

The Translational Research Working Group Developmental Pathway for Image-Based Assessment Modalities

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Abstract The Image-based assessment modality (IM) pathway refers to one of six Translational Research Working Group (TRWG) pathways that, together, describe the core domains of early translational cancer research. This pathway focuses on approaches that are based on the interaction of energy and living organisms to analyze tissue noninvasively so as to reveal properties relevant to the detection, diagnosis, or prognosis of cancer and precancer; or the response of the cancer to therapy. Examples include, but are not limited to, magnetic resonance imaging and positron emission tomography, as well as contemporary contrast agents designed to probe specific molecular constituents of tumors. The IM pathway is presented as a general outline of the steps required for the effective development, optimization, testing, and validation of image-based modalities. The distinctive features of the IM pathway and issues encountered that represent obstacles to effective and efficient progress through the pathway are discussed. The IM pathway also forms a framework to identify opportunities to address current barriers and is expected to adapt and evolve as the field advances.

Oncologic image-based assessment modalities harness the interaction of energy with *in vivo* tissue to reveal clinically relevant properties of the tissue. These modalities may be devices, including magnetic resonance imaging, computed tomography (CT), and positron emission tomography (PET) scanners. They may also be exogenous agents or biologics delivered to enhance the interaction of energy with tissue, including imaging agents, contrast agents, imaging enhancers, and therapeutic agents with secondary imaging attributes. Imaging modalities are often built from multiple, interdependent components, and can include combinations of any of the following:

- type of energy applied to the *in vivo* tissue;
- quality assurance protocols for the imaging modality;
- acquisition variables (including temporal and physical stipulations);
- administered agents as well as the interactions between imaging hardware platforms and these agents;
- “standard” data processing variables used in forming the “basic” imaging modality output;
- higher level data analysis algorithms that might use data from single or multiple imaging modalities, serially or contemporaneously obtained (often known as postprocessing);

- method of archiving ‘raw’ data as well as secondary data resulting from data processing and postprocessing;
- operator- and human-user interface issues including operator training (especially regarding workstations and qualitative and semiquantitative outputs); and
- agreed upon metrics of interpretation.

The data sets produced by imaging modalities are the end point of multiple, interdependent components and may be analyzed qualitatively, semiquantitatively, or quantitatively. Hence, the translational development of imaging modalities should always be considered at the system level rather than at the level of individual components within the system.

Herein we describe the distinctive features of the Image-Based Assessment Modality pathway compared with the Generic Pathway (see ref. 1 for an introduction and overview to the TRWG pathways), and some implementation issues that are particularly pertinent to the IM pathway. The IM pathway is depicted in Fig. 1.

Credentialing

The IM pathway, like the other TRWG developmental pathways to clinical goals, is envisioned to carry a basic research discovery through a series of steps to credential the imaging modality—scientific validation of the biomarker, determination of clinical need, and a feasibility assessment—as marked by the diamonds at the top of the pathway. Although this is an accepted trajectory, the IM Pathway is characterized by a disproportionately large contribution of applied research, as opposed to basic research, as the point of entry. This occurs for two main reasons.

First, the regulatory approval mechanism for devices is very different than the mechanism used for drugs and biologics.

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Although imaging modalities may or may not use imaging contrast agents and/or enhancers (which are most frequently regulated as drugs or biologics), they always involve hardware devices. Devices, such as drugs, are approved for use in patients on the basis of safety and efficacy, but by way of a process that, unlike drugs, is most often not related to a specific clinical utility (e.g., screening, diagnosis, staging, and response assessment) in a specific clinical disease state (e.g., a specific stage and cell type of cancer). For example, CT scanners are approved on the basis of their radiation dosimetry and the resultant imaging information but not for a particular disease state. These generic types of approval are often based on preclinical, engineering testing rather than on the basis of a clinical trial. Once the imaging modality is approved, it achieves relatively widespread dissemination and use for one or more clinical utilities, in a variety of disease states. On the basis of the empirical use of the modality, preliminary data are generated (applied research), and these preliminary data derived from applied research might provide the entrée into the developmental pathway for utility-specific translation.

Second, imaging modalities often undergo horizontal rather than vertical translation. That is, the modality may be developed for—and clinically accepted as—an assessment modality in one clinical scenario but is then used sporadically for a different clinical purpose. The preliminary experience in the second clinical scenario then provides the credentialing for the proposed new use.

An example of horizontal translation is the clinical role of ^{99m}Tc-sestamibi. Sestamibi is taken up by both normal and malignant cells (2). The degree of uptake is driven by the state of metabolic demand of the cells; it is high in metabolically active normal and cancer cells but low or nonexistent in cells that are poorly perfused or dying. Sestamibi was thus initially found to be clinically useful as a myocardial perfusion agent (3). Food and Drug Agency (FDA) approval was obtained for myocardial perfusion imaging and the agent became commercially available. In addition to its utility as an imaging agent for irreversible and reversible cardiac ischemia, it was noted that the agent also had utility as an imaging agent for cancer cells on the basis of their increased metabolic activity (4). The ability to image cancers by increased accumulation of radiotracer was the first step in horizontal translation, and is the basis for Breast Specific γ Imaging, for example (5). In addition, sestamibi is also a substrate for transmembrane P-glycoprotein, a multi-drug transporter that is capable of pumping a variety of molecules out of cells. One mechanism that tumor cells use to escape the cytotoxic effects of chemotherapeutic agents is to increase the expression of P-glycoprotein. Therefore, as physicians began to explore the potential value of the commercially available sestamibi as a tumor imaging agent, it also became apparent that sestamibi could give an indication of the P-glycoprotein activity in tumors and, thereby, predict which tumors were most likely to express multidrug resistance (6). This new oncologic use of sestamibi has matured, and has been studied extensively at the cellular and molecular level, but it has not been clinically optimized as rigorously as would be desirable.

KEY POINTS

- *The Imaging Modalities Pathway can provide a formal structure to link oncology imaging researchers at academic institutions and in industry to focus on achieving specific goals in a precompetitive, collaborative environment.*
- *The Imaging Modalities Pathway assists in identifying regulatory, fiscal, and cultural barriers to the translation of imaging modalities to aid in devising viable solutions.*
- *The Imaging Modalities Pathway enables uniformity in analyzing imaging modalities for specific clinical conditions to permit promulgation of guidelines and standards that can be adopted for clinical research and by healthcare providers.*
- *The co-development of imaging modalities and interventions provides significant opportunities for the accelerated development of image-based assessment modalities and for the associated interventions as well.*

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Supporting Tools

Imaging modalities are themselves Supporting Tools for other modalities. However, depending on the specific assessment for which the imaging modality is intended, it may be necessary to have supporting tools for its translation as well. Unlike the imaging modalities themselves, the supporting tools

used in the translation of imaging modalities will likely not be carried forward for use in later phase clinical trials, or for the dissemination of the interventions into clinical practice—or there would be little utility in the development of the imaging modality itself. For example, consider the development of a drug that was most effective in hypoxic tissue, such as tirapazamine. One example of a relevant imaging biomarker would be PET scanning with a hypoxia imaging agent, such as 18F-fluoromisonidazole (7). Development of the 18F-fluoromisonidazole radiopharmaceutical and the associated optimized PET imaging acquisition protocol would proceed according to the IM pathway. However, in this circumstance an independent measure of hypoxia (perhaps on the basis of a biospecimen assay) would likely be needed to optimize and validate this imaging assessment. Once validated, the imaging modality would replace the assay in the translation of the targeted drug and its eventual clinical deployment.

Creation of Modality and Preclinical Development

The Creation of the Modality step of the pathway reflects the potential for parallel development of an imaging agent, a technique, and/or a platform/device as reflected by the three green boxes in Fig. 1. These steps flow into the Preclinical Development phase of the IM Pathway, which focuses on safety, efficacy, and GMP production as in other pathways, but is notable in the emphasis on regulatory and intellectual property issues. Because horizontal translation is common, the answer to the initial green decision diamond “Is there an existing imaging platform for the agent or technique?” is often “yes.” A somewhat disorganized progression occurs when imaging modalities—which have broad and clinically nonspecific label indications—become widely available and commonly used “on label” for a broad variety of clinical utilities. The upside of these circumstances is the rapid translation of image-based assessments to the clinic. The downside is the frequent lack of system optimization before use for specific clinical indications—and often the lack of subsequent comparative clinical trials to substantiate purported utility.

There are several underlying reasons for the lack of rigorous following of the IM pathway as opposed to the more standard pathway approach to the development of an agent or biologic (see Agents Pathway; ref. 8). One is financial: the period of uncontested market share for imaging modalities is generally shorter than for most agents and biologics. Although the overall cost of development for a drug or biologic is debated, the per unit cost during the iterative refinement and eventual production of the agent is relatively modest when compared with the per unit cost of many imaging platforms and software analysis tools. It is financially prohibitive to create a large number of fully functional devices for research purposes. The “research” devices made available are most often premarket (late-stage) prototypes with design and function features already “locked down” for large volume production. Therefore, in many respects system optimization cannot be done, save within a rather narrow range.

There are additional intellectual property and regulatory concerns that influence the systematic adherence to the IM pathway. Imaging agents are often produced by corporate

entities that are separate from the producers of hardware devices and distinct from the manufacturers of software tools and workstations (although recent corporate acquisitions have led to greater integration in this respect). If an imaging modality consists of both an agent(s) and a device(s), the agent most likely will need to achieve approval through a different regulatory pathway than will the device-based components of the imaging modality. Finally, there is an additional regulatory burden for those imaging modalities that use agents/devices that must be regulated by the Nuclear Regulatory Commission.

Paradoxically, a potentially useful imaging modality could be found ineffective through later phase clinical trials and abandoned, not because the modality itself is ineffective, rather because the modality had never been optimized for the particular role and clinical condition. Hence, lack of rigor in following the pathway might lead to abandonment of a potentially viable modality. A possible example is the development of computer-assisted detection algorithms (CAD) for use with mammography (9). Based on results from applying CAD to mammograms from a few hundred patients, CAD modules have been approved by the FDA for clinical use. However, follow-up studies on the efficacy of CAD in screening mammography have suggested no benefit from the CAD (10). It is likely that the discordance between results from premarket and postmarket studies is linked to the different populations of patients and radiologists in the two different types of studies, and that the CAD algorithms have not been adequately optimized for the distribution of mammographic findings and radiologist population seen in routine screening settings. This is still an active area of investigation, development, and validation (11).

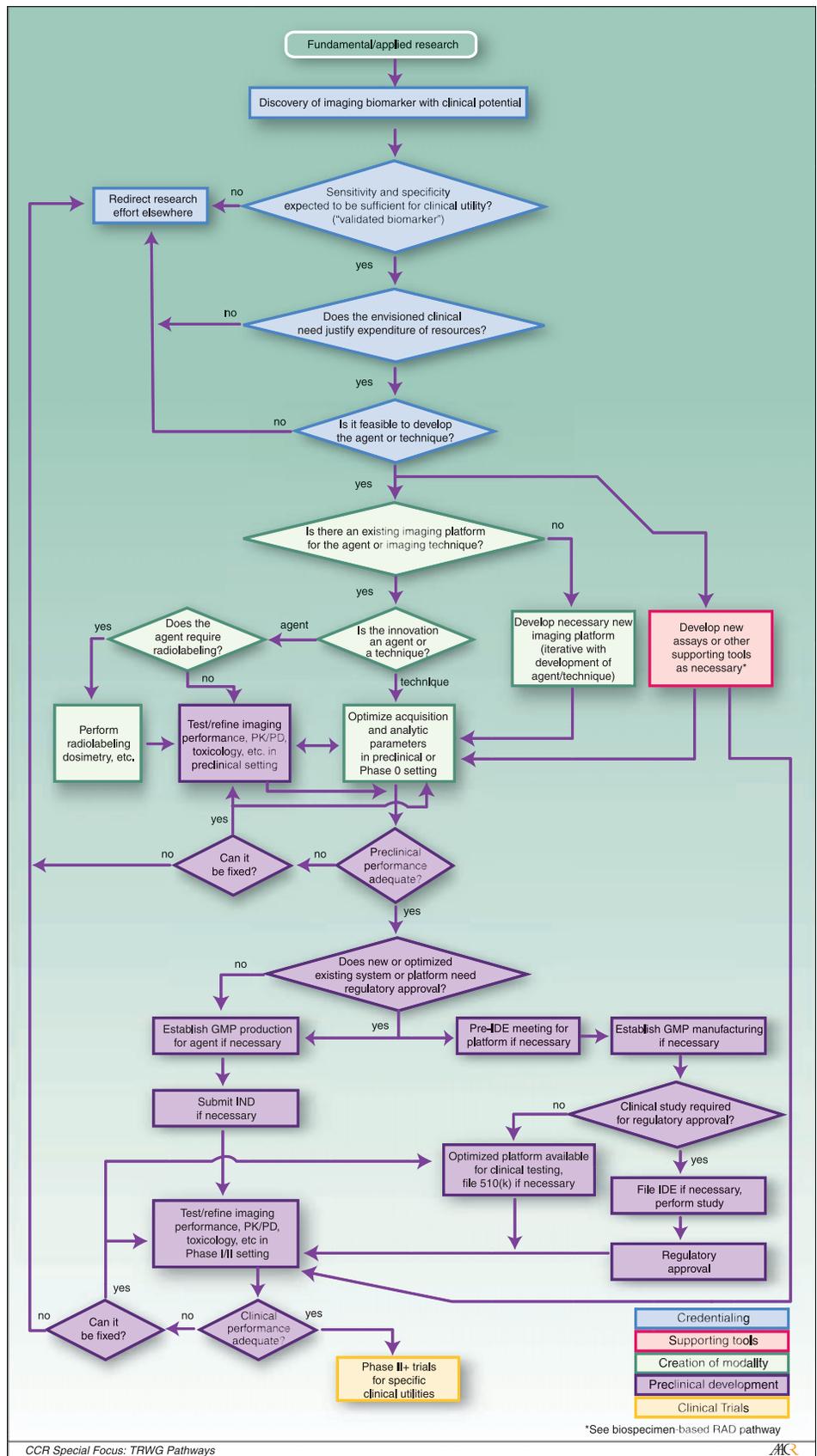
As another example, some argue that the Response Evaluation Criteria in Solid Tumors criteria are used as the major imaging assessment of end points during oncology clinical trials not because they are particularly useful, but because they are not particularly intrusive and are not inferior to more advanced imaging assessments that are also not very useful (12). Perhaps more advanced imaging assessments optimized for a specific clinical utility, if properly stipulated and implemented, might show more usefulness. This would require optimization above and beyond what is currently required by the regulatory pathways—and therefore above and beyond what industry must invest to achieve widespread dissemination of the imaging modality.

One should note the iterative feedback loop in the detailed diagram for this pathway related to radiolabeled agents. This involves the “perform radiolabeling” and “optimize variables” green boxes and the “test/refine imaging performance, PK/PD, and toxicology” preclinical development boxes. In addition to the increased complexity that this loop introduces into the creation, development, and optimization of a radiolabeled imaging modality, it should be noted that there is also an additional regulatory burden inherent in the commercialization of such agents.

Early-Phase Clinical Trials

Unlike the majority of the other TRWG Pathways to Clinical Goals, including biospecimen-based assessment devices (13), imaging modalities often involve clinical research during the

Fig. 1. Image-Based Assessment Modality (IM) pathway. The IM developmental pathway is depicted as a flowchart, a schematic process representation widely used in engineering. *Rounded rectangle (top)*, the origin of the process. *Square-cornered rectangles, activity steps.* *Diamonds,* conditional tests or decision steps. *Unidirectional arrows,* direction of the activity sequence, and the direction of transfer of supporting tools from their parallel development paths to the main path of modality development. *Bidirectional arrows,* codevelopment or concurrent, interactive refinement. The three diamonds in the initial steps of the pathway (*blue*), represent the credentialing step. Subsequent steps include the development of supporting tools (*red*), the creation of the modality (*green*), preclinical development (*purple*), and early stage clinical trials (*yellow*). For each activity, decision point, parallel path, or feedback loop, it is understood that there are many more variations that can occur, and that not all steps may occur in each instance. The pathway does not address the ways in which insights gained from late-stage clinical trials can influence the development process. Image-based assessment modalities can be used for screening, early detection, diagnosis, prediction, prognosis, or response assessment. The pathways are conceived not as comprehensive descriptions of the corresponding real-world processes but as tools designed to serve specific purposes, including research program and project management, coordination of research efforts, and professional and lay education and communication.



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“Creation of Modality” and “Preclinical Development” process steps.

Biospecimen-based assessment devices are usually created and developed using previously obtained biospecimens that are harvested during routine care or during clinical trials that were not primarily focused on the assessment devices themselves. As the assessment itself is done outside of patients, there is no need to test the safety and efficacy of the device until the phase I and II clinical trials that are the end point of the Development Pathway. Imaging modalities on the other hand, are done on the subject or patient directly. Therefore, before the phase I and II clinical trials that show clinical utility, phase 0 to II trials are often necessary to optimize the system components in conjunction with one another, and to show the safety of the proposed imaging device(s) and/or agent(s). Fewer such clinical trials might be required if the devices and/or agents already have FDA-approved indications that include the intended new application. However, creating and developing this class of assessment modalities usually involves clinical trials to be conducted during the process steps described as “preclinical” in the generic pathway. In this regard, the IM pathway is similar to the Interventive Devices Development Pathway (14).

Examples of the IM Pathway

The development and dissemination of the combined PET/CT scanner represents an example of the development of a device-based imaging modality. The first prototype PET/CT scanner was produced in 1998 at an academic center with funding from an National Cancer Institute grant (15). The major vendors of imaging devices quickly adopted the concept and made such devices commercially available. No rigorous assessment was done to show clinical superiority of the combined PET/CT scanners compared with existing practice. Furthermore, to reduce the cost of the combined units, vendors used PET and CT components that were not considered “state-of-the-art.” The “market” (i.e., hospitals and radiologists buying the scanners) soon decided that the combined scanners were more desirable than individual scanners, and that the “low-end” PET and CT components should be replaced with “high-end” components. In response, imaging device manufacturers went through the equivalent of four generations of combined PET/CT scanners in as many years. No large, rigorous trials were done on any of the scanners produced during this period.

The development of fluorodeoxyglucose-PET as an agent/device combination imaging modality illustrates many of the unique features and difficulties associated with the IM pathway. One of the strengths of PET scanning is the ability to label biologically occurring compounds or analogues to obtain physiologic information *in vivo* (16). However, many of those compounds are in the public domain, which limits the ability to establish market exclusivity. Radiolabeled fluorodeoxyglucose is one such molecule. Evidence of its clinical utility accumulated for more than a decade (17), but there was no commercial sponsor interested in supporting large clinical trials or taking the compound to the FDA for marketing approval. Many years of protracted negotiations with Congress, the FDA, and multiple commercial vendors ensued before

fluorodeoxyglucose-PET scanning could receive FDA approval and widespread dissemination. However, the lack of rigorous, confirmatory trials demonstrating the role of fluorodeoxyglucose-PET in a variety of clinical scenarios continues to create problems with both reimbursement and appropriate clinical implementation.

Barriers to the Translation of Imaging Modalities

The examples of imaging modalities that have been translated serve to highlight the fact that many of the barriers to realization of an optimal developmental pathway for imaging modalities relate to the existing regulatory and fiscal environment. We do not expect this environment to be fundamentally altered in the foreseeable future. Nevertheless, the pathway points to important opportunities for improvement.

In contrast to the market returns expected from therapeutic agents (drugs, biologics, and immunologics), the return on investment for the development of imaging modalities, especially for imaging agents and enhancers, is usually low or nonexistent. In some ways, this situation is similar to the development of biospecimen-based assessment devices. However, the issue of little or no return on investment in imaging modalities is exacerbated by the fact that these assessment modalities are done on or in the subject/patient. Liability concerns are therefore even greater than for biospecimen-based devices. This perceived lack of return on investment, coupled with greater liability exposure, has dampened the enthusiasm for commercialization of imaging modalities.

A significant barrier to more effective translation of imaging modalities is that collaboration and the use of consensual standards are infrequently seen among the industry and end-users involved with the various components of the imaging modality system. As the imaging industry continues to consolidate, entities focused on hardware platforms for image-data acquisition, software-based analytic tools, and agents remain largely independent. Furthermore, although there is increasing collaboration among the various entities that are focused on the same general components of the system, the degree of such collaboration is still relatively modest. There are standards for certain aspects of imaging data sets (e.g., the Digital Imaging and Communications in Medicine standard that specifies file format for digital image files). In many cases, however, the standards are not unambiguously and rigorously defined. This leads to a range of interpretations by the various manufacturers with subsequent incompatibility issues. As none of the various manufacturers has undisputed market dominance, the variety of outputs makes it difficult to standardize, optimize, and validate the imaging modalities for specific clinical utilities in specific disease states.

As is highlighted in the IM Pathway diagram (Fig. 1), there are iterative feedback loops for each of the system components during each of the overarching process steps. Changes in one component are likely to affect the optimum implementation of the other components—or it must be shown that such effects have not occurred. It would be very desirable that impediments to standardization among various competitive entities be eliminated by collaborations in the precompetitive space. This

could likely be achieved through the auspices of federal agencies, professional organizations, and trade groups.

Opportunities to Improve Imaging Modality Development as a Component of an Intervention

The development, optimization, validation, and qualification of imaging as a biomarker is cited as one of several strategies to improve the efficiency with which new interventions (drugs, biologics, and devices) are brought to market. The FDA recognized the importance of this activity and outlined opportunities in their Critical Path Initiative white paper.⁵ The articles in this volume describing this suite of pathways describe an integrated approach to the codevelopment and codependence of proposed new interventions and the prerequisite accompanying assessment modalities (1). The very act of documenting these relationships represents a significant opportunity for the field of imaging biomarker development and validation.

A barrier to the use of qualified imaging modalities in the clinical trial environment is the lack of uniformity in the performance and analysis of imaging modalities. The problem of uniformity could be overcome by optimizing and validating imaging modalities for specific clinical conditions through the use of the IM pathway, and by carefully controlled clinical trials before disseminating the modality for widespread use. This would allow professional organizations to promulgate guidelines and standards that could be adopted by health care providers. Such guidelines, based on supporting data, would likely create less variance in test performance and analysis. An additional barrier is the lack of payor reimbursement for emerging imaging modalities. The reimbursement problem could be overcome by the funding of trials that would provide information as to the appropriate use of imaging modalities and facilitate the development of rational, cost-effective coverage and payment policies.

The opportunity to accelerate the development of imaging modalities might be realized by encouraging funding for the codevelopment and validation of imaging modalities and recognizing this secondary objective in the scoring of proposals in applications that primarily focus on interventions. Dual PI applications where one PI would focus on the development and validation of an intervention whereas the second PI would focus on the development and validation of the accompanying imaging modality may provide a successful model. The

outcome of such funding would be clinical trials testing of both the intervention and the imaging modality.

There is an opportunity for organizations that produce pharmaceuticals, biologics, and devices to designate specific funding for the codevelopment, validation, and qualification of imaging modalities within the business plans for the development of proposed new interventions. The preclinical and early clinical phases of development of the interventions themselves represent the best opportunity for creating appropriate imaging modalities. In fact, early-phase clinical trials (phase 0 and I) are the ideal settings to show the safety and efficacy of imaging modalities so that they may be available for use in later phase III and IV trials. It is likely that the cost of embedding early phase imaging modality studies within phase 0 and phase I drug trials will be relatively modest, especially in relationship to the likely decreased cost of subsequent phase II to IV trials that could use the validated and qualified imaging modalities to improve identifying subjects and evaluating the targeted end point(s). Furthermore, disseminating the imaging modality along with the intervention to the clinical setting may improve the risk/benefit ratio of the intervention, potentially providing improved value to the health care system.

Further qualification of imaging modalities would be enhanced by including advanced imaging protocols within later phase clinical trials once preliminary data were made available. For this to occur effectively, however, protocols under development would need robust and early involvement of investigators who are knowledgeable in the implementation of imaging modalities appropriate to the specific intervention(s) used in the protocol. Furthermore, when such imaging modalities are to be used for end point evaluation, metrics beyond Response Evaluation Criteria in Solid Tumors would be necessary.

Conclusion

We believe the advent of the TRWG developmental pathways represents a significant opportunity. This developmental pathway for IMs has not yet been implemented in its entirety for any currently available imaging modality. As an idealized model, however, it points to a range of opportunities for enhancing imaging modality translational research and for achieving the benefits of an optimized translational process. The IM pathway can provide the framework and play a pivotal role in facilitating the collaboration that will make this vision a reality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

⁵ *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, Food and Drug Administration, March 2004. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>.

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