The Translational Research Working Group Developmental Pathway for Interventive Devices

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Abstract  The interventive device pathway refers to one of six pathways developed by the Translational Research Working Group (TRWG) that, together, describe the core domains of early translational cancer research. This pathway focuses on the development of devices (as classified by the Food and Drug Administration), designed for local ablation of cancer or precancerous lesions (e.g., radiation therapy, microwave, radiofrequency ablation, and high-intensity focused ultrasound systems). This article describes the distinctive features of the pathway and issues that are encountered in the real-world development of interventive devices for the treatment of cancer. The interventive device pathway is envisioned to be a general guideline of the steps required for effective development, optimization, testing, and validation of developing devices, to be dynamic and adaptable, and to form a framework for discussions focused on improving the efficiency and effectiveness of new device development.

Oncologic interventional devices are modalities for the prevention and treatment of precancerous lesions and cancer as well as its sequelae that use modalities classified as devices by the Food and Drug Administration (FDA).

Although these modalities are occasionally delivered in an untargeted manner (e.g., systemically or “whole body”), they are most frequently targeted toward local-regional abnormalities using direct vision or in vivo imaging methods (e.g., computed tomography, ultrasound, magnetic resonance imaging, and positron emission tomography). Examples of interventive device modalities include radiation therapy, cryoablation, radiofrequency or microwave ablation, interstitial laser thermal therapy, high-intensity focused ultrasound, and minimally invasive surgery tools, such as robots, scopes, and articulated operating instruments to be used therewith.

These modalities may be delivered noninvasively, percutaneously, endoscopically, laparoscopically, transvaginally, or by open surgery. The translation from preclinical development to clinical utility may focus on the interventive device, the mechanism for guiding/monitoring, the device and its effects, or the combination of the two (the interventive device and the mechanism for guidance/monitoring). Furthermore, such devices are often used in combination with other intervention modalities (device based, agents, and/or immune response modifiers); translational research on combination applications should be based on a “systems optimization” approach.

The interventive device pathway is depicted in Fig. 1. As is the case of all six of the development pathways, the interventive device pathway is a tool designed to be used strategically in the planning, implementation, and management of early translational research. To properly use the pathway, it is important to understand the elements of the pathway itself as well as the environmental factors that might affect its use. The reader is advised first to review the article dealing with the overarching concepts of the generic pathway (1). This pathway-specific report focuses on two aspects of the interventive device development pathway: the distinctive features of the interventive device pathway details compared with the generic pathway and the issues related to the real-world application of this pathway. The original intent was to organize the discussion based on the structure of the pathway as described by Fig. 1. However, the overwhelming majority of environmental factors that affect the real-world implementation of the pathway affect multiple pathway steps and would have resulted in needless redundancy. Thus, we focus on overarching themes that affect the pathway and translational research in the area of device-based cancer interventions with reference to the pathway steps on which these themes have their greatest effect.

Distinctive Features of the Interventive Device Pathway

Point of pathway entry. The rounded rectangle at the top of the interventive device pathway indicates the point of pathway entry. Although any of the six pathways might begin with either basic or applied research, the interventive device pathway is characterized by a disproportionately large contribution of applied research as opposed to basic research as a point of entry. This occurs for two main reasons. First, the regulatory approval...
mechanism for devices is very different from the mechanism used for drugs and biologics. Devices are approved for use in patients based on safety and efficacy but by way of a process that is most often not related to a specific clinical utility (e.g., palliation, improved disease-free survival/time to progression, and cure) in a specific clinical disease state (e.g., a specific stage and cell type of cancer). For example, radiofrequency ablation devices currently available were first approved for the destruction of soft tissue rather than the treatment of any specific cancer or precancerous lesions. Radiation therapy delivery systems might be approved on the proven ability of the system to deliver a specific dose of radiation to a specified volume of tissue with specified lesser doses of radiation to surrounding nontarget tissue. This type of approval might be based on preclinical, benchtop, engineering testing rather than based on a clinical trial. Once an interventional device is approved by the FDA, the modality achieves relatively widespread dissemination and use for one or more clinical utilities. Based on the empirical use of the modality, preliminary data derived from applied research often provide the entry into the developmental pathway for utility-specific translation.

Second, interventional devices often undergo horizontal rather than vertical translation. That is, the modality is accepted for one clinical utility. Once widely disseminated for that initial clinical utility, it is used sporadically for one or several alternative clinical purpose(s). The preliminary experience in the alternative clinical utility then provides the point of entry into the developmental pathway for this proposed new use. Unfortunately, the intermediate step of optimization during translation may not occur rigorously under current environmental conditions. Although these two features primarily affect the point of pathway entry, they also secondarily affect all subsequent pathway steps.

**Use of assessment tools.** There are critical differences between how assessment tools operate in conjunction with device-based, local-regional interventions as opposed to systemically administered interventions, even within the same clinical entity. These critical differences include the use of assessment tools not only for cohort selection but also for planning and guiding the intervention itself, when and how the response assessment observation should be obtained, by what variables the response assessment observation should be assessed, and the implications of the response assessment result for decision making.

These critical differences are currently not acknowledged in many arenas. For example, the commonly specified Response Evaluation Criteria in Solid Tumors criteria for response assessment by unidimensional anatomic imaging measurements are not appropriate when used with local-regional thermal or with embolization therapies, nor are WHO bidimensional criteria appropriate for response assessment. In certain clinical and anatomic areas, these deficiencies have been overcome by revised criteria; an example is the European Association for the Study of the Liver modifications to the WHO criteria, which are specific for hepatocellular carcinoma assessment in the liver but not for extrahepatic lesions. The issue of inadequate response assessment criteria may also apply to certain targeted noncytoreductive systemic interventions as well, but it is without doubt a prominent feature of this pathway.

Although assessment modalities are used to identify subjects or patients appropriate for inclusion in the targeted cohort, in the case of device-based interventional modalities, these cohort identification modalities are often used to plan, guide, and monitor the intervention. To date, purely anatomic criteria have dominated this utility. However, with increasing frequency, physiologic and molecular assessment modalities are used, most often in conjunction with anatomic criteria.

In some of the more advanced interventional devices, specific advanced imaging systems are integral to the delivery of specific therapeutic intervention. In such instances, a compelling case
could be made that the interventive devices and the advanced imaging modalities used to provide them should be translated as a system. Such a systems approach would often allow the interventive device to be optimized before later-stage clinical investigation. This is rarely done, however. In some clinical scenarios, more than one type of imaging modality is available (and potentially appropriate) for use in treatment planning, guidance, monitoring, and end-point determination. In other

![Interventive Device Developmental Pathway](image)

**Fig. 1. Interventive Device Developmental Pathway.** The interventive device pathway is depicted as a flowchart, a schematic process representation widely used in engineering. The rounded rectangle at the top indicates the origin of the process (point of pathway entry). Square-cornered rectangles indicate activity steps. Conditional tests, or decision steps, are represented as diamonds. Unidirectional arrows indicate the 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 are used to indicate codevelopment or concurrent, interactive, iterative refinement. The initial steps of the pathway (blue) are required to proceed through the pathway, with the entry represented by either fundamental or applied science followed by three blue diamonds representing the credentialing steps of scientific validation, clinical need, and feasibility. Thereafter, the pathway includes three parallel paths, representing creation of the modality itself (green) as well as development of two different classes of supporting tools (red): tools for characterizing and evaluating the effects of the modality (i.e., response assessment) and tools for defining the cohort for which the modality is appropriate. Parallel paths have been made explicit to acknowledge that some of the required tools may not exist and their parallel or codevelopment will be prerequisite for the viability of the new modality. The more detailed development of these supporting tools, or assessment modalities, is represented by either the biospecimen- or imaging-based assessment modality pathways. Subsequent steps to the initial creation of the interventive device include preclinical development (purple), which in the case of interventive devices may actually include limited clinical studies required to optimize or refine certain aspects of the modality, and the final step of early-stage clinical trials (yellow), which will form the basis for later-phase clinical studies. 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. This pathway is conceived not as a comprehensive description of the corresponding real-world process but as a tool designed to serve specific purposes, including, for example, research program and project management, coordination of research efforts, and professional and lay education and communication.
scenarios, different imaging modalities might be better suited to each of the various phases of planning, guidance, monitoring, and end-point determination. Finally, in some clinical situations, a combination of imaging/sensing modalities might be optimal. Unfortunately, these alternatives are rarely, if ever, explored in a rigorous and systematic manner during the translational phase of research. Thus, either optimization may not occur or divergent methods of application might evolve, often with widely divergent outcomes. Accelerated translation of interventional devices to the point of care depends on the creation and implementation of common platforms and systems standards for use by academic and corporate researchers.

Rarely are the same companies engaged in the development of the interventional devices and the associated imaging modalities, so the various developers may well have different business objectives and strategies. Exceptions are rare; one example is the involvement of General Electric Medical Systems in the development of the InSightec MR Guided Focused Ultrasound system. Furthermore, the academics engaged in the development of these interventional devices, and/or the tools used for treatment planning and guidance, are often not involved early in the process and therefore unable to influence development to the extent desirable. This issue of inadequate standards and insufficient collaboration among industry and academic researchers related to the integration of supporting tools during the creation of modality has subsequent effect on the preclinical development and early-phase clinical trial process steps.

Regulatory and intellectual property issues. As with imaging-based assessment modalities, the effective period of uncontest- ed market share for device-based interventions is shorter than for most agents and biologics. An in-depth analysis of these critical differences is beyond the scope of this article. However, there are critical differences to be considered along the pathway to regulatory approval for devices as opposed to drugs or biologics, prominent among which are the availability of the 501(k) approval mechanism and the shorter market cycle time for devices. Other issues include the large number of relatively small, start-up companies engaged in the development of interventional devices compared with drugs/biologics (and less capitalization of even the larger, more established device companies than is true with their counterparts in the drug/biological industries), as well as the aforementioned differences in the FDA regulatory “hurdles” for devices (approval based on substantive operational similarity to already approved devices, approval based on some general effect separate from proven clinical utility in a specific disease state, etc.).

Within this environment, the orderly progression of intervention devices through the process steps of the generic pathway often occurs in a somewhat disorganized manner. Some interventional devices may be widely available with broad and clinically nonspecific label indications, thereby allowing their use “on label” for a broad variety of clinical utilities but often without supporting data. Although these circumstances allow for the rapid “translation” of interventional device–based therapies to the clinic, frequently systems are not optimized before being disseminated and used for specific clinical indications and often lack subsequent comparative clinical trials to substantiate purported utility. Furthermore, should rigorous translation be attempted, the next generation of similar devices would likely become available prior to, or shortly after, the completion of the prerequisite optimization and validation of the now “outmoded” generation.

Paradoxically, a potentially useful modality could be found ineffective through comparative clinical trials and thus abandoned not because the modality itself is ineffective but because the modality was never optimized for that particular clinical condition. Hence, failure to follow the pathway sequentially could lead researchers to abandon a potentially viable intervention.

This feature of interventional device development affects all the pathway steps from the point of entry through early-phase clinical trials.

Financial issues. Although the overall cost of development for an individual drug or biologic is debated, the per-unit cost during the iterative refinement and eventual production of the agent is relatively modest compared with the per-unit cost of many interventional devices. It is financially prohibitive to create a large number of fully functional devices for research purposes. This is especially true early in the development process, less so after FDA approval and immediately before clinical availability. The “research” devices made available are most often premarket prototypes where the design and function features have already been “locked down” for large-volume production, thus obviating significant system optimization, save within a rather narrow range of variables. Hence, although clinical research may be done on such interventional devices, earlier translational research is rarely possible.

This feature disproportionately affects the pathway process steps of creation of modality and preclinical development.

Clinical research. Clinical research plays an important and indispensable role during both the creation of modality and preclinical development process phases of the pathway. For numerous reasons (some of which have been presented earlier in this discussion), interventional devices are frequently translated from one clinical utility to another rather than from basic discovery to an initial clinical application (i.e., horizontal translation as opposed to vertical translation). Because of this, the modality is already “created and developed” and thus must instead be “recreated and optimized” to the new purpose. Ideally, some portion of these two process steps would use benchtop and/or animal models. However, as these devices most often have indications approved by the FDA that are broad and likely to include multiple clinical uses (often without specifying any disease-specific clinical utility in particular), these two process steps most frequently involve a significant contribution from clinical research (phase 0 and phase I). In fact, even with adequate benchtop and animal models available, some portion of these two process steps usually involves clinical research, at times requiring an investigational device exemption beyond the then-current clearance from the FDA.

This feature affects the creation of modality and preclinical development process steps in the majority of cases in which interventional device undergoes translational research.

Grant funding. Although multiple issues related to the evaluation/review of translational science (as opposed to basic or clinical science) are discussed in the Translational Research Working Group (TRWG) report, additional issues
apply specifically to the support of translational research for interventive devices. Many of these issues are due to the “engineering” or “applied” nature of interventive device translational research. This type of research is often not considered hypothesis driven and therefore may not be scored favorably by NIH study sections. Consequently, most translational research along this pathway is funded by industry rather than federal agencies. Industry has different drivers and constraints than do academic researchers, which can lead to less independent research than might be ideal.

This feature affects all of the process steps in the pathway to varying degrees.

Integrated systems optimization approach. Interventive devices are often implemented in conjunction with other modalities (agents, immune response modifiers, and/or other interventive devices). Ideally, such combinations of interventions would undergo translation using a systems approach. However, the companies developing and translating these various modalities do not often collaborate, and the clinicians responsible for various components of the combination intervention may not have sufficient incentives to overcome “cultural” impediments to such collaborations. Multiple-PI, investigator-initiated funding might provide a way to overcome some of the barriers to interdisciplinary collaboration but would probably not lead to industry collaboration early in the design and optimization phase of translational research.

This feature affects all process steps of the pathway.

Pathway Example: Three-Dimensional Conformal Radiation Therapy

Summary of the interventive modality. Radiation therapy requires careful planning to direct energy to tumor tissue while largely sparing surrounding healthy tissue. In the 1970s, for the first time, the arrival of computed tomography scan technology gave clinicians detailed anatomic information about the location of a tumor and surrounding healthy tissue (2). Three-dimensional visualization of the tumor and anatomy was done manually by using multiple two-dimensional computed tomography images to determine the optimal geometry to deliver radiation. Although computers were applied to radiotherapy treatment planning as early as 1955, the huge growth in computer power through the 1970s and 1980s made possible the development of algorithms for accurate three-dimensional visualization of a tumor and thus creation of a more conformal radiation treatment plan, offering the potential to increase doses of radiation to cancerous tissue and to decrease error rates.

During the late 1970s and early 1980s, development of computer-assisted three-dimensional tumor visualization and radiation therapy treatment planning was undertaken simultaneously by many groups of investigators (3, 4). By 1987, many groups were developing three-dimensional planning systems (5–7), and routine clinical use of a fully integrated three-dimensional planning system started in 1986. During the mid and late 1980s, National Cancer Institute (NCI) used the N01 contract mechanism to fund development and comparison efforts for both photon and electron three-dimensional planning, further documenting the potential and value of three-dimensional planning in parallel at multiple institutions to ensure reproducibility when used by different machines and operators.

The first phase I trial of this three-dimensional tumor localization and treatment planning system began in 1987 with dose escalation trials in prostate (8) and liver (9), followed by a larger-dose escalation trial in prostate in 1991 (10). During the late 1980s and early 1990s, investigators at several institutions continued to make improvements in the algorithms and capabilities of the systems, which was aided by dose phantoms (11). These improved calculational approaches were then used in the conduct of additional clinical trials. Several phase I/II trials were done in single institution settings through the late 1990s, some with NCI funding. These showed that dose could be safely escalated above the standard doses permissible with the use of two-dimensional planning—in lung cancer, prostate cancer, and liver cancer. Although there has never been a randomized trial directly comparing three-dimensional planning to two-dimensional planning, three phase III trials that have included three-dimensional planning have shown that the higher dose permitted by three-dimensional planning prolongs biochemical disease-free survival in prostate cancer compared with previously reported outcomes achieved with the maximum doses permissible using two-dimensional planning.

Relating the three-dimensional conformal radiation example to the interventive devices developmental pathway. The history of the development of three-dimensional conformal radiation therapy followed the interventional device pathway at a very broad level, although some of specific developments deviated from the pathway. There was no “fundamental research” to initiate three-dimensional planning—it grew out of the application of computed tomography scanning as it applied to treatment planning. Three-dimensional planning did emerge when it was recognized that it was simply too laborious to assemble the series of two-dimensional slices manually. Thus, a small group of physicians and physicists who led this effort became convinced that there was a basis for “attributing clinical potential” (12). No formal assessment was made as to whether the envisioned clinical need justified the expenditure of resources. Indeed, the overall feeling of the radiation oncology community was that, in the initial cases, “the expenditure of resources was too great to justify the clinical need,” particularly because there was no additional reimbursement for the extra complexity of treatment. The clinical need ultimately justified the expenditure of resources as experience showed ways to economize. Thus, the pathway as written may not take into account the anticipated difficulty in doing the first 5 cases (very difficult) versus case number 100 (much easier with experience).

Three-dimensional planning thus skipped directly to “is it feasible to develop the technology?” without a formal resource assessment. The dose calculation algorithms were tested in phantom studies, but three-dimensional therapy using nonaxial beams was directly implemented in clinical studies. This latter step was, again, resisted by much of the radiation oncology community because of cultural issues related to beam verification. Standard axially oriented fields in the two-dimensional era could be verified by axial (typically
anteroposterior or lateral) images. The new three-dimensional approaches produced verification films from unfamiliar oblique views or sometimes could not be directly verified by imaging at all (e.g., vertex beams in the treatment of brain tumors). The treatment fields were determined to be correct based on known patient landmarks and three-dimensional geometry, but these approaches were not part of radiation oncology training in the mid-1980s. Animal testing was never done, as this would not have advanced our understanding of the key elements of the technology. There were continued efforts to improve three-dimensional planning by adding more and more features to improve tumor and normal tissue visualization and the speed and accuracy of dose calculations (“does technology function as intended?”), so in this manner all treatment planning systems (and most technologies) are always a “work in progress.”

In several university settings, formal clinical trials were initiated several years after basic three-dimensional systems were implemented. Regulatory submissions typically followed sometime later when commercial systems were ultimately developed.

Opportunities

Many of the barriers related to implementation of a translational research developmental pathway for interventional devices are related to the current regulatory and fiscal environment for such modalities. We do not expect this environment to be fundamentally altered in the foreseeable future. Nevertheless, the pathway points to important opportunities for improvement.

The opportunities, in part, are broadly outlined in the white paper that launched the FDA’s critical path initiative. Since the time of that publication, there has been significant activity in the areas of drug and biological development and also in the area of biomarker qualification (both imaging and biospecimen based). There has been relatively little attention, however, paid to interventional devices by FDA, the device industry, the NIH, or academia. An important potential outcome of the TRWG initiative might be to invigorate the critical path initiative for device-based interventions. This pathway might prove useful not only for oncologic interventions but for device-based interventions across a broad range of clinical applications.

The evolution of device-based interventions is increasingly dependent on the integration of advanced imaging devices for planning and real-time guidance and monitoring. Such integration faces multiple barriers, however. First, although there has been significant standardization of imaging data through Digital Imaging and Communications in Medicine, only recently has the Digital Imaging and Communications in Medicine standard construct been to actively address standards for image-guided interventions. Academics and industry representatives from the imaging and interventional device sectors must become engaged in this process. Federal agencies such as the National Institute of Standards and Technology could likely enhance this effort. Second, the companies engaged in developing the imaging platforms and interventional devices, with only rare exceptions, do not work together to develop integrated systems. The Radiation Research Program and the Cancer Imaging Program within the NCI could facilitate such collaboration through workshops and white papers, with contributions from academia and industry. Finally, the pertinent professional societies and trade organizations could form standing committees and working groups where the express purpose would be to enhance collaboration among manufacturers and academics with expertise in imaging- and device-based interventions.

As was described previously, another major impediment to the early phases of translational research in this category of interventions is the lack of early engagement; that is, academics typically are not engaged in the development and optimization of interventional devices. The preceding strategies, at least in part, would also address this barrier. The recently announced industry-academic partnership multiple-PI R01 program announcement from the Cancer Imaging Program presents an opportunity to overcome this impediment. However, this PA is not restricted to device-based interventions; thus, responses may not be evaluated primarily by reviewers with expertise in device-based interventions. We believe that more and better applications would be received if this funding opportunity were marketed to academicians and industry with a focus in interventional devices. With a greater number of interventional device applications, and evaluation by reviewers with expertise in this field, more academics might become engaged in the earliest phases of development and optimization of such devices. Perhaps a similar program announcement focusing on interventional devices, issued jointly by the Cancer Imaging Program and the Radiation Research Program, would be a useful strategy.

Another mechanism that might increase early collaboration between academics and industry would be to place industry scientists within the academic research environment, working together on a models of the interventional devices. These devices would then be developed and validated in the academic environment, which is generally more focused on the translation from discovery to delivery rather than in the industrial environment where the focus is driven by manufacturing priorities. This model has already been deployed in a few academic sites to foster the codevelopment of imaging modalities and image-guided interventions. However, the use of such collaboration models is rare and, although unlikely to become a common occurrence, should be encouraged.

Another barrier to further development of device-based interventions is the dearth of validated biomarkers (both in vitro device-based and in vivo imaging-based risk assessment devices). Although this barrier is also pertinent to the other types of interventions, many of these biomarkers likely will need to be validated separately for local-regional interventions even if already validated for systemic interventions. We therefore suggest that the prerequisite biomarkers for these device-based interventions be developed and tested in conjunction with the

early-phase translation of the devices; they could thus be validated and available for later-phase clinical research and eventual dissemination.

Currently, there is significantly less emphasis on device-based interventions than on pharmacologic interventions in the Specialized Programs of Research Excellence and Cancer Centers. We suggest that the guidelines for funding and the subsequent evaluation of applications encourage programs in this type of translational research, including the integration of biomedical engineers and scientists, with a variety of subspecialties, such as electrical and mechanical engineering, advanced computer skills, such as image analysis and visualization, and medical physics. Researchers at sites with successful applications that include programs for the development of device-based interventions could form inter-Specialized Program of Research Excellence and Cancer Center working group(s). Furthermore, such a focus would likely engage the device industry in ways similar to how the pharmaceutical and biological industries have been engaged.

In light of the regulatory and intellectual property environment surrounding interventional devices, it would be very useful if translational research could also be designed to support regulatory evaluation of these devices. We suggest that the FDA, the NCI, academic researchers, and representatives of the device industry establish an ongoing dialog to this end. Ideally, this coordination could extend into later-phase clinical trials as well.

Conclusion

We believe the coming era of personalized medicine will require many of the changes we have discussed: not only targeted pharmacologic therapies with associated risk assessment tools to identify cohorts and evaluate important end points but also validated device-based interventions for the local-regional prevention, preemption, and treatment of cancers. Realizing this vision, however, will depend on a significant improvement in the infrastructure to support the development, optimization, and validation of such devices. The TRWG developmental pathway can facilitate coordination of effort by NCI, academia, agencies, philanthropies, and industry, as well as prioritizing, budgeting, and tracking additional investment by NCI in this essential branch of translational research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


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