Chapter 6
Medical Imaging in Drug Development

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Abstract Imaging technology when appropriately employed can provide a competitive advantage in the development of pharmaceuticals. Key success factors include (1) a clear vision for the project that incorporates current and anticipated future treatment options for the primary disorder targeted by the proposed treatment, (2) understanding of standards of care across the world, (3) current and evolving imaging standards, and (4) regulatory authority precedent and emerging standards specific to the therapeutic indications being sought. Imaging biomarkers provide the ability to detect change in disease much earlier than standard clinical endpoints. They can also provide timely, functional information at the molecular, cellular, or tissue level regarding the impact of pharmacological intervention in a disease process. These properties can make imaging a valuable tool in preclinical as well as in clinical development.

Keywords Biomarker • Regulatory • Benefit to risk • Pharmaceutical market

Introduction

Over the past decade the pharmaceutical industry has been investing increasing funds into research and development, yet fewer new drugs or biologics have been approved by global health authorities [1, 2]. Scientific milestones during this time period include the sequencing of the human genome, advances in genomic technologies, and advances in medical imaging. The Critical Path Initiative (CPI) is FDA's national strategy for transforming the way FDA-regulated products such as

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Table 6.1 Phases of drug development and associated milestones

Development phase	Desired outcome
Basic research	Target identification
Discovery/candidate optimization/ prototype development	Molecule or prototype that has suitable properties to interact with the pharmacological target in vivo
Preclinical development	Demonstrate proof of principle in animal models
Early clinical development	Pharmacokinetics, pharmacodynamics, proof of concept, dose selection
Late clinical development	Demonstration that the product is efficacious and safe

human drugs, biological products, medical devices, and veterinary drugs – are developed, evaluated, and manufactured [3, 4].

One of its objectives is to improve the number of pharmaceutical and medical device products developed in order to improve the health of the nation. It is acknowledged that advances in imaging technology have not translated into improvement in clinical trial productivity. In an effort to close the gap between imaging potential and the use of imaging to improve the clinical development process, FDA in August 2011 released a draft guidance for industry titled: "Standards for Clinical Trial Imaging Endpoints." This chapter will review the development process for new pharmaceutical agents with a focus on the role of imaging. The same general principles apply to the development of medical devices.

New Product Development

Drug development involves a series of activities beginning in the research laboratory and culminating in the marketing of a new pharmaceutical agent (Table 6.1). This multidisciplinary process requires professionals with diverse skills to contribute to projects that span several years. Drug development begins with basic research into human physiology and pathophysiology. From this basic research, one or more hypotheses are formed which predict that increasing or decreasing a particular substance will have a beneficial effect on a targeted disease state. A strategy to modify the concentration or biological activity of this substance will be developed. One example is the inhibition of CNS neuronal uptake of serotonin, which is characteristic of the class of drugs known as serotonin selective reuptake inhibitors (SSRIs). Once a pharmacological target is selected, its activity may be modified with a monoclonal antibody, interference RNA, a recombinant protein, a small molecule, or other strategies. If a small molecule approach is selected, then potential molecular structures must be assessed for physical chemical properties, and known structure function correlations. The potential for both on target and off target safety effects must be assessed. In essence, the discovery group is responsible for discovering/developing a molecule that has the desired effect on the selected target, with minimal off target effects. Once a molecule is developed that meets these in vitro specifications, the manufacturing will be scaled up to enable preclinical or animal testing.

The objective in preclinical research is to demonstrate that the investigational product performs as desired. For a cholesterol ester transfer protein (CETP) inhibitor, this would mean that it increased HDL and lowered LDL. For a rheumatoid arthritis treatment, it may mean improvement of inflammatory biomarkers or improvement at the level of the joint. The criteria used to satisfy proof of principle and the animal model(s) selected can have a significant influence on subsequent steps. Whenever possible, it is recommended that the criteria used for proof of principle in animal models be similar to the criteria that will be used in phase II trials in humans. Once proof of principle has been demonstrated, distribution and metabolism of the pharmaceutical product is known, and appropriate toxicology experiments have been conducted, an investigational new drug application to test the drug in humans can be considered. The investigational new drug application is a major milestone in the drug development process which requires careful documentation of years of preclinical work. Guidance documents from health authorities such as FDA and EMA can be found on their websites and are helpful in the preparation of regulatory submissions.

The phase I or first in human studies are usually conducted in specialized facilities where the study subjects are closely monitored. Initially a single dose is administered to a single subject. Once a specified number of study subjects have completed a single dose and no clinically significant side effects are observed, the dose of the study drug can be increased. These studies are referred to as single ascending dose studies. The objective is to determine the dose range where efficacy is observed and side effects are minimal and within an acceptable rate. Next multiple dose studies are performed. In these studies, subjects receive multiple doses of the study medication. These are usually one daily dose for oral medications (dependent of the half-life) in order to better delineate the therapeutic dose range. For monoclonal antibodies, the rate of administration may be less frequent such as twice weekly, weekly, or monthly. Pharmacokinetic and pharmacodynamic assessments are performed as part of most phase I studies. The objective at the end of phase I is to have sufficient information regarding the dose range that will be required to demonstrate proof of concept in humans.

During phase II several dosing regimens will be assessed using a placebo-controlled or an active comparator experimental design. The objectives are to prove that the pharmaceutical product achieves the desired clinical effect (proof of concept in humans) and to determine the optimal dose or doses to be carried forward to larger phase III trials. In the design of the phase II trial, at least one dose should be higher than the anticipated optimal dose and at least one dose should be lower than the minimally effective dose such that the optimal dose or doses become apparent as a result of the study. In reality, this is seldom the case. Due to the limited number of subjects in these studies, surrogate endpoints are heavily relied upon to determine dose selection. Well-conducted imaging studies can add significant value during early clinical development [5]. This is because imaging studies can often accurately measure changes in pathophysiological processes, thereby providing valuable information for either efficacy or safety.

Phase III clinical trials require substantial strategic, technical, operational, and financial resources. The objective is to demonstrate that the new product in its studied route and frequency of administration provides a clinically meaningful benefit compared to the risks involved for the study population that has been investigated. The concept of benefit to risk ratio is paramount. Historically sponsors focused on demonstrating benefit while collecting adverse events in a routine fashion during phase III trials. Today, that strategy is unlikely to be successful in many therapeutic areas. Safety must be actively assessed by identifying potential safety risks and designing studies to evaluate the risk relative to placebo or active comparators. A recent example is the serotonin 2b antagonist lorcaserin for weight loss where echocardiography was performed to assess cardiac valvular function [6].

In retrospect, identification of a clinical target appears simple. We will use the example of hypercholesterolemia to demonstrate this concept. Basic research identified the key physiological steps in the pathway for cholesterol synthesis. This revealed several potential steps in which the synthesis of cholesterol could be inhibited to lower serum total and LDL cholesterol. Pharmaceutical developers targeted the HMG-CoA reductase enzyme and the products known as statins emerged.

A more recent target that was selected for the treatment of hypercholesterolemia is the cholesterol ester transfer protein. CETP transfers cholesterol from HDL cholesterol to very low-density or to low-density lipoproteins (VLDL or LDL). Inhibition of this process results in higher HDL levels and reduces LDL levels. Torcetrapib was the first molecule of CETP inhibitors that demonstrated a dose-dependent increase in HDL and a decrease in LDL with and without an added statin [7]. In the phase III trial, there was a 58 % increase in deaths among patients taking torcetrapib and atorvastatin versus those taking atorvastatin alone [8]. Some scientists believe that the increased mortality observed with torcetrapib was secondary to unintended increases in blood pressure [9]. These scientists and their organizations have continued to develop their CETP inhibitors by evaluating their prospective compounds for changes in blood pressure. Due to current limitations in the understanding of lipid physiology, there is uncertainty as to whether CETP will be a viable target for pharmaceutical intervention.

At the conclusion of a phase III program, there is a large amount of data that is available pertaining to the pharmaceutical product. Analysis of this data can be valuable in determining the potential for use of this drug in additional indications. Bevacizumab (Avastin®, Genentech, San Francisco, CA, USA) which is a monoclonal antibody to vascular endothelial growth factor will be used as an example of closely related additional indications. In February 2004 the FDA approved Avastin for use in combination with intravenous 5-FU-based chemotherapy as a treatment for first-line metastatic colorectal cancer. In June 2006, the FDA approved Avastin in combination with intravenous 5-FU-based chemotherapy for patients with metastatic colorectal cancer who have been previously treated for their cancer (or second-line metastatic colorectal cancer). Investigation of additional tumor types followed such that in October 2006, the FDA approved Avastin in combination with carboplatin and paclitaxel for the first-line treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous, non-small cell lung cancer. Subsequently approval for glioblastoma and metastatic renal cell carcinoma followed.

At times, the emerging data may indicate potential application for a very different patient population. Zoledronic acid will be discussed as a representative example of this situation.

Zoledronic acid is a bisphosphonate drug that works by inhibiting osteoclast-mediated bone resorption. It was first approved by the FDA in 2001 for the treatment of hypercalcemia of malignancy at a dose of 4 mg per infusion with retreatment permitted after 7 days. In 2002 zoledronic acid was approved for patients with multiple myeloma and patients with documented bone metastases from solid tumors at a dose of 4 mg per infusion every 3–4 weeks. During its development for oncology uses, it became apparent that zoledronic acid would also be useful in patients with metabolic bone disease. A development program for metabolic bone diseases was initiated. In 2007 it was approved first as a single 5 mg infusion for the treatment of Paget's disease of bone. Studies were performed to support additional indications within metabolic bone disease. It was approved as a 5 mg once-yearly intravenous treatment for osteoporosis in postmenopausal women. In 2008, zoledronic acid at a dose of 5 mg annually was approved for the prevention of fractures following a hip fracture and for the treatment of osteoporosis in men. In 2009, it was approved for the treatment and prevention of glucocorticoid-induced osteoporosis in patients expected to be on glucocorticoids for at least 12 months and for the prevention of osteoporosis as a single 5 mg dose that is effective for 2 years.

Marketing authorization is based on all the discovery, preclinical, and clinical studies performed to date in clinical trials through phase III. Phase IV studies are designed to provide additional data that are of value to patients and healthcare practitioners that were not collected during the phase III studies. These must be conducted within the current prescribing instructions. They may investigate specific populations, compare dosing regimens, monitor a safety parameter, or investigate a new efficacy endpoint. It is common for health authorities to make marketing authorization contingent upon the conduct of additional post-marketing studies to assess potential safety concerns. In conjunction with use of the pharmaceutical product outside of the clinical trial setting, it is also common for safety issues to arise. These safety issues will need to be evaluated using the clinical trial data as well as various epidemiological sources. Imaging studies within the phase IV environment are relatively common and add value by objectively measuring the impact of the pharmacological intervention on either efficacy or safety parameters.

Imaging as a Biomarker

Advances in imaging technology have enabled scientists to detect events at the cellular level. Hardware and software manufacturers have increased the resolution of their products such that detection sensitivity and resolution have improved markedly. It is clear that imaging technologies have revolutionized the practice of medicine over the past few decades. This has contributed to improved diagnostics as well as improved monitoring of response to therapy. The result is a quantifiable

improvement in the quality of care in most therapeutic areas resulting in improvements in both quality and duration of life. The percentage of the population living into their 70s, 80s, and beyond is among the most rapidly expanding segments of the population in many countries.

Many individuals who work in drug development view imaging endpoints as a biomarker analogous to C-reactive protein (CRP) for inflammation. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal or pathological biological processes [10]. Biomarker programs within clinical development organizations typically assess serum markers, DNA, and RNA for *association with the disease process*. In an autoimmune inflammatory disease such as rheumatoid arthritis, CRP may be used to assess disease activity. Changes in CRP can be used to select doses of a therapeutic agent used to treat rheumatoid arthritis.

In contrast, imaging is the *measurement of an in vivo biological process*. For rheumatoid arthritis this would involve imaging of specific joints. While CRP is a systemic biomarker, imaging can provide additional information by demonstrating changes at specific anatomical locations (e.g., joints impacted by arthritis). Imaging is performed on the organ of scientific interest such as the heart, bone, or joint, while many other biomarkers are derived from the serum or circulating cells. During the development of a biomarker strategy, several biomarkers can be used together to derive a model predictive of a particular disease. Imaging may be considered as the net effect of both local and circulating factors on the disease process. As such, it is highly clinically relevant for many diseases.

A key property of imaging modalities is that they can provide critical data regarding disease progression. It is important to be able to detect progression of disease when patients are asymptomatic because often a disease process becomes less amenable to medical treatment as it becomes more advanced. From the perspective of drug development, demonstration of an improvement in patient signs and symptoms, while clinically relevant and necessary, is often not sufficient to gain regulatory approval. In diseases such as arthritis where pain is a key symptom, agents that reduce pain can be approved on this basis. From a payer perspective these agents will be considered alongside aspirin, acetaminophen, and NSAIDs. Pharmacological therapies which modify the disease process are much more highly valued. In order to gain approval for a product that modifies the disease, it is also necessary to show either an improvement or a reduction in the rate of disease progression which often requires the use of imaging.

The potential that imaging technologies have within clinical development has barely scratched the surface. While there are many reasons for this gap between potential and realized benefit, it is important to focus on the key elements required for success. The consensus opinion among imaging researchers and healthcare regulators is that the potential for the use of imaging in clinical trials for drug development hinges on appropriate use of standard principles. With appropriately rigorous trial conduct, the clinical trials will be more robust, require fewer subjects, and will be more likely to provide conclusive results that will allow for effective decision making. Simply incorporating imaging endpoints into a clinical trial does not guarantee that useful data will be generated. Rather it is the how the

imaging component is designed and implemented that is critical to the generation of high-quality data that will facilitate interpretation of the trial results. As will be discussed next, there is a trend to collect key data to determine whether the drug candidate will be likely to garner regulatory approval and, if so, whether it will be competitive in the marketplace earlier in the development process than may have occurred in the past.

Key Elements for Product Approval

Advancing a product from the laboratory into the clinic or from early to late development while necessary for product approval will turn out to represent a failed investment if the product does not get approved. Therefore, it is important for all individuals working in drug development to have a sound understanding of the elements that are required for marketing authorization of pharmaceutical products globally. Whether one is working to register a new chemical entity, a new biologic agent, or a new medical device, the same principles apply. Demonstration that a product is effective followed by a listing of the adverse events experienced during the clinical trials will rarely be sufficient for approval with a few exceptions. These exceptions include diseases with high unmet need where no treatments are available.

The key measure for health authorities in 2010 is the benefit to risk ratio (BRR) for the specific indication and specific population. For example, one may get approval for a product for hypertension, colon cancer, or rheumatoid arthritis. It may be approved for first-line therapy, or it may be approved for use after first- or second-line therapy. How the BRR of the product compares to other available alternatives will determine whether approval is for first-line, second-line, or salvage therapy. It is also a function of whether or not the sponsor has developed the product in a manner that highlights its benefits in specific populations, or relative to other products. These can be defined by means of demographic, disease, or genetic characteristics.

Approval truly boils down to whether the sponsor can genuinely demonstrate and communicate a sound understanding of how their product works. This requires building upon the foundation of the mechanism of action (MOA) to select a patient population that should benefit based on the MOA. The next step is to validate the working hypothesis by demonstrating efficacy in the target population. Finally, one must show a comparable or better overall BRR compared to other available treatments for the specific population to be used as first-line therapy.

These changes in regulatory attitude are part of the change in medicine towards individualization of therapy. While this is being led in oncology through the increased use of tumor antigens to determine prognosis and treatment, it is occurring in many other disease areas through the use of patient characteristics including laboratory and imaging variables [11]. Defining the patient population(s) that will benefit is a key part of any clinical development program.

How have these changes in health authority decision making impacted clinical development programs? These changes have resulted in the selection of molecules with very specific actions that maximize their effect on the desired pharmacological target, while minimizing unintended off target effects. Monoclonal antibodies have experienced a marked increase and represent an increasing percentage of new products reaching the market [12].

Earlier Decision Making

Unfortunately, pharmaceutical product development will have more products that do not make it to market relative to those that succeed. A product that does not make it to market generates no revenues. Within organizations there is often a desire by team members to continue projects despite extremely low probabilities of ever recovering the associated expenses. As the competitive landscape intensifies, successful organizations will be those who are able to generate scientifically robust and clinically relevant data early in the development process and those who make evidence-based decisions on therapeutic agents within the development portfolio [13].

During phase I studies individuals with the targeted disease are being studied earlier and more extensively than they were historically. This is because while healthy volunteers can be used to determine the basic pharmacokinetics, effects on vital signs, and routine laboratory parameters, they are not informative in providing data relative to the pharmacodynamics of the disease process. Phase I studies provide the opportunity to explore the effects of the drug on the pathophysiology of the disease. Proof of principle is often established in phase I. A good understanding of the impact of the drug on the various components of the disease guides the doses to be taken forward into phase II.

Phase II studies will prove that the scientific concepts leading to clinical improvement in the target disease have been met. They will hone in on the population(s) that will derive the greatest BRR, as well as the dosing regimen to be used in phase III. Increasingly, active comparators are being included in phase II studies so that sponsors can determine where (e.g., first versus second line) in clinical practice their therapy will be used.

Inevitably, at the end of phase II, there remain unanswered questions regarding the product and its potential to modify the targeted disease. Could these data have been collected earlier in the development process? In many cases, the answer is yes. Phase III studies are becoming increasingly larger and often represent major investments even for the large multinational companies. While it is relatively easy to make a good decision when the information quality is excellent, as the ambiguity of the data increases, the probability of making an investment error in the hundreds of millions of dollars for the initiation of a large phase III program increases. The take home message is to invest in understanding the MOA of the product and the impact of the drug on the pathophysiology of the targeted disease population by the end of phase II such that informed investment decisions can be made. Companies that do not do this are unlikely to remain viable in their current form.

Opportunities for Imaging

From a regulatory perspective, health authorities are looking for a logical sequence of events that give them a high probability that the product will perform as suggested by the sponsor in their marketing application. Health authorities do not want surprises. They are charged with protecting the public health which means that the public needs to be fully aware of any actual or potential safety issues. A thorough development plan will utilize early data such as the MOA and drug distribution to outline potential efficacy and safety effects. Potential safety issues if clinically significant will need to be assessed promptly. The use of imaging to evaluate potential safety issues is increasing. The observation of some fractures during a phase II study in a drug with a theoretical risk of impacting bone metabolism can be assessed by adding a bone mineral density sub-study into phase III. The risk of heart valve dysfunction can be addressed with echocardiography. The risk of direct CNS effects can be mitigated by demonstrating the absence of drug in the CNS using PET. Studies addressing specific safety concerns may be best performed during phase II since the presence or even the probability of certain safety issues can have a major impact on the approval of a product and may therefore influence the decision of whether to proceed into phase III.

In summary, imaging studies can be very useful in understanding how the pharmacological product modifies disease progression. This can lead to better decisions regarding the dosing regimen, the probability of clinically significant safety issues, and, ultimately, whether to progress further in developing the product. In many therapeutic areas imaging studies are required for initial approval or approval of specific indications.

Detection of Disease Progression

Many diseases remain asymptomatic until they are relatively advanced. Examples include atherosclerosis, osteoporosis, and certain malignancies. In many diseases including rheumatoid arthritis, patient symptoms both at the level of the joint and systemically may not correlate with disease progression obtained through imaging studies. Imaging may be considered more objective than documentation of clinical symptoms. This is not surprising since reporting of clinical symptomatology is dependent upon several factors which are difficult to precisely control in the context of a clinical trial.

One major challenge facing pharmaceutical companies is that in certain therapeutic areas, there are already high-quality medicines available to treat the disease. This may mean performing a head-to-head trial against existing options or comparing the existing therapy to a combination of the new and existing therapy. In both situations, the difference in therapeutic effect will be less than a comparison of the new agent to placebo. Since imaging is in essence “a sharper scalpel,” the use of this

instrument to demonstrate a relative improvement in either efficacy or safety can greatly modify the use of the product. An increase in progression free survival relative to existing standards of care in oncology is one example. For all late stage clinical development programs, imaging endpoints should be considered in evaluating the BRR relative to existing therapeutic options.

Do the Results of the Imaging Study Answer the Key Scientific Question?

Unfortunately the answer is often not to the degree that is necessary for health authorities. Why is this so? Suleiman and Gorovets in April 2010 presented their observation that the FDA desires scientifically robust evidence. However, many of the imaging trials lacked standardization, calibration, and reproducibility. They compared the standards for drug quality and purity required for chemistry manufacturing control and stated that similar rigor should be applied to imaging [14]. They note that several studies did not have sufficient power to detect a difference between treatment groups due to the large variability observed for the imaging parameter. This becomes particularly relevant when conducting non-inferiority studies for efficacy. It is also pertinent for safety studies because results which show no difference between a drug in development and placebo may not be considered sufficiently robust if there are no data on within subject variability of the imaging parameter to enable determination of study power. If a clinically meaningful difference is not detectable using the imaging technology due to inherent limitations in the technology employed in the study, or due to poor implementation of imaging standards, this will be considered an irrelevant study and will not diminish a safety risk.

Imaging studies are used to measure one or more variables associated with disease progression. This requires attention to detail for each of the steps involved in the process analogous to the manufacturing of marketed drugs. Lack of attention to critical details will result in a study that has similar value to a batch of a pharmaceutical product that does not meet desired product specifications.

Key Considerations for Successful Imaging Studies

Creating a Successful Imaging Team

The clinician(s) within the clinical development team are usually responsible for the task of clinical trial design with input from their statistical colleagues. The key component of a successful imaging trial is the recognition that specialized skills beyond those of the lead clinician and the core development team will be required. These imaging professionals, whether they are within the organization or external, should be involved early in the process of trial design. As a team leader, it is helpful to map out the key questions that will need to be addressed and to seek input from

individuals with the appropriate knowledge and experience to provide constructive input. Table 6.2 outlines some key questions that will need to be answered in order to develop the imaging component of a clinical trial and the skills that are required to answer these questions. For illustrative purposes a proposed study evaluating a novel agent for rheumatoid arthritis will be discussed. Management would like to know if this compound will modify disease at the level of the joints prior to investing in a phase III program which will cost in excess of 500 million US dollars.

Imaging Endpoints

In responding to management's request, there is a multitude of information that must be acquired and processed by the team in order to develop reasonable designs for their phase II study. This includes all of the parameters listed in Table 6.2. Generally, the first aspects of trial design that need to be agreed upon are the key endpoints and the associated imaging technology through which they will be measured.

In rheumatoid arthritis only a small percentage of patients will demonstrate progression of joint damage over a 12-month time period using radiographs. The size of a study using this imaging technology will require 300–500 patients per group [15]. MRI and ultrasound can detect changes in the joint that cannot be detected with standard radiographs. Therefore, changes can be detected at earlier time points and in a greater percentage of patients enabling a smaller sample size.

Another consideration is that as the imaging technology becomes more sensitive to detecting smaller changes, one must determine which specific imaging changes are temporary and reversible and which specific changes represent disease progression. This is part of the evolving advances leading to improvements in standards of care. In drug development, one must also have a firm understanding of what changes are predicted to be improved based on the mechanism of action of the molecule under development, over what time period, and in what patient population? The answers to these questions will be important in the design of the clinical trial program.

Invariably, there will be different answers to these questions based on which literature source is referenced and whose clinical opinion is sought. There will be variability in the imaging data reported depending on the patient population studied, the acquisition method, hardware, software, and reading methodologies. Professionals skilled from a clinical perspective in conducting research in this area can be helpful. Likewise, experienced musculoskeletal imaging professionals especially those who have conducted clinical trials with similar endpoints will provide significant value. Ultimately, one will be required to estimate the incidence of imaging changes, the rate of change over time, and the effect of the pharmacological intervention in the population under investigation in order to design and adequately power the studies.

Say that a preliminary decision is made to proceed with MRI as the imaging modality and the anatomical areas for evaluation include the hands, wrist, and feet

Table 6.2 Key elements in the design of imaging parameters within clinical trials

Key questions	Relevant parameters/examples	Skills required
Endpoint(s) to be measured and selection of imaging modality	Joint space narrowing and bony erosions by X-ray are the regulatory standard for approval in phase III. Synovitis, tenosynovitis, bone marrow edema and bursitis can be detected by MRI or ultrasound	Rate of change over time in the population of interest. Determination of the change that is most likely to be impacted by the treatment over the intended duration of the trial
Availability of validated metrics for the selected endpoint	Scoring systems validations conducted	Knowledge regarding test validation and regulatory standards in imaging
Imaging hardware	Acceptable hardware for imaging of key endpoints	Ability to detect changes in the selected parameters. Differences between available hardware and impact on imaging endpoints
Image acquisition	Protocol for image acquisition	Performance characteristics of imaging devices
	With or without contrast Image type and desired resolution	Experience with the pros and cons of different acquisition protocols
Precision (reproducibility)	Difference between two measurements from the same patient on the same day	Knowledge of the conduct, analysis, and interpretation of reproducibility studies
Accuracy	Comparison to gold standard (phantom)	Determination of whether phantoms are required for this study
Image analysis	Hardware and software	Knowledge of the clinical relevance of differences in hardware and software
Image interpretation	Read methodologies	See Chap. 5
Data management	Identification of key imaging metrics for both operational purposes and statistical analysis	Experience in the therapeutic area with the specific imaging technology and operational experience
True potential for detecting change	Following selection of the patient population, imaging modality, and image acquisition protocol an estimate of the change that will be demonstrated in the control group and in the treatment groups	Experienced individuals in translating potential for detecting change into an accurate estimate of expected change between groups in the clinical trial

joints. Are there scoring systems that are recognized for MRI in rheumatoid arthritis? Are these scoring systems validated and if so by what methods? Are they acceptable to health authorities? In addition to the professionals mentioned previously, individuals experienced in validation and with the evolving regulatory position on imaging endpoints will provide significant value to the team.

Imaging Hardware

Once the imaging modality has been identified, the question of which equipment to use for this clinical trial arises. Manufacturers of MRI scanners improve their products over time. Published literature may be based on single-center studies with scanners that are not currently used by many imaging facilities. Knowledge regarding scanners from different manufacturers and even models within the same manufacturer are relevant. Scanners in use at sites that will be considered for the study will need to be determined. Biomedical engineers can explain these differences. Discussion between the biomedical engineer and clinician will be helpful in making decisions regarding the tradeoff between hardware consistency and models available at potential sites. Manufacturers are usually very willing to have their engineers go through the specifications and performance characteristics of their products. Most will explain to you why their products are superior to those of their competitors. This process can be confusing as it can be difficult to determine how these differences in technical parameters will impact the images acquired for the study. It can also be quite challenging to determine the magnitude of the impact that these differences will have on the imaging endpoints proposed for the study. CROs with professionals experienced in imaging often have staff members who are familiar with manufacturer upgrades and understand the differences including the impact that these differences will have within your trial. Consulting them will save time and get you the information needed in a timely fashion.

Image Acquisition

For purposes of discussion, image acquisition includes all of the steps from when a patient enters the imaging suite until the images are digitally stored. Ideally image acquisition should be identical for all scans in the study. In reality, numerous factors that vary over time limit us to approximating this goal. A standard acquisition protocol must be developed. This includes all of the variables that may impact image metrics. These include patient positioning, slice thickness, image type (e.g., T1 or T2), and use of contrast. Having the same technician perform the scans is the most important variable. Incorporated into a particular technician's routine is not only positioning but also many other factors involved in their management of the patient through the process. It is good practice to speak with site technicians regarding whether the proposed acquisition protocol is easily understood and reasonable to conduct in their facility.

Precision

Reproducibility refers to the difference obtained between two scans, obtained with the same scanner, by the same technician on the same patient; see Chap. 2 for comparison of precision and accuracy. In some publications this is also referred to as the

precision of the measurement. Typically a scan is performed using the study protocol. The patient is instructed to get off the scanner table and a few minutes later the process of performing the second scan is initiated. The difference between the two scans represents the intra-subject variability. This should be performed on a group of patients with different degrees of disease to assess the intra-patient variability across the disease spectrum. These studies are usually performed at 1–3 sites. Good technicians will be able to point out sources of variability within the acquisition protocol. This will serve as the basis for site training that is required to qualify imaging personnel at the site and ongoing training and monitoring procedure to minimize variability between sites [16].

When conducting clinical trials, consistency is extremely important. Even the same scanner will generate different results over time. How does one detect and manage these changes? Also when we get a reading from a scanner, how close to the truth is it? Accuracy is the term used to describe how close a measurement comes to a "gold standard." Phantoms can be utilized to describe accuracy and to monitor consistency. If phantoms do not exist for the anatomical area under investigation, you may want to consider having one built. This will be a costly procedure, so it is best to discuss this with an experienced imaging professional. Typically phantoms are imaged at regular intervals during a clinical trial in order to detect variation in machine performance over time. Minor changes in machine performance can be managed by applying correction factors to the study images generated, but more significant changes may make some of the images unsuitable for reading. Images which do not meet the predefined study quality standards will require a repeat image for reading. If this does not occur within a specific time period as defined in the protocol, there will be no usable data for this patient. Since imaging endpoints are typically calculated as the change from baseline, the baseline and final images are the most critical. Statistical analysis will commonly be performed using a last observation carried forward methodology. Therefore scans which are missing will tend to reduce the change detected with the effect of reducing study power.

In addition to imaging hardware, the software provided by manufacturers is routinely updated. These software programs contain instructions for assessing the pixels acquired during the scan. These instructions result in a digital image or a numerical value.

When a digital image is generated, it must be quantified by readers trained according to study-defined prespecified criteria. Strategic thought is required to develop an appropriate read methodology. All data must be maintained with a full audit trail in compliance with ICH and CFR part 11.

Statistical Considerations

Several statistical inputs will be required in order to intelligently design the studies. The minimal detectable change refers to the minimum change that falls outside the measurement error for an instrument. These determinations are usually performed under idealized conditions with highly experienced imaging professionals. In

statistical terms for normally distributed data, this is defined as [$1.96 \times \sqrt{2} \times$ standard error of the mean]. The standard error of the mean is the standard deviation of the measurements divided by the square root of the number of measurements.

Another key variable is the minimal clinically important change which represents the smallest change that is clinically relevant. Ideally, one powers a study sufficiently to detect a change that is greater than the minimal clinically important change. While it seems obvious, this change must also be greater than the minimal detectable change. Studies have been performed where the variability of the imaging measurements were sufficiently large such that the minimal detectable difference was greater than what the study had been powered to test.

The design of imaging endpoints in clinical trials involves the estimation of the difference between treatment groups for the population under investigation. Additionally estimates of the variability in measurement must be performed. It is important to have productive discussions regarding tradeoffs between scientific precision and operational efficiency regarding patient recruitment. Investments in minimizing variability may be greater when imaging is the primary endpoint compared to when it is a secondary endpoint. Lastly, many of the team members involved in the study design should remain engaged in the project as the study is initiated. When a handoff of a protocol occurs to an operational team, it is easy for the operational team to focus on recruitment which can sometimes be at the expense of image quality and consistency. Therefore maintaining a degree of project history including the rationale for specific aspects of protocol design will increase the probability of a successful study.

Core Principles Pertinent to Imaging Studies

The practice of clinical medicine where patients are treated on an individual basis is very different from the design and conduct of clinical trials. When evaluating and treating a patient, the core information is their clinical signs, symptoms, comorbidities, lifestyle priorities, values, etc. One then uses your knowledge base as a healthcare provider, consisting of the literature and personal experiences to present treatment options to that particular patient. In contrast, clinical trials are performed with the objective of determining the impact of a specific intervention such as a new pharmaceutical agent on a specific treatment outcome. In order to achieve this objective, we standardize the patient population that can participate as well as the treatment regimen. While we allow some variability in the patient population, we are more stringent regarding the treatment protocol. We do this because we know that increasing the variability in the treatment regimen by permitting variations in the dosing regimen (e.g., varying the dose intervals or drug quantities, skipping doses) or variations in the assessments (e.g., morning versus evening, month 2 or 4 versus month 3 of the study) will make it more difficult to determine the effect of the treatment being investigated.

When we use imaging to measure a biological variable, we are often trying to detect relatively small but clinically significant changes. Therefore minimizing

variation in the conduct of the imaging assessments requires planning and attention to key details during trial execution. We have divided key considerations pertinent to the design and conduct of imaging endpoints in clinical trials into the following four categories: scientific, regulatory, financial, and operational. While these categories will contain items that overlap, they are broken out in this manner because they require a different focus and as such are often the responsibility of distinct team members within biopharmaceutical organizations. For early phase studies, we have integrated these four functional areas and subsequently describe them separately for clinical trials in phase II and beyond.

First in Man Studies: Role of Imaging

Despite extensive testing of new chemical entities in animal models, differences in bioavailability, pharmacokinetics, tissue distribution, and metabolism are significantly different in humans, resulting in modifications that can cause considerable delay or termination of a project. To address these issues, phase 0 also known as microdosing studies can be performed. Guidance for conduct of these studies can be found on the websites of the EMA and FDA. The dose administered must not have any pharmacological effect. It has been defined as the administration of 100 μg of candidate drug or 1/100th of the pharmacological dose determined from animal models and in vitro systems, whichever is lower. PET scanning is the most common imaging technique used to determine pharmacokinetics, pharmacodynamics, and tissue distribution in these studies [17].

PET scanning requires labeling of the compound with [^{11}C] which has a half-life of 20 min or [F18] which has a half-life of 110 min. Fluorine-18-labeled glucose (FDG) is widely used to measure glucose uptake in tissues. The use of [^{11}C] necessitates that the radiolabeling laboratory be within a few minutes of the imaging facility as the rapid decay will not usually permit accurate detection for determination of pharmacokinetics of the compound beyond 2 h (6 half lives) from the time of synthesis. These studies can determine whether a compound is getting to its intended location and also whether it is distributed to unintended areas. The use of FDG-PET or F-18-labeled investigational drugs with its longer half-life allows greater flexibility.

Phase 0 studies have been used for candidate selection [18, 19], for example, when there are 2–3 potential molecules that have the desired activity in animal models. Since humans and the animal models may differ significantly, administration of each of these molecules in a phase 0 study to 3–5 study subjects will provide data that can determine which of these molecules (if any) should be advanced further. Pharmacokinetic parameters and tissue distribution can aid in this important decision. These parameters as well as bioavailability, tissue distribution, and metabolism are estimated to differ materially in humans from estimates based on animal data in one third of cases. Candidate selection can also be performed in an iterative manner. In this paradigm changes to the structure of the molecule are made based on initial phase 0 study results. The new molecule is then tested in another phase 0 study until acceptable parameters are obtained. These phase 0 studies are also informative for determining the first dose for the subsequent phase I study.

Once a drug is being introduced into humans, an early readout regarding standard bioavailability, pharmacokinetics, and pharmacodynamics is desirable. While bioavailability, pharmacokinetics, and basic safety parameters can often be obtained in healthy volunteers, pharmacodynamic parameters may only be informative in individuals with the targeted disease. This favors the inclusion of patients for whom the new therapy is targeted to be included early during phase I. For some therapeutic areas such as oncology, the risk to benefit ratio is such that only individuals with the specific-targeted tumor may be included. Imaging provides a key pharmacodynamic measure in early phase trials within oncology and neurosciences.

Currently a biomarker plan which is a consideration of the key anticipated pharmacodynamic effects of the drug is part of the clinical development plan. Individuals charged with developing this plan may have little or no familiarity with imaging and may restrict their plan to evaluation of parameters that can be assayed from serum samples. For several indications such as prostatic hypertrophy, osteoporosis, and oncology, imaging early in development provides information that will increase the quality of subsequent decision making.

Often there is an argument that the incorporation of imaging parameters into phase I trials will exceed the planned budget for a specific phase I study. This is more common in organizations where the phase I unit is organized into a distinct group with a limited operating budget. As stated previously, when viewed as an integrated development effort, if imaging assessments can provide scientifically valuable information regarding efficacy or safety that will impact subsequent development decisions (including project advancement versus termination), then they will be highly cost-effective. Of course the inclusion of imaging parameters when their outcome will not be used in the decision-making process is in essence for academic interest only. In this situation, they are simply a cost with no preplanned value.

Phase II and Beyond: Scientific Considerations (Strategic and Technical)

Imaging endpoints differ in many respects from patient-reported outcomes or binary clinical outcomes such as the occurrence or nonoccurrence of a myocardial infarction. Therefore assuming that well-trained clinicians can implement imaging parameters into clinical trials within their area of therapeutic expertise can lead to unanticipated outcomes. The implementation of imaging endpoints requires a much greater attention to operational detail than occurs at most clinical visits during a research study. Since clinicians responsible for study design and conduct may not be sufficiently experienced in imaging principles, it is not surprising that the most common criticism from imaging authorities or experts regarding the design and implementation of imaging endpoints in clinical trials is that they are poorly conceived from a scientific perspective. Studies which are flawed scientifically can be well executed but will still not result in regulatory approval and will not recoup the

initial investment. Therefore a firmly grounded scientific basis is the foundation for the successful use of imaging endpoints.

Many of the key questions involved in developing a design for imaging parameters are listed in Table 6.2. Conceptually, one needs to determine what information related to the physiology of the disease process will be obtained through the use of imaging. The question that follows is whether this information will be of practical use either in the clinical development process or in clinical practice.

For example, say you are evaluating a drug that is intended to slow the rate of decline in disease for patients with emphysema. You can use pulmonary function tests to follow the severity of emphysema, so what additional information, if any, would be gained from the addition of imaging endpoints to the trial? You perform some investigative work and determine that there is evidence that CT findings correlate with the presence and severity of morphologic emphysema better than do results of pulmonary function tests [20]. Your initial assessment is that incorporation of pulmonary CT into your phase II trial will improve clinical decision making. Therefore you wish to employ an imaging endpoint in your trials.

Now that you have decided from a strategic perspective to pursue the use of imaging, technical considerations arise that need to be worked through. What are the appropriate imaging modality and appropriate technique to use? Assuming that high-resolution CT is selected as the imaging modality of choice, additional questions that require the involvement of technical experts remain. Should the CT scans be obtained using 10 and 1.5 mm collimation, or should 5 and 1.0 mm collimation be selected? Should software programs be utilized to highlight areas of abnormally low attenuation? If so, which model scanners and which software programs will provide reproducible data? What are the advantages and disadvantages of proceeding with one approach versus another? The need to involve individuals with expertise not only on the clinical side but also with technical expertise related to image acquisition early in the process of study design becomes apparent.

You have been diligent in your research and are now presenting your protocol to the protocol review committee. This committee includes individuals with highly variable skills and knowledge regarding the therapeutic area. How do you increase the likelihood that sound scientific decisions will be made in a timely manner? Table 6.3 provides a framework for making decisions on whether to incorporate imaging endpoints into clinical trials.

Rather than attempting to quantify the value added by the imaging data from low to high, we have categorized the value into essential, supportive, and nice to have.

Essential Studies

Imaging endpoints may be performed to assess efficacy or safety endpoints. In 1997 fenfluramine which was used for weight loss was withdrawn from the market due to evidence that its use caused a thickening of the leaflet and chordae tendineae. Fenfluramine and its active metabolite norfenfluramine are agonists of 5-HT_{2B}

Table 6.3 Strategic consideration for incorporation of imaging endpoints

Category	Scientific standards	Example (s)
Essential	Scientific standard of care	Echocardiography for the evaluation of valvular function
	Regulatory standard	Radiographs for rheumatoid arthritis
	Required to demonstrate proof of principle	PET imaging to demonstrate presence or absence of a new chemical entity to specific areas in the CNS
	Proof of concept	Bone mineral density as a surrogate for fracture risk
	Mechanism of action	Demonstrates the intended MOA of the compound in either preclinical or clinical studies
	Increased sensitivity for detection of change relative to regulatory standard	MRI for changes in the joint in rheumatoid arthritis
	Defining a target patient population prospectively through imaging	Fracture reduction based on bone mineral density at time of study initiation
Supportive	Adds information regarding treatment induced changes in physiological parameters	CIMT, pulse wave velocity
	Data are anticipated to be informative relative to subsequent development decisions	Imaging in phase II studies for rheumatoid arthritis, oncology
Nice to have	Studies that provide evidence of additional benefit	Body composition for diabetes
	Characterization of specific populations that benefit	Subpopulations not identified in the registration studies
	Use of the pharmacological agent in clinical settings	Demonstrating how use of imaging in practice can improve clinical outcomes
Potential for future development	Enhancement to currently labeled treatment regimens	Lifecycle management
	Mechanistic studies	Improved understanding of disease pathophysiology

receptors, which are postulated to have led to a pathological increase in cell division in the heart valves. Supporting evidence for this mechanism is the finding that other drugs acting on 5-HT_{2B} receptors are associated with similar findings [21]. Therefore in the development of lorcaserin which is a selective 5-HT_{2C} receptor agonist, with a 100:1 relative binding affinity for 5-HT_{2C} relative to other receptors, it was necessary to evaluate the impact on cardiac valvular function. The performance of echocardiograms prior to and during treatment is the current scientific standard for evaluation of cardiac valvulopathy.

Regulatory guidance is available online from FDA and EMA regarding specific indications. These guidances are built upon historical precedent. Most

health authorities are risk averse consistent with their mandate to protect public health. They will often insist upon maintaining the current imaging modality within the phase III registration trials (e.g., radiographs for rheumatoid arthritis) and will enable the incorporation of additional imaging data into the product label if a case can be made that these new data are clinically pertinent. If the imaging modality (e.g., MRI for rheumatoid arthritis) is used in clinical practice beyond research purposes, then this will usually meet the criteria for clinically pertinent. It is essential to meet with global health authorities and to provide your scientific rationale for the use of specific imaging modalities within the development program. If the health authorities can follow the scientific rationale, they are more likely to support its inclusion in the prescribing information upon approval.

While some use the terms proof of principle and proof of concept interchangeably, we will use them distinctively for the purpose of drug development. Proof of principle involves the interaction between the drug and its intended target in the species of interest which is usually the human. For a drug intended for depression, localization to specific anatomical regions in the CNS by PET scan, in conjunction with in vitro receptor-binding studies and in vivo animal studies together, may demonstrate proof of principle. The principle being that the drug binds selectively to a particular receptor that is localized in its anticipated area in the human brain. Proof of concept is the demonstration that this drug through binding to this receptor will translate into a clinical improvement in depression. This proof of clinical concept will occur by evaluating specific dosing regimens in patients with depression.

In drug development for osteoporosis, the demonstration of increased bone mineral density by DXA (Dual energy X-ray absorptiometry) was sufficient for securing a marketing license until fluoride was marketed. Fluoride administration resulted in marked increases in bone mineral density but was associated with an increased fracture risk. The reasons for this were subsequently elucidated through evaluation of bone biopsies. Currently demonstration of an increase in bone mineral density in conjunction with bone biopsy data demonstrating good bone quality represent proof of concept for osteoporosis. A phase III trial is still required in order to demonstrate a reduction in fracture risk [22].

Advances in imaging technology may include the development of new modalities, novel applications of existing technology and most commonly improved precision and detection limits with a new generation of hardware. If the technology has been validated, which is a requirement for commercializing a new generation of scanners, and presents some advantages over existing methods, then it should be considered for use up through phase II. One example is the use of a new generation of high-resolution CT to determine if a product [23] for emphysema can favorably modify lung structure or delay disease progression. Another is the use of MRI in rheumatic diseases. The imaging modality used for phase III will require discussion with key global health authorities.

Supportive Studies

Imaging may at times serve as both an efficacy and a safety endpoint. In oncology, imaging of tumors is standardized. The primary endpoint in most clinical oncology studies is patient survival or progression free survival. Reduction in tumor size is often a secondary endpoint. From a drug development perspective, tumor size is also a safety parameter and most dosing regimens that document increases in tumor volume will not be progressed further.

For purposes of discussion, we classify supportive indications for imaging as circumstances where imaging data have a high probability of adding value to the clinical development decision making, but they are not expected to be pivotal in driving decision making. In cardiovascular development clinical outcome trials are commonly required. Surrogate parameters such as lipoprotein changes are not sufficiently robust in predicting the result of outcome studies. Therefore imaging studies such as carotid intima-medial thickness (CIMT), pulse wave velocity, or other assessments can be used to determine if there is an additional effect beyond lipid changes. These studies may assist in dose selection or in determining whether to invest in phase III. However, these studies are not considered essential.

Many circumstances occur during drug development when decisions regarding the timing of specific assessments must be made. In the previously discussed example for rheumatoid arthritis, management accelerated the imaging data into phase II in order to have higher quality data in planning for phase III. Strictly speaking, these data are not required and a dosing decision could have been made based on traditional biomarkers such as C-reactive protein. As is the case for much of the data that fall into the supportive category, if they have meaningful economic value, they will merit consideration.

For assessment of multiple sclerosis examples of imaging parameters include optic nerve magnetization transfer ratio, retinal nerve fiber layer thickness (by optical coherence tomography), brain lesion magnetization transfer ratio, MRI brain T1 hypointensity load, or new T2 lesions, the latter of which is the regulatory standard. PET scanning is being used more commonly in CNS disorders. In summary, this therapeutic area will involve imaging studies that have a high probability of yielding scientific information that will be of value during the clinical development program.

Nice to Have Studies

Imaging studies that are essential in phase IIIb studies to gain approval for additional indications are considered essential. This category of "nice to have" is defined as imaging studies that will not affect decisions regarding whether or not to continue development of a compound for its primary indication and will not affect a decision by health authorities regarding marketing authorization for that indication. These studies are

commonly performed to provide additional evidence of clinical benefit. Examples include body composition studies for diabetes drugs which have been used to highlight differences between agents, QCT in osteoporosis, and MRI in osteoarthritis [24].

Imaging studies to better understand the pharmacological effects of a new chemical entity may be performed as a nested sub-study in a phase III program or in a phase IV trial. In general the rationale for their conduct is primary based on marketing considerations. Phase IV studies that can have a considerable public health impact are those which evaluate the use of an imaging assessment on patient care and clinical outcomes. Examples include the role of bone mineral density measurements in the management of osteopenia or the role of radiographs in the management of rheumatic disorders.

Potential for Future Development

This category refers to studies designed to test a hypothesis for which there is no immediate return on investment for the current compound. They may be performed with the intention of a return on investment that is beyond the time horizon for the current compound. These may include the development of new imaging biomarkers for specific diseases. For example, one may wish to validate MRI endpoints for disease progression such that these endpoints may be discussed with health authorities. If these new imaging endpoints are more sensitive in determining disease progression and are accepted by health authorities, then phase III clinical trials may be able to be performed with fewer subjects. Similar paradigms hold for other therapeutic areas such as osteoporosis.

Many of these studies are carried out in partnership with academic institutions. They may seek to improve upon the clinical outcomes achieved in the registration trials by modifying the treatment regimen according to the data from imaging endpoints. For instance, disease progression may not be associated with clinical symptoms until late in the disorder. A demonstration of disease progression through use of imaging endpoints (e.g., in rheumatoid arthritis, osteoporosis, atherosclerotic heart disease) may result in more aggressive therapy and/or improved patient compliance that will yield improved outcomes. Healthcare practitioners will compare different treatments for different populations in order to prioritize amongst available therapeutic options. This may include a comparison of medical to surgical options. Researchers interested in better defining the pathophysiology of the disease may utilize a pharmacologic agent as a probe to define disease subtypes. It may also be used as a proof of concept for a new indication. The potential scope of imaging studies outside of industry related clinical trials is expansive and beyond our intended scope.

Protocol Development

When one is primarily mimicking a predecessor's clinical development strategy, protocol development is straightforward. For first in class compounds and for novel therapeutic indications with high unmet need, the potential for a huge success is

apparent, but so is the risk of failure. In the end, the one individual who has the greatest impact on the success of a clinical trial is the person charged with protocol development. Success is not predicted on a specific IQ score, but rather on the wisdom of seeking and interpreting seemingly disparate information and most importantly being diligent in working through all of the scientific issues. If the imaging component of a protocol is written with statements along the line of "high-resolution pulmonary CT will be obtained at baseline and at the end of study visit," this must be accompanied by a detailed explanation of what is meant by high-resolution pulmonary CT. This information is best suited to the imaging charter which can be referenced in the body of the protocol. Since the protocol should describe all of the study procedures, the imaging charter is considered part of the protocol and needs to be included in health authority communications regarding scientific guidance.

No matter how expert you feel that you are in a certain area it is important to listen to others both internally and externally. Engaging staff at prospective clinical sites can provide a good reality check that is pertinent. It is important to understand prior to study initiation, what will really happen at clinical sites and how they will manage specific protocol instructions. Engage a number of external consultants, but rapidly determine which ones provide value to you and forge ongoing relationships with these individuals or organizations. Keep internal and external stakeholders informed regarding your progress and decision making. Stay focused; thousands or even millions of patients may be eagerly awaiting the outcome of the trial you are designing.

Regulatory Considerations

The pharmaceutical and medical device industries are highly regulated due to the potential for adverse events as a consequence of their products. Earlier in the development process, the risk of adverse events relative to any clinical benefit that may be derived is higher. The benefit to risk ratio continues to increase throughout the development process such that at the time of marketing authorization the benefit to the patient significantly outweighs the risk. Health authorities are charged with protecting patient safety throughout the development process. Interaction with global health authorities is required at key points during development. These include but are not limited to the investigational new drug application which is required to administer the product to humans.

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies – Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experiences with the drug in humans (often foreign use).
- Manufacturing Information – Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

- Clinical Protocols and Investigator Information – Detailed protocols for proposed clinical studies to assess whether the initial phase trials will expose subjects to unnecessary risks; also information on the qualifications of clinical investigators – professionals (generally physicians) who oversee the administration of the experimental compound – to assess whether they are qualified to fulfill their clinical trial duties; and finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk (FDA.gov IND Application).

One should not assume that if no response is forthcoming within the specified time interval that the regulatory agency is in full agreement with the sponsor's plan. Regulators may find themselves in situations where there are more documents to review than is possible within a particular time. If there are key areas that should be resolved prior to initiating first in man studies, it is best to be proactive and to indicate to the agency that communication on a particular topic is sought. Depending on the complexity of the topic and work tendencies within a health authority, communication may be in writing, by teleconference, or at a face-to-face meeting. Requesting a pre-IND meeting is highly recommended as this is an excellent opportunity to discuss issues where there is any level of doubt.

Given that regulators are very busy, it is important to provide them with high-quality documents that clearly state the key questions which need to be agreed upon. The scientific considerations need to be stated in a logical and easy to follow manner. Regulators need to balance patient safety risks with the potential benefits of the product under investigation. Their objective is aligned with industry in that they want safe and effective products to be brought to market. It is critical to listen very carefully to the guidance provided, to clarify the scientific advice, and also to challenge it based on either scientific evidence or regulatory precedent.

Global health authorities are available to meet with sponsors throughout the drug development process to resolve issues that arise. It is important to realize that health authorities are responsible for protecting patient safety during the development process, but are not responsible for deciding how to develop the drug. While formal scientific advice is available from several health authorities, it is "advice" and does not mean that following the advice is mandated nor does it guarantee that if the advice is followed and the primary endpoint is met, that approval will be granted. On several occasions, sponsors have asked health authorities their opinion on the best way to proceed with a specific drug candidate in development. These questions are out of scope for the regulators. It is up to the sponsor to propose a development plan. The regulators will review the plan and provide concerns, objections, or endorsement of its components. Be respectful of the agencies time and communicate professionally. Frequent communication on trivial matters will be more likely to cause a health authority to view the sponsor as incompetent rather than fostering a positive relationship.

When meeting with health authorities, "there should be free, full, and open communication about any scientific or medical question that may arise during the clinical investigation" (CFR title 21). This directive means that full disclosure is required. Therefore, all potentially pertinent data need to be presented. Suppression of potentially unfavorable data is unacceptable and will lead to difficulties in the future. Potential safety signals should be clearly identified, and the sponsor should present a plan for their evaluation during the ongoing clinical development.

Considerations for Trial Design and Conduct

Your imaging partner should be versed in the regulatory standards for the therapeutic area and also be up to date and in compliance with good clinical practice (GCP) standards and with CFR 21 part 11. Most contract research organizations with good imaging services and expertise will be able to provide consulting services during study design for nominal fees in comparison to the total study costs. Getting your imaging partner or an imaging consultant involved early in protocol design will expedite the process and will enhance the quality of the trial.

Table 6.4 outlines different situations that may be encountered as part of the clinical development process. Similar principles apply whether we consider a laboratory parameter such as glycosylated hemoglobin, a patient-reported questionnaire, or an imaging parameter. The first and most important principle is that the sponsor is responsible for and accountable for the development program and its outcomes. The health authority will provide guidance and may mandate certain procedures to maintain patient safety including placing a program on clinical hold, but the sponsor is ultimately responsible for their program. When guidances exist that are current, the task is straightforward. Regulatory guidances for imaging parameters are behind those of other clinical endpoints such that interaction with imaging professionals who have been involved in health authority interactions with successful programs are currently recommended. As published guidelines are written by FDA and others, followed by accumulation of experience with these guidelines, the need for such interaction may be reduced. When changes in the imaging endpoint are sought due to emerging endpoints which may have enhanced predictability for disease progression, discussion with health authorities regarding methods used to validate these endpoints will be required. Differences in image acquisition, read methodologies, or other parameters should be detailed in the imaging charter and posed as specific questions in briefing documents.

Advocating for a modification of the traditional regulatory pathways in the absence of scientific information that clearly justifies modification of the existing approach is likely to be futile. If new scientific information is available that is compelling for say a change in endpoints despite no change in the standard of care, then a change can be effected. In order to successfully modify existing regulatory precedent, a sponsor will need to be very well organized with the support of the appropriate professional organizations and key individuals therein. The rationale and

Table 6.4 Regulatory paradigms in clinical development

Regulatory standard	Available guidance or precedent	Sponsors' objective
Established	A guidance exists which is current with the standard of care	Sponsor wants to follow this regulatory path
	Sponsor wants to modify existing regulatory standards to optimally position their new product	Sponsors' target product profile involves a modification to current product labels in the existing class (will need compelling scientific arguments supported by well-respected scientists)
Evolving	A guidance exists which the sponsor does not consider to reflect current or emerging standards of clinical practice	Sponsor proposes an alternative path to approval
Absent or rudimentary	No guidance exists	Opportunity to set standards
	The new chemical entity is partially addressed by some existing guidances but with conflicting direction	Challenging as the health authority may prefer to adopt a single related guidance rather than create a new one to accommodate this therapeutic agent

benefits to the public will need to be apparent to all involved. A modification that benefits one sponsor over another is less likely to be ratified.

In situations where the guidance is ten or more years old and practice standards have evolved considerably, it will be helpful to meet with the health authorities early in the development process to propose your anticipated development plan leading to approval. When given sufficient time and faced with obviously outdated guidances, the health authorities will usually update the guidances during the conduct of your development program. Risks are best managed by working closely with the health authorities such that your scientific rationale that is driving the need for updating the guidance is reflected in the final document. In this situation, it is prudent to thoroughly map out all of the options and to consider opinions external to one's organization including providers across different geographic regions. Since one prefers to have a single global standard, the sponsor will need to engage team members with effective communication skills who can develop that single global standard in a series of interactions with various health authorities.

When no regulatory guidance exists, this may mean that you are in the process of solving a significant unmet medical need. Health authority staff want to participate in bringing novel and safe treatments to market. They will be energized at the prospect of satisfying an unmet medical need and will usually prioritize your meeting over others especially if the treatment under investigation has promising preliminary data. When moving along this path, try to maintain maximum flexibility and try to avoid committing to a final strategy until you have fully interpreted the end of phase II data. The reasoning for this waffling is that when you are going into

unchartered territory, the potential for unanticipated situations is increased. The health authorities also do not want to err or retract their position, so the delay in commitment should be mutual.

The most complex situation is when your product does not fit neatly into any of the existing guidances. Say you have a product which counteracts some of the cytokines that are thought to be responsible for the increased cardiovascular morbidity and mortality associated with rheumatoid arthritis. If one follows the cardiovascular guidances, a clinical outcomes trial is recommended. However, patients with painful arthritis will not agree to be randomized to a placebo, so a placebo-controlled trial is impractical. There are no proven agents with this capability so an active comparator trial is not scientifically valid. In these situations modifications to the existing guidances should be made in order to provide the opportunity to bring such a therapeutic entity to market. Negotiating this path will involve considerable challenges.

End of Phase II Meeting

The sponsor has the right to request a meeting at the end of phase II. At this juncture, the product has demonstrated a positive proof of concept for efficacy, and safety appears to be acceptable. In general all sponsors should take advantage of this legislated opportunity. A briefing book should be submitted in advance that reviews the key efficacy and safety data to date. Proposals for the phase III program and the specific indications that are sought should be clearly described. Be thorough and include the imaging component and all key aspects of the proposed program. Agreements from this meeting are put into official minutes that will be used when evaluating the phase III program for product approval. Preparation for this meeting is a crucial step in the development process. A face-to-face meeting is preferred in most cases. External consultants should be utilized as needed and can be brought to the health authority meeting. One expert may include an external imaging consultant. They may attend in person or via teleconference even for a face-to-face meeting between the sponsor and health authority.

At times different scientific advice will be obtained from different health authorities. If the sponsor takes the advice of the health authority that recommends the most comprehensive phase III program, then no further interactions are required. Often there are differences in the recommendations that warrant further interactions with specific health authorities during the implementation of the phase III program. A special protocol assessment will be performed by the FDA at a sponsor's request. EMA will provide scientific advice. Many health authorities will not be current with imaging standards; therefore briefing documents must be well written and should not assume any specialized knowledge. It is good practice to have your regulatory documents pertinent to imaging endpoints drafted and reviewed in conjunction with your imaging partner.

Pre-submission Meetings

While optional, this meeting should be considered essential for several reasons. A phase III program takes several years to conduct during which new information becomes available. This meeting provides the health authority the opportunity to notify the sponsor of any potential deficiencies in the overall development program to date. This may include safety issues that the agency is aware of that have been observed with other products that are approved or are under investigation. It can also include updated regulations or changes in policies regarding toxicology, manufacturing standards, or other aspects of the pending application. Secondly, it provides the agency with a summary of the key issues involved in review of the sponsor's application. It enables them to more efficiently allocate their resources. It also speeds up the review process for the primary reviewers and provides for a scientific exchange between the reviewing division and the sponsor.

Advisory Board Hearing

Presentation of a drug's clinical research program either in a closed session to regulators from member states in the European Union or in a public forum in the United States is becoming more common. These are typical for drugs with a new mechanism of action and for drugs with clinically relevant safety concerns or potential safety concerns. Preparation for these meetings is extensive and should include one or more imaging experts who were involved in the reading and interpretation of the imaging results.

Financial Considerations

Within the pharmaceutical industry, a small number of projects provide exceptional financial returns which provide the financing for overall R & D. A product's revenues drop precipitously upon patent expiration. This has the consequence of needing to factor in the remaining patent exclusivity into clinical development decision making. Different organizations adopt varying approaches in managing R & D budgets. It is intriguing that the adoption of innovative methodologies such as phase 0 studies is more common in biotechnology companies than in large pharmaceutical organizations. Perhaps it is a reflection of the types of individuals who are drawn to the smaller biotechnology companies, or it may be that limited availability of funds drives more innovative solutions.

Invariably, the use of imaging technologies can increase the cost especially in early phase studies. In organizations where decision making is compartmentalized (e.g., a fixed budget for all phase I or early development studies), or where

the goal is simply to advance the compound to the next phase of development, one may face challenges in the incorporation of imaging parameters. The smaller biotech companies generally have fewer assets and are focused on the value of these assets over their entire life cycle. These organizations are also pushed harder to demonstrate results early so that they can attract future funding. While these factors will influence decision making, a thorough analysis regarding the potential advantages of imaging early in the development program relative to later stages should be performed. This should then be compared with overall program costs. It may be useful to consult with individuals experienced in conducting these imaging studies who will be able to assist in flushing out the advantages and limitations of various approaches.

Imaging is being increasingly utilized to evaluate potential safety signals. In many of these situations, it is prudent to initiate these studies during phase II for several reasons. First, a dose-dependent change may be observed which supports a pharmacologically mediated effect. This can then be factored into the decision of whether to proceed to phase III and if so with what doses. Secondly, if no evidence of the potential safety issue is observed, in addition to being reassuring, the experience in phase II will be helpful in the design and implementation of the larger phase III program.

In phase III when imaging endpoints such as fracture are the primary endpoints required for product registration, the trials are powered accordingly. For secondary imaging endpoints in large phase III programs, it is often cost-effective to perform these sub-studies in a limited number of centers where historical performance has been good. Decisions will also need to be made regarding the incorporation of imaging variables that are not essential for registration but have financial value post approval for commercialization. These can be placed into the phase III program but for regulatory and financial reasons are often better served as standalone studies conducted independent of the phase III program.

Estimating Costs for Imaging Endpoints

The cost for image acquisition represents a minority of the overall imaging costs for a phase III clinical trial. Therefore, while the cost for an MRI may be many times that of radiographs, the overall cost between imaging modalities will not be as large. The largest driver of costs in phase III will be the overall number of subjects enrolled. Patient retention will impact the number of evaluable subjects. Since the analysis is usually performed as intent to treat with last observation carried forward, patients who discontinue participation early are more likely to demonstrate a reduction in pharmacological benefit relative to those completing a full course of treatment. Therefore, patient retention programs need to be incorporated not just for the overall trial but also specific to the imaging component since this component is frequently managed at a location distinct from the clinical study site by different study personnel. Site performance will also affect the trial outcome as increased

variability in image acquisition will diminish the ability to detect a true difference with treatment even when one exists. Therefore selection of an imaging partner with the ability to effectively manage the study sites with a focus on minimizing variability at the sites is essential for success. The central imaging lab that is selected is the single most important investment decision and should be made early on as the clinical protocol is being developed. It is also important that the imaging partner selected be independent of the clinical investigators. Submissions have been rejected on the basis of a potential conflict of interest when the cooperative oncology group enrolling patients in the trial also controlled the imaging data and its assessment.

Key facets that are the cornerstone of a successful imaging laboratory include their operational focus on quality control. This starts with site selection, training, and maintaining active dialog with the sites. Challenges arise with all trials. The skills and experience of the imaging team to manage through these issues are relevant. Other pertinent aspects include the setting up and maintaining of an imaging database, the read methodology, and operational aspects of conducting the reads, and aligning the imaging assessments with the other trial activities.

Value of Imaging Partners

Whether your imaging partners are internal or external to your organization, the degree of success achieved within the project will be driven by the people involved. Red flags should go up when an external organization espouses their new technology which moves images around electronically with remarkable efficiency such that this can all be conducted flawlessly without human interaction.

This is the antithesis of the requirements for the successful conduct and management of imaging in clinical trials, which is still a people-based system. It is the technologist interacting with study subjects who acquires the images. It is the technologist or study coordinator who will transmit the images to a central location. Following the development of an acquisition protocol, it is the study management team who will train the sites, provide ongoing supervision, detect anomalies, and reeducate the site staff that is pivotal.

Demand from your imaging partner professionals both technical knowledge and superior communication skills. Consider the tradeoff between low-budget proposals that have insufficient human resources versus those who have ample personnel and quality controls in place. The technology platform should be proven, should be compliant from a regulatory perspective, and should provide operational efficiencies. However, the technology should not be the only variable considered. Also keep in mind that nothing works flawlessly. Issues will be identified during the conduct of the trial. If your partner is good, these will be identified promptly. This requires significant human interaction. Excellent communication which is dependent on the individuals on the imaging and study teams is the most important variable for both the study outcome and workplace satisfaction.

Operational Considerations

The process by which clinical trials are managed in many large pharmaceutical companies can place the imaging component at risk. A common industry practice is to develop a study protocol for late development which is then provided to an operations group that conducts a feasibility study. This feasibility study will ask a potential study site regarding the anticipated number of patients that they can enroll, whether they have equipment available for the imaging modality, and if they have participated in other clinical trials with similar requirements. The study protocol design will be finalized. Clinical trial research organizations will be asked to bid on the project. The CRO may bid for the imaging component of the trial, or specialized imaging central labs may be invited to bid. Finally an imaging "vendor" is brought on board to execute the agreed upon "scope of work." The group of individuals responsible for the imaging is charged with an operational task. There is minimal or no opportunity to contribute to the strategic imaging elements of the trial. Imaging strategy that is significantly flawed often will not be detected until well into the trial conduct. The imaging vendor as they are commonly referred to may be treated as subservient to the sponsor's personnel. Since they are not true partners, the management of the imaging vendor may be reluctant to communicate inadequacies in the imaging component to the sponsor in a timely manner with the result that some trials may not yield the intended imaging results.

Skilled professionals dedicated to conducting imaging trials often are able to contribute significant value. It is highly recommended that imaging core labs be interviewed early and usually more than once in a consulting role as the trial design is being developed. By engaging potential imaging "partners" early on, it will be apparent which organization is a better match for the particular project. Your imaging partner will be able to provide guidance regarding variables that can impact variability in image acquisition (e.g., hardware, software, patient positioning). They will also likely have experience with some study sites under consideration and will also be able to share characteristics of reliable sites as well as early warning signs for sites with poor quality control.

They will draft and discuss a trial-specific imaging charter. The imaging charter is a detailed protocol specific to the imaging component of the trial. It should be completed at the same time as the overall study protocol and should be submitted with the study protocol for a special protocol assessment (FDA) or scientific advice (EMA). In addition to the imaging charter, detailed training materials for the clinical sites specific to the trial should be prepared by the imaging partner. Formal imaging training should be a key component of the investigator meeting. Depending on the situation, study sites may be required to qualify for participation by demonstrating proficiency within predefined standards. Usually study site monitoring is performed in a timely manner following enrollment of the first subject and is usually more intense early on until the site becomes more familiar with the study expectations and is more self sufficient. A similar practice should be used for monitoring of the imaging data. Instruction of site personnel regarding imaging should

be viewed as a study long endeavor. A standard regarding acceptable image acquisition and a system for notifying the site of substandard images requiring repeat scans are required.

The statistical analysis plan for the imaging data, especially if it is the primary endpoint, will be discussed in the imaging charter. It is worthwhile to put together a comprehensive analysis plan prior to the final study protocol. The reasons for this are not only regulatory, but also scientific and operational. Unintended events will almost always occur in the conduct of clinical trials. In the writing of a statistical analysis plan, items such as visit windows, handling of out of window, missing and duplicate data, and unscheduled visits all need to be addressed. Events that may influence the imaging endpoints such as surgical procedures, specific concomitant medications, or development of specific comorbidities need to be discussed. Decisions will need to be made regarding whether to control for these effects in the statistical analysis. If a decision is made that these are clinically relevant, it will require accurate capturing of these events. This will impact design of the case report forms as well as study monitoring. Standards for acceptable images, time windows for repeat imaging studies, and other considerations may influence the imaging charter and final protocol. It is best to work through these considerations up front rather than engaging in protocol amendments.

When assessing an imaging core lab, it is important to request a dedicated study team. The experience and leadership capabilities of the team leader and whether team members will be dedicated to your study or will be juggling multiple responsibilities are relevant and should be captured up front and if deemed appropriate included in the scope of work or other relevant document. There will be turnover of personnel at the study sites during the conduct of the clinical study. Therefore, additional training of site staff will be required as this occurs. Equipment changes will also occur especially if the study duration is longer than 1–2 years. Planning for this should also be performed, and rules for managing the situation should be part of the initial study documentation.

In the previously mentioned example, where high-resolution CT scans are being used to evaluate lung density in COPD patients, it is critical to know in advance of study initiation, whether the clinical sites can provide high-quality data using the specified protocol. Variability both within sites and between sites is a critical factor in determining the success or failure of the study. From a statistical perspective, for a fixed number of subjects, the higher the variability of a particular study parameter, the higher the p-value and therefore the less likely one is to demonstrate a statistically significant treatment effect. If the variability increases, more patients will be required to achieve a similar p-value to that which could be achieved with fewer patients and lower variability. Therefore minimizing variability is a key operational objective within clinical trials. Large multinational phase III clinical trials involve differences in imaging equipment (hardware and software) as well as differences in patient positioning and related imaging procedures. Discussion will be required in order to decide on appropriate tradeoffs between minimizing variability and conducting the trial within a reasonable time frame. Usually, more industrialized regions will have more recent equipment compared to other regions, although many exceptions exist. Different manufacturers will tend to have dominant market share

in different regions. Individuals familiar with the hardware and software across manufacturers are needed in order to estimate the difference in measurements that will occur between products for the endpoints under investigation.

If clinical assessments are made prior to and following an intervention, some individuals will conclude that the selection of equipment will not be relevant since in essence the delta should be similar between all equipment. In practice post hoc assessment of data from clinical trials commonly reveals differences between patients assessed with different scanners. These differences may be greater in specific patient subgroups such as the obese. Therefore, specification of the equipment that is acceptable for the clinical study is required for all trials. All efforts should be made to ensure that equipment does not change at the site level during the conduct of the clinical trial.

It follows that minimizing variability at the site level can be best achieved by employing consistent procedures for image acquisition. This can be best managed through training, maintaining a consistent staff, and providing ongoing feedback from the central imaging laboratory to the sites. Excellent and ongoing communication between the sites and central lab is essential to achieve this objective.

Compliance

All clinical development programs which result in a health authority submission will be reviewed by health authority personnel prior to approval. It is critical that good clinical practice and ICH standards be adhered to throughout the clinical program. Documentation of all actions taken during the trial with a full audit trail including all entries clearly identifying the study personnel, time, and date is mandatory. One must be able to reconstruct all activities from an audit trail. Ideally study site monitors should be familiar with the imaging component. When it is the primary endpoint, 100 % source verification is appropriate. If there is any concern regarding the quality control procedures of an imaging provider, do not retain them until you are satisfied. When quality issues arise, try to work through them with your imaging partner. If this is not possible, a second provider may need to be brought in. There is a precedent for non-approval of imaging submissions due to compliance issues. Imaging standards are evolving rapidly. To the extent possible, management of anticipated issues should be prespecified in the imaging charter. An open and transparent relationship between the sponsor, CRO, and imaging provider in conjunction with well-defined responsibilities and a detailed scope of work is the best recipe for success.

Summary

In summary, medical imaging continues to evolve rapidly. We are beginning the process of applying consistent scientific principles to the design, implementation, analysis, and interpretation of imaging parameters. Health authority guidances

regarding imaging are emerging. The use of imaging to assess disease pathophysiology should be considered for all development programs. Once a decision is made to proceed with imaging parameters, experienced professionals should work together to minimize variability so that pharmacological effects can be demonstrated most efficiently. The use of imaging within development programs has been and will continue to increase over time. The acquisition of skills pertinent to the design and implementation of imaging parameters within clinical trials will be an asset to most biopharmaceutical organizations.

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