issues and corrective actions will have to be implemented during the trial. The better performing imaging core labs through their experience know how to mitigate commonly experienced issues and demonstrate proficiency in rapidly identifying and successfully managing deviations from the operational plan. One recently published peer-reviewed paper published in conjunction with the MCC details the advantages of using metrics for imaging in clinical trials with case examples [1].

All of the MCC metrics are important, but there are key metrics that require additional attention as they feed directly into the quality delivered by the investigational sites and imaging core lab. I have never worked on a clinical trial that has no investigational site issues. There will always be at least a few sites that require intervention and these metrics will help identify them early. Metric 5 is a common metric that does not meet its target and prevents the imaging core lab from providing the best quality control as possible for the image data received. When investigational sites batch the image data as stated previously, it does not allow the imaging

core lab to proactively manage the image quality from the investigational sites. It is important for CRAs assisting in monitoring this activity via accessible reports from the imaging core lab to remind the investigational sites to send the images promptly following acquisition. This will greatly improve this metric of time from image acquisition to submission. Metric 6 measures the imaging core lab's ability to provide feedback to the investigational sites in a timely manner. When a protocol allows a window for having repeat images performed, it is based off of when the image data was acquired thus requiring a short cycle time for metrics 5 and 6. Metric 15 measures the time an imaging query is outstanding which closes the loop ensuring that the corrective action is taken by the investigational site as quickly as possible in order to avoid repeated imaging acquisition issues. This is another metric which requires cooperation from the CRAs and investigational sites. We personally feel that metric 11 is the most important metric to determine the level of quality applied to the clinical trial as all of the other 5 key metrics are contributing factors to metric 11, percent of non-evaluable images. You could have a high percentage of queries across the study, but if you have a low percent of non-evaluable images, it tells you that the CRO and imaging core lab took the appropriate steps for maintaining quality. Metric 13 is the best indicator of the level of communication between the imaging core lab and CRO. If the percentage of missing image data is high, it means that you will effectively be losing study subjects from inclusion in the independent central read for either the primary endpoint of the study or secondary time points. Last but not least is metric 14 which allows you to measure if the investigational site training applied was appropriate or not. This metric also will tell you if problem sites were identified and the proper corrective actions mentioned previously in this chapter were taken.

Culture and Financial Strategy

The culture of an organization is heavily influenced by its leadership. Corporate leaders hire, retain, and advance individuals based on performance characteristics that are valued. Look for organizations where the team is striving towards success. Be wary of teams that do not delve deeply into the project details who seek primarily to reassure you of their capabilities. For complex projects one may consider retaining one or more individuals from the imaging core lab as consultants during study design to ensure that the technical and communication skills are up to expectations. Finally, ensure that the goals and objectives are aligned between the sponsor and imaging core lab teams. The imaging core lab should benefit from the delivery of high-quality imaging data. The challenge is that the quality as reflected in within subject variability will not be evident until well into the trial. The culture of the imaging core lab, the thoroughness with which the sponsors' project proposal is worked through and the willingness to tackle ongoing challenges can be assessed. A face-to-face meeting with the prospective project team leaders is highly instructive.

Different imaging core labs utilize different contracting strategies. For discussion purposes, these are divided into 3 categories. The first is the low-bid strategy where the high-level project description provided by the sponsor is covered with a focus on the imaging parameters. Many details are not specified and several tasks that can reasonably be anticipated are not present. The bid is the lowest because it covers the least with respect to contracted services. The risk here is that as the trial progresses and additional services are needed, the sponsor is in fact hostage to the imaging vendor such that the initial low bid may turn out to be the high-cost selection. In addition it is much more difficult to implement new processes midway in a trial. This may lead to regulatory complications if some patients are managed differently from others.

The second strategy which can also be influenced by the sponsor team is the take-no-risk strategy. A good core lab will discuss sources of variability within an imaging program. A somewhat inexperienced but highly motivated study leader may opt to provide the same imaging hardware and software for all investigational sites. Similarly, training and investigational site monitoring may be performed at intervals that are more than usual and have not been demonstrated to improve results. Similar within and between reader variability assessments may be performed many more times than required. The adjudication process may be overly complex. While there are times when certain elements of this approach may be prudent, teams should be able to make reasonable tradeoffs in structuring their imaging program.

The third strategy is one where the imaging core lab has the experience to outline in sufficient depth and with contingencies for anticipated issues such as retraining of a percentage of investigational sites a complete study proposal. Their proposal should explain the rationale behind key decisions. When meeting face-to-face to discuss the proposal, the imaging core lab representatives should be able to explain the available options for each component in the proposal, along with their recommendation and rationale. Based on the nature of the project, the imaging core lab should be able to guide the sponsor regarding where investments have historically had a positive return. This works best when the imaging core lab is transparent and sufficiently experienced. The best situation is predicated on having experienced personnel working on the project from both the sponsor and imaging core lab sides. This will enable generation of a fair and comprehensive scope of work contract that enables sound project planning with few if any events that occur beyond those specified in the contract.

In summary, evaluating and deciding on which imaging core lab to use for one's clinical trials is a very important decision for the sponsor. A critical aspect is to get the imaging partner on board early in the process when the protocol design is still being developed. Developing a strategic partnership with an imaging core lab automates this critical aspect. Since this selection can make the difference between a successful program and one that is not, appropriate time and attention should be made in this process. Key considerations include the corporate metrics, the imaging core lab culture and work approach, as well as their systems and track record of success. A checklist incorporating all of the points we discussed can be found in Appendix 7.1 at the end of this chapter as an easy-to-use tool to assist you when evaluating and working with an imaging core laboratory.

Appendix 7.1: Checklist for Selecting an Imaging Core Lab

Imaging core lab capabilities	Yes	No	Not required	Comments
Is there global infrastructure?	☐	☐	☐	
Is there a sufficient amount of employees?	☐	☐	☐	
Is there a high turnover rate?	☐	☐	☐	
Is this an established organization (How many years have they been in business)?	☐	☐	☐	
Is the organization financially stable?	☐	☐	☐	
Is imaging an established core competency of the organization?	☐	☐	☐	
Is there ready access to senior management within the organization?	☐	☐	☐	
Does the organization have well-established SOPs that are reviewed and updated on a regular basis?	☐	☐	☐	
Does the organization have current investment in R&D?	☐	☐	☐	
Does the organization have a track record with successful health authority approvals?	☐	☐	☐	
Does the organization have relationships with key imaging leaders within the FDA and EMA?	☐	☐	☐	
Does the organization have experienced and sufficient medical and scientific staff?	☐	☐	☐	
Does the organization have the capabilities to capture, track, analyze, and take appropriate actions from MCC metrics or a variation of MCC metrics?	☐	☐	☐	
Does the organization have sufficient training methods for the investigational sites, CRAs, and sponsor?	☐	☐	☐	
Does the organization have an in-house electronic solution for transmitting image data?	☐	☐	☐	
Is the database tracking system and independent read system 21 CFR part 11 compliant?	☐	☐	☐	
Does the organization's study team at the organization have sufficient experience?	☐	☐	☐	
Does the organization have a dedicated experienced team developing imaging charters?	☐	☐	☐	
Does the organization's study team develop a risk mitigation plan as a standard practice?	☐	☐	☐	
Does the organization have experience with the required specification of the view system used by the health authority reviewers?	☐	☐	☐	
Does the imaging core lab have the ability to apply a governance structure via a relationship/alliance director?	☐	☐	☐	

Reference

1. Yu HJ, Miller CG, Flitcraft D. Metrics in medical imaging: changing the picture. ACRP: The Monitor. Aug 2012. p. 36–40.