IMAGING DIAGNOSTICS AND THERANOSTICS: MEETING CLINICAL DEVELOPMENT CHALLENGES

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Introduction

Molecular imaging has become increasingly important in the diagnosis, detection and treatment of cardiovascular, oncologic and other diseases. Advances that provide new radionuclide molecules, contrast agents, novel therapeutic devices, targeted delivery and increased patient safety are occurring at an incredibly fast pace. The human genome project, combined with bioinformatics and mining of big data, has led to the identification of key biomarkers in cancer and other diseases. Furthermore, with advancements in physics and engineering, the field of theranostics has emerged, bringing together predictive, diagnostic and therapeutic agents to detect and treat highly specific diseases.

It is an exciting time in the research and clinical development of new molecular imaging radionuclides. By demonstrating safety and efficacy, real-world evidence and a good risk-benefit profile, many new products are currently being marketed.

The most commonly used imaging platforms include X-ray, computed tomography (CT), magnetic resonance (MRI), ultrasound (US), positron emission tomography (PET) and single photon emission computed tomography (SPECT). With the advent of combined platforms such as PET/CT in the earlier part of the decade, multiple acquisitions, or scans, with a hybrid imaging platform are possible, helping clinicians make better and faster patient care decisions. Since molecular imaging can assess biological activities at the cellular level, changes in cell biology can be observed before structural changes are noted by means of MRI or CT. Moreover, molecular imaging can help determine whether a therapeutic agent is having its intended effect.

Therefore, molecular imaging considerations have moved far past the decision of which type of scan to use, to now include the:

▶ Best approach for diagnosis and staging
▶ Best approach for detection of changes in disease progression and clinical utility
▶ Best approach for delivery of therapeutics
▶ Best approach for reducing patient and clinical staff exposure

Because of the numerous benefits of molecular diagnostics, pharmaceutical companies are increasingly interested in bringing new diagnostic and theranostic agents into commercialization. The United States Food and Drug Administration (FDA) has published multiple guidance documents to aid in the development of imaging agents. The new imaging modalities show advantages over standard of care treatments, such as high dose radiation and systemic chemotherapy. The advantages to the patient may be huge in reducing the overall exposure and toxicity by providing a localized approach to treating just the disease, whether a tumor or atherosclerotic plaque. Gene expression data and biomarker identification have also fueled the progress and, if successful, will provide better accuracy and the ability to predict which patients will, or will not, respond to a particular therapy.

As published by BIO, BioMedTracker and Amplion (2016), a 10-year analysis of clinical development success rates demonstrated that the probability of successful FDA approval of a product through new drug application or biological license application pathways using biomarker selection in Phase III trials increased to one in four for those products using biomarker selection from one in 10 in those not using biomarkers.

Historically, therapies targeting heterogenous populations — for example, oncology and cardiovascular disease — have suffered the worst success rates. The FDA realizes this and encourages an evidence-based approach for successful approval. Although the number of therapies using targeted treatments is much smaller, those that do use these targeted treatments have much higher successful approval rates in part due to development and use of novel endpoints, surrogate endpoints and adaptive design, which allow for achievement of statistically significant results.
In this paper, we highlight some commonly used imaging modalities and the exciting technological advances that increase our ability to provide the best patient care, alongside some of the challenges in getting these products on the market and considerations for overcoming them.

**Background: Imaging Agents and Modalities**

Radiodiagnosics have been used in medicine for years. For example, technetium 99 ($^{99}$Tc) has been used as a radiation source for isotopic bone scans; phosphorus 32 ($^{32}$P) is preferentially taken up by cancers; and iodine 131 ($^{131}$I) has been used to diagnose thyroid disorders. We have come a long way in a short period of time, owing to the development of radionuclides with labeled analogues, as these products are being used to detect and treat different types of tumors. Information gained from the fields of molecular genetics, biomedical engineering, chemistry and physics are leading to new fields such as nuclear oncology and peptide receptor radionucleotide therapy.

Examples of imaging probes that are combined with molecular peptides, or aimed at targeting specific tumors that overexpress these receptors, are somatostatin (e.g., octreotide, NeoTect®) and fluorodeoxyglucose/FDG ($^{18}$F), a non-metabolized glucose analog and prostate-specific membrane antigen. With the advent of these peptide-based targeted agents, special considerations need to be given to the sensitivity of the imaging modalities used as the detection devices. The receptors at which these peptides are targeted are localized on the surface of tumor cells. Although the peptides and their receptor targets demonstrate highly specific affinity or binding to the target tissue, the dose is typically delivered in the nano- or micro-molar range since higher doses may lead to serious adverse effects. For this reason, the imaging modality of choice is SPECT or PET imaging due to their sensitivity and ability to detect small amounts of radioactivity.

There are a number of different radionuclides in use today, each having different properties — including radioactive half-life — that may have a significant effect on the benefits they provide as a therapeutic or diagnostic agent. Some of the radionuclides with a longer half-life — such as indium-111 ($^{111}$In) or yttrium-90 ($^{90}$Y) with 67 hours or lutetium-177 ($^{177}$Lu) at 160.8 hours — are typically used for a therapeutic indication. An example of this is Zevalin®, which is a monoclonal antibody radiotherapy that utilizes either $^{90}$Y or $^{111}$In to target the CD20 antigen on the surface of B cells for the treatment of non-Hodgkin’s lymphoma (NHL).

What are the advantages and disadvantages of different imaging modalities? Use of hybrid imaging modalities such as PET/CT in conjunction with radionuclide like such as $^{18}$F have been highly successful for cancer diagnosis, staging and treatment response. The combination of the detection of a lesion by CT, and the visualization or non-visualization of uptake of FDG by PET scanning, can be life-saving in determining the predictive risk of cancer.
In areas of oncology and cardiology imaging, there is a debate on whether PET or SPECT imaging is better. Seemingly, both provide good results and each has its drawbacks and advantages. PET scanners have several drawbacks including the cost of the scanner, the requirement for an on-site cyclotron, a short half-life and the higher cost of tracers. However, when compared to SPECT scanners, PET scanning requires shorter scan times, yields quantitative measurements and higher resolution images with less artifact. Imaging centers can conduct more PET scans in a day due to shorter scan times. However, the development of new radionuclides with a longer half-life and the advent of new software and new cameras are leveling the playing field between these technologies.

Up and coming advances in cardiology with PET/SPECT will allow imaging of fatty acid uptake, coronary flow, norepinephrine uptake and plaque. These advances aim to address the patient's overall risk for sudden cardiac death. On the oncology front, PET/CT scanning has become the gold standard in detecting and staging cancers.

One of the concerns with cancer therapy, particularly with immunotherapy or theranostic treatments, is the detection of “pseudo-progression.” A difficult problem in clinical development, pseudo-progression may indicate disease progression in patients following therapy, when, in fact, it is later discovered that these patients had favorable responses. Determining whether there is true progression or pseudo-progression is critical to avoid withdrawing a patient from a treatment that is working and/or leaving a patient on a treatment that is not. New imaging techniques may provide the ability to detect whether there is actual tumor growth or cellular edema due to tumor cell death. Clinical trials with immunotherapies or nanotechnologies may increasingly turn to the use of 18F in PET as well as diffusion MRI, to better distinguish responders from non-responders. This will be an important advancement as accurately determining typical endpoints of overall survival, progression-free survival and response rates are key to a successful trial.

Combined approaches that allow for more selective detection and delivery in the treatment of diseases are the cutting edge of medicine and are key to developing patient-specific treatment modalities. Although early in development and yet to have successfully overcome regulatory hurdles, radionanoparticles are the future for the detection of ischemia, inflammation, graft rejection, angiogenesis and lipoprotein aggregation. These nanoparticles serve as the perfect platform for combined therapies in part due to different flow distribution compared to small molecules. Nanoparticles have been developed to not only carry several types of contrast agents with the ability to increase signal to noise, but to also deliver targeted immune- or other ligand-mediated therapeutic agents directly to the tissue or organ of interest. The imaging modalities most commonly used for detection are again PET, SPECT, CT and MRI; however, ultrasound/echocardiology has shown great utility in assessing flow dynamics for nanoparticulate detection.

In Chiltern's experience, clinical development of a radiolabeled investigational imaging or a therapeutic drug can take up to seven years. After completing preclinical studies, sponsors then look to completing Phase I/II studies; collecting information about pharmacokinetics, how the product affects the human body, and dosage safety in humans.

At a minimum, the radiation dose absorbed would be estimated utilizing the publications and standards established by the Committee on Medical Internal Radiation Dose and the effective dose estimated per recommendation of the International Commission on Radiological Protection (ICRP). Use of radioactive substances in nuclear medicine, research, diagnosis and
treatment needs to be ethical, and scientifically and clinically safe. As of the date of this publication, the draft ICRP report on Ethical Foundations of the System of Radiological Protection, describing use of ethical values in developing a system of radiological protection and how ethics plays an integral part of this system, is available for public comment. Sponsors are advised to reference guidelines published by FDA and the European Medicines Agency to satisfy regulatory expectations for radiation safety assessment for diagnostic imaging products.

In the following section, we highlight a few important challenges during the clinical development of radiodiagnostic imaging agents and discuss considerations that have led to solutions to overcoming them.

**Challenging Areas**

**Study Design and Endpoints**

While the indications for a radiodiagnostic imaging product can fall within a few general categories — structure delineation; disease detection or assessment; functional, physiological or biochemical assessment; and diagnostic or therapeutic patient management — approval can be sought for additional indications per the sponsor’s intended use and labeling. Efficacy analysis of study data must support desired indications for use. Study design and primary endpoints can become a major point of discussion with regulatory agencies. Attention is needed to ensure study design is scientifically sound, the study is safe and endpoints clinically achievable to improve patient outcomes and acceptability by the agencies.

**Clinical Diagnostic Performance of Test**

The pivotal clinical trial for an imaging product evaluates clinical diagnostic performance where validity and reproducibility of the diagnostic parameter are estimated. In a pivotal trial, the diagnostic performance is characterized by measures that quantify how closely the diagnostic test is associated with a clinical reference standard (sometimes referred to as the “gold standard” or “standard of truth”) that is used to assess subjects for the disease condition.

Per the FDA guidance, the goal for the clinical diagnostic performance trial is to establish the diagnostic performance and support a favorable benefit/risk analysis related to the clinical performance of the test in the target population. The clinical diagnostic performance trial should support the intended use of the test such as a stand-alone diagnostic, in conjunction with other diagnostic information to assess the subject’s disease condition.

As to the clinical reference standard, the measure ideally is required to provide independent knowledge of the subject’s true disease condition. However, this ideal clinical reference may not be available; in which case, the best available method to assess the subject’s true disease condition may be used.

Additionally, blinded image evaluation by multiple independent readers is performed to provide information on the reproducibility of the diagnostic and accuracy parameters and details and requirements are indicated in the independent review charter (IRC), discussed in more detail in sections to follow. The diagnostic endpoints (sensitivity, specificity, positive predictive value, negative predictive value, agreement/concordance) are determined relative to the clinical reference standard. The kappa statistic is often used as a measure of agreement with its 95% confidence interval; and a value of 0.4 or greater indicates good agreement. In some instances, a comparative clinical diagnostic performance trial is performed where the investigational diagnostic test is compared to the clinical diagnostic performance of an established diagnostic test relative to the reference standard. In such trials, a comparison of diagnostic endpoints may be performed using McNemar’s test.
Therapeutic or Companion Diagnostic Trials

Once the validity of the diagnostic test has been established, the utility must next be established. The predictive marker should allow the optimization of the therapeutic treatment by differentiating between those subjects who would have the best efficacy outcome, and those a poor outcome. This leads to the concept of a companion diagnostic test, which is one that permits the selection of subjects in whom the treatment is likely to work and therefore provide benefit among those diagnosed with the disease condition. In addition, the biomarker can be used for subject management such as reoccurrence of the disease or progression of disease. Common clinical trial designs are treatment interaction design and targeted (enrichment) design.\textsuperscript{13}

The treatment interaction design allows the effect of the treatment in marker (+ve) and marker (-ve) subjects — the marker information is determined and then the subjects are randomized to the treatment. This is the only design that can simultaneously demonstrate the clinical utility of the diagnostic test.

The targeted (enrichment) clinical trial design is appropriate for demonstrating the efficacy of a novel treatment in a subpopulation of subjects who are defined by the presence of the marker detected by the diagnostic test. However, the trial does not demonstrate the lack of effect in marker (-ve) subjects. In this design, the diagnostic test is performed and those subjects with marker (+ve) are randomized to treatment and those who do not have this marker would not be treated or would be placed in another treatment. The clinical endpoints and analysis would be appropriate for a therapeutic area such as oncology that would have a time-to-event endpoint such as overall survival or disease-free progression and the analysis would then be proportional hazards with covariates.

In Chiltern’s experience, the endpoints, design and statistical method adopted for a study are entirely dependent upon the imaging, therapeutic, or companion diagnostic utility of the investigational product.

Independent Review Charter

In clinical research, particularly where image interpretation comprises a critical component for determining safety, efficacy or trial eligibility, and where such interpretation is vulnerable to variability among local reviewers, a centralized, independent image interpretation process becomes necessary. Whenever imaging is used in the primary endpoint determination to assess the therapeutic efficacy of a pharmaceutical, all involved processes, including a centralized image interpretation, must be standardized. An independent review charter (IRC) is developed to fulfill this need and becomes an integral part of an investigational imaging product’s protocol. The IRC describes how images are received, handled and stored; how the review is performed; how qualified and independent imaging reviewers are selected, trained and assigned; how quality issues are identified, managed and resolved in the process; and how various quality control (QC) procedures pertaining to the images are performed and recorded. The reviewers follow the IRC to conduct image reviews to help meet the indications of the imaging agents under investigation.

Chiltern recommends that the IRC be developed and submitted for regulatory review simultaneously with the clinical protocol and a statistical analysis plan.

Half-Life of The Radionuclide Used

Knowledge about the half-life of the investigational radioactive imaging agent and whether centralized or local distribution would be appropriate is a consideration. If the half-life of the product is long, the biopharmaceutical or peptide can be radiolabeled at, and distributed from a centralized location. However, if the half-life of the agent is short, such as in the case of 68Ga, the radiopharmacy would need to be located at the same site as the site of diagnostic administration. In such a case, qualification and training of the radiopharmacy and staff become important considerations during site qualification.
Many of the limitations to PET imaging in the past have been due to supply chain disruption, in particular with rubidium-82 (\(^{82}\text{Ru}\)), however, the advent of new fluorinated positron emitters, clinical utility and issues associated with supply have been mitigated.

**Investigational and Non-Investigational Components**

Investigational imaging products have nuances that the study team must be knowledgeable about to conduct the trial successfully. The imaging product, a pharmaceutical, is administered to a patient and is visualized by a camera or probe, which are medical devices. In some trials, it is possible that multiple investigational components are part of the trial, such as an investigational imaging agent and investigational imaging modality. For example, the use of a new fluorescently labeled antibody may require imaging or endoscopy advancements due to the wavelength considerations of the fluorescent dye. It would be important for the site and study staff to understand adverse events and device deficiency reporting requirements for both the imaging agent and the device.

**Site Qualification and Selection**

The site qualification and selection process, another critical component in the clinical development of a contrast or radionuclide agent, can present challenges. The IRC should describe the site qualification and selection process, including questions to ask to ensure and verify equipment capabilities and performance, to ensure availability of technical staff, and compliance to the IRC throughout the duration of the study.

To help sites to turn around the qualification questionnaires faster, questionnaires could be divided into two parts, one each for the nuclear medicine physician and the technologist. The nuclear medicine physician and technologist have different levels of clinical expertise and technical knowledge and therefore the questions posed are different. Questions for the physician may include administrative capabilities of the site and staff organization, radiopharmacy capabilities, patient population and IRB processes. In contrast, questions for technologists may be more geared toward assessing the capabilities of the site's imaging equipment and related staff experience. Answers sought may include the experience with a certain modality (i.e., PET/CT, PET or SPECT), the name of the manufacturer, the type and version of the acquisition software used and the standard reconstruction for whole-body PET. In general, we have found the site technologists to be more knowledgeable about site QC processes, logs for equipment and software used, and frequency of maintenance and upgrades.

A set of specific questions that relate to the specific radionuclide used to label the investigational biopharmaceutical compound needs to be included. For example, if the study involves gallium as the radioisotope, the questions may include what type of germanium calibration cylinder for 3D normalization is used at site, how attenuation correction is achieved, and what specific protocols are used for CT scans for certain types of anatomical imaging when using, for example, the 68Ga-labeled peptide.

**Radiation Exposure**

Patient safety and exposure due to repeated imaging, as may be required during the clinical development radio imaging or therapeutic product, are concerns of regulatory agencies. Improving radio-contrast or therapeutic agents, increasing detection sensitivity with better imaging modalities and utilizing a more targeted radiolabel requiring use of less product are key to decreasing exposure and ensuring safety. Additionally, reducing imaging time by changing imaging protocols, as described in the May 2017 Journal of the American College of Cardiology: Cardiovascular Imaging, will go a long way in ensuring patient safety and decreasing regulatory concerns from the FDA and IRBs.\(^4\) Chiltern recommends clinical study designs that aim to develop imaging protocols that minimize radiation exposure to patients and trial staff. Training and education of the trial staff on patients and staff safety from exposure must be considered and conducted. Radiation exposure can continue to become a consideration when the study design involves further laboratory testing of patient samples after imaging or therapy processes are complete. In such instances, partnering with a logistics team experienced in the safe handling of radioactive samples for pharmacokinetic studies is recommended.
Study Data Management and Analysis

The clinical data is collected on electronic data capture (EDC) software and then placed into a database structure that is compliant to standards of the Clinical Data Interchange Standards Consortium. In this paper, we will only present the database structure related to the diagnostic test procedure and output.15

The procedure agent domain would contain the record of the start and stop time of the tracer administration, and type, category, and unit dose of investigational product. The procedure domain would contain the type of image (e.g., PET, PET/CT), anatomical region imaged and start and stop of the imaging procedure. The device domains are the device identifier (DI), device properties (DO) and device in-use (DU). The DI domain contains the imaging type, manufacturer of the imaging modality and the model. The DO domain contains image modality control information. The DU domain contains the information including image slices, number of slices, the thickness of the slice, decay correction, software version, pixel spacing, attenuation correction. The findings domains (FA, SUPPFA) contains the results of the test; i.e., standard uptake value ratio (SUVR) and/or the positive/negative test result, the reference region for the SUVR and scanner type. The SUPPFA would have the individual region, and the SUV for each region. For the independent image reads, the FA domain would include the randomized image number, the reader and associated reader number. The concept map below illustrates PET imaging.

PET Imaging Concept Map & Considerations

Additional considerations for the database electronic case report form (CRF) design, such as whether the independent read is captured in a separate database or in the database that also houses the site-reported imaging review, must be thought through to ensure there is consistency between the information captured by the site investigator and the independent review. One pitfall for analysis can occur when the CRF design for the independent review is managed by a third-party vendor such as a core lab while the clinical database questions are developed by a clinical research organization. Site-reported endpoints should be aligned with core-lab reported endpoints to prevent mismatch during analysis. Chiltern recommends that the data management and statistics experts from the sponsor, CRO, and core lab organizations collaborate closely in the review and development of CRFs, data management, communication, EDC build and analysis plans.
Images Process Flow

Understanding how diagnostic images are processed during a research study is important not only to data management and statistics, but also to study staff. At the site level, de-identified Digital Imaging and Communications in Medicine DICOM image files are uploaded and transferred to a core lab. There are QC steps, both at the site and core lab, such as de-identification of images prior to independent reviewers being notified that the image is available for review. The independent reviewers follow the paradigm described in both the IRC and the study protocol. Data transfer and communication plans, clearly describing the responsibilities of the reviewing lab, database management and statistical teams will need to be in place. In many instances, data management would not integrate the reviewer image data in the study EDC. Image data would be received in a pre-determined format such as *.SAS or *.CSV. If an eligibility read is part of the study protocol, plans should be in place indicating the parameters that the pre-study scans need to meet to be accepted by the imaging core lab. Chiltern recommends these parameters be developed as part of the protocol and the IRC. A concept map of image flow from the reviewer/reader perspective is depicted below:

Reviewer/Reader Concept Map & Considerations

Conclusion

This paper provides a summary of the diverse array of technological advances that are available for molecular imaging and are on the forefront of emergent diagnostics and theranostics to provide targeted patient care. Future growth and advancement of available products are dependent on a thorough understanding of the regulatory, site, patient and study-specific challenges to achieving market approval. The timeline for conducting preclinical to clinical research and market approval is lengthy, but as research supports, use of targeted therapies to identify responders or sub-populations where treatment effect can be maximized may have greater success. This approach is welcomed by the FDA in providing an evidence-based approach to medicine and improving clinical outcomes and patient care. Chiltern recommends careful and extensive discussions with the Agency on critical topics early on to avoid regulatory and investigational challenges during study conduct.
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