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Guidance for Academics to Transfer ‘Bench-ready’ Medical Technology into Usual Clinical Practice:

Case Study: Sensors and Spectrometer used in EPR Oximetry

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Abstract

This paper considers the critical role that academics can have in the development of clinical innovations and especially how their impact can be optimized. The focus should be on establishing the safety and efficacy of new approaches while also incorporating human factors and human use considerations into the inventions. It is very advantageous to work in concert with the end-users (operators and clinicians) to help ensure that the innovation will be useful and feasible to be incorporated into actual clinical practice as intended. This strategy enables developments to tackle real clinical needs by providing novel strategies to improve patient care while using solutions that fit into clinical practice and that are welcomed by patients and clinical staff. These principles are illustrated by a case study of the development of clinical in vivo PER oximetry.

Keywords

EPR oximetry; human factors; clinical applications

1 Introduction

This paper addresses why and how academic medical researchers, during the early phases of developing their innovations, should incorporate human factor enhancements to improve the likelihood of their invention being adopted into actual clinical practice. The focus should be on early identification and implementation of those technical and process adaptations that facilitate the ‘usefulness’ for its intended end-users. While safety and efficacy are always important goals, it behoves academics to also focus on addressing the question: ‘why would end-users be willing to change their current practice to use your product?’ We provide some real examples using our developments of clinical EPR, especially for oximetry in tissues, in a clinical setting.

Many have remarked on the difficulties of bringing new medical devices and drugs to market. The magnitude of the costs and total length of time involved tell part of that story.

Drugs have been estimated to take on average about 12 years and billions of US\$, while medical devices require ‘only’ 3–7 years and many millions of US\$ [1, 2, 3, 4]. These estimates from discovery stage to market-ready may inflate the true costs, in that they include costs associated with products that fail to reach the market and exclude the shorter and easier path that is available for some types of devices.

While the magnitudes of these resources sound prohibitive for any would-be academic inventor to contemplate, these costs, and the equally daunting regulatory requirements to bring a medical invention from discovery to market, typically occur in the more advanced stages. For example, Phase III clinical trials may necessitate enrolling thousands of patients to obtain final approval. However, Phase II and III, as well as requirements during the post marketing Phase IV studies, are typically undertaken by industry. Industry not only shoulders the lion’s share of costs for these expensive activities, but it also tends to focus on obtaining the lion’s share of the profit. For example, company leaders may choose to abandon promising inventions with low yield in investment returns in favour of pursuing those with the greatest financial reward, independently of their relative value for society [5].

Academia, in contrast, is most likely to take the lead roles during the discovery phases of basic science, preclinical proof-of-concept studies, and first-in-human or early Phase 1 clinical trials¹. Indeed, the overwhelming majority of new inventions begin in academia, with mostly federal dollars providing the support for basic science, preclinical, and early clinical work. Here too the story may be daunting, e.g., it has been estimated that only 1 in 1000 inventions is likely to wind up in clinical practice [3]. The National Institutes of Health (NIH), as the major funder of basic science developments in human health, has made several attempts to identify failure points in the translation of basic science to the bedside, with the goal of improving the likelihood that more safe and effective devices and drugs will be adopted into clinical practice. Recognizing that one failure point is that academics and academia are not trained in, or rewarded for, taking on some of more entrepreneurial translational steps, NIH now funds opportunities that encourage partnerships between academics and industry. These include Small Business Innovative Research (SBIR) funding that incorporate start-up companies led by academics and Academic and Industrial Partners grants. NIH and other federal agencies have also expanded their vision of which sciences need to be integrated into the process of translating scientific inventions from bench to bedside, including understanding how to make the devices and drugs acceptable to end-users in usual clinical practice [6]. These efforts have led to focussing more on sciences that inform dissemination of innovations, regulatory sciences that impact the processes available, and integration of human factors and end-use evaluations that allow the device to be welcomed into clinical workflow (by demonstrating value and minimizing disruption) [7]. While the Food and Drug Administration (FDA) has long focused on human factors considerations, especially for medical devices, their focus has been on insuring safety and sufficiency of training and communications to end-users, rather than on transitioning devices into clinical practice in a way that both patients and clinical staff will embrace [3, 4, 8, 9].

¹Academic medical centers may also be involved in multi-site studies at Phase II and III as well, but these are often industry-sponsored trials where academics are not welcome to deviate from or contribute to the protocol. Here we focus on academics as the inventors.

Comparing Design Features in Drug vs. Device Studies

Many authors, when explaining the differences in costs and time between drugs and devices, contrast the differences in regulatory burdens and expectations for clinical studies [1, 3, 4]. For example, several have remarked on the relative burden of evidence required for devices vs. drugs, i.e., the use of randomized controlled trials vs. observational studies, allowing evidence from more novel designs such as noninferiority or equivalency designs, escalation trials, patient vs. observer reported outcomes, or design issues in evaluating more novel and complex products such as drug-device combinations or device-related diagnostics as a secondary use [10, 11, 12]. In this paper, we, following the approach of Grunkemeier et al. [13], instead focus on the differences between devices and drugs regarding the fundamental scientific questions that underlie the design features necessary to build an evidence-base for safety and efficacy.

Table 1 presents a comparative overview of some of these design features, particularly as they impact the design of clinical studies at the discovery and early stages most impacting academic inventors. Noted in the first column are the basic disciplines most involved in addressing the issues of providing evidence and addressing the difficulties where they occur. In comparing drugs and devices in the last three columns, we differentiate between medical devices that are implanted or injected into the body versus those that are applied only externally. We then use bold text to highlight wherever a feature is more difficult to address for drugs vs. devices.

The first pattern to observe is that, in virtually all of the design features that require using basic sciences or basic clinical sciences to address the scientific question, drugs have to tackle a more difficult set of problems when compared to devices. For example, drugs in general are addressing a biological problem involving a chemical interaction with the body, usually with systemic implications that involve effects (and biological responses to the effects) that may take days or weeks to observe and the full mechanisms of action may be incompletely understood. In contrast, devices are usually solving a defect using bioengineering solutions that are not intended to interact chemically, but only physically with the body part most locally impacted by the device. The outcome (e.g., opening of a valve or observation of oxygen) occurs virtually immediately and the intended mechanism is relatively simple and well understood. Nonetheless, implanted devices may encounter a more difficult burden of proof if there is a need to establish the intended biocompatibility of the device or if the device is intended to deliver a drug to a targeted area in the body.

However, the situations reverse when the design features relate to incorporating the products into clinical practice. These aspects include ergonomic, human factors or other human behavioural issues such as compliance of patients or skills and training required to administer the product. Here, by and large, the more difficult tasks to solve tend to be for devices, especially those that are implanted.

These differences help to enlighten why there are important regulatory differences in drugs versus devices at later stages. Drug studies receive greater attention to having sufficient patients in order to assess safety and outcomes that are related to the scientific questions in

the basic and clinical sciences. Devices, in contrast, receive greater attention to safety and efficacy related to human factors and engineering issues (e.g., insuring electrical safety, user training, avoidance of common errors of use, technical reliability of the device).

What is also importantly illustrated by this table is that human factors need to be addressed, and addressed early on in the process of development, especially in trying to improve the rate at which promising inventions are to move beyond the bench and then beyond the academic medical centre into widespread clinical practice. Also essential, but only indirectly emphasized in this table, is the need to make the product realistically usable in a busy clinical practice. The latter requirement falls more heavily on devices than drugs to solve, because they need to be acceptable to patients and clinical users as well as needing to add more in value (i.e., value in terms of being clinically useful as well as reimbursable) than they remove from the activities and time available in a typical clinical encounter.

Case Study Examples from EPR Oximetry

Based on our experience in developing an EPR spectrometer for in vivo clinical applications, especially in recent experiences using EPR oximetry for assessing oxygen in tumours during radiation treatment, we illustrate four cases where we have needed to significantly modify the design and use of the EPR spectrometer in order to address some very important clinical problems that arose and to deal with ‘real people’ with real constraints and preferences.

Clinical issues involving patient²/user comfort and tolerance

Fig. 1 illustrates several issues in adapting our ‘rigid’ resonator (detector) technology. It was originally developed for small animal applications, and then had been optimized for use in human in vivo EPR dosimetry [14]. It was revised again to meet several new considerations for use in human in vivo EPR oximetry.

For in vivo tooth dosimetry, the rigid resonator was used in 5-minute measurement sessions where the patient sat in a chair, resting his/her upper jaw comfortably on a specially designed mouth rest and the resonator loop was then placed horizontally against an upper incisor during a measurement session. The resonator’s technical performance (see details in Schreiber et al. [15] and Flood et al. [16]) was excellent, and so we adopted it for use in in vivo oximetry.

However, the conditions for human oximetry measurements differed substantially: a) depending on the tumour location, the patient may be lying down on a gurney or sitting in a special chair inside a large magnet; b) the resonator’s loop needed to be placed on the skin or inside a mucous surface, e.g., for tumours on the tongue, which was both much more lossy and prone to being responsive to involuntary actions like the patient’s breathing; c) the surface over the tumours may be tender to touch, e.g., due to breaking through the skin or becoming friable due to radiation-induced dermatitis; and d) currently our measurement sessions are ~30 minutes instead of 5, so that patient comfort and ability to stay sufficiently

²Note: all volunteers being measured by either EPR dosimetry or oximetry and all who received implanted devices have signed informed consents and are under IRB approved protocols.

still while remaining in the same region of the spectrometer's magnet was much more challenging.

Consequently, as shown in Fig. 1A on a patient with a tumour on the neck, the original rigid resonator produced unexpected technical complications. Namely it could interfere with tissue oxygen measurements near the surface, when excess pressure was applied to the body surface due to gravity from the resonator's being held from above by an artificial arm for 30 minutes. Additional problems arose when the body surface moved as a consequence of breathing or other movements. These movements changed the relationship between the body surface and the rigid resonator loop during data acquisition, resulting in adding noise and instability to the detected signal.

Fig. 1B shows the revised flexible resonator that is held in place with virtually no pressure using a fixation ring with an adhesive backing, allowing the resonator to rise and fall with any small movements, making it much less perturbing to the measurement. Even with this solution, we learned that the fixation ring could be uncomfortable for some patients with friable skin, e.g., with radiation-induced dermatitis. For these patients, who would typically have an EPR measurement just prior to their next radiation treatment, we opted to use medical grade honey to hold the ring to the skin, because it was easily washed off (important because their skin must be free of anything topical before their treatments) and very acceptable to the patients. Fortunately, the technical performance of the revised resonator, at least for oximetry, was significantly improved and the patients (and operators) are also happier with the ease and comfort of this model.

Fig. 2 illustrates developments that need to be taken into account when encountering both large variation in sizes of the patients and the operators; (the particular application shown is the simulation stage of human factors designs for EPR tooth dosimetry). These include the ergonomic difficulties in fitting some people into the magnet and in operator fatigue when performing multiple measurements during a given day. Fig. 2A shows the use of CAD software to plan for both safety issues (e.g., holding the patient's weight and the stability of the instrument if connected to the chair) as well as feasibility of fitting obese individuals into the instrument, i.e., taking into account body dimensions other than height and weight. Fig. 2B shows maximum and minimum anatomical figures used in the design of the overall instrument to accommodate for height differences of the operators ranging from small women to large men. These also took into consideration operator actions during a measuring session, e.g., to assist the patient, prepare the instrument for measurement, and operate the spectrometer.

Clinical issues involving operator skills and training

Fig. 3 illustrates the need for expertise and additional instrumentation to accurately place an implant into a tumour below the surface. For EPR in vivo tooth dosimetry, there was no need to pair an implanted device (the sensor) with EPR spectroscopy because the effect of interest, potential unexpected exposure to clinically significant levels of radiation, resulted in the generation of free radicals in the teeth. These could readily be assessed by simply placing the resonator on the exterior of the tooth. However, for EPR in vivo tissue oximetry, the sensor needs to be injected or implanted into the tissue of interest. Our initial efforts to

use EPR oximetry involved injection of paramagnetic India ink into tissues within 5 mm of the surface. While we did develop ‘best practice’ standards for injecting the ink and for training new injectors, the skills needed for injection are those readily available in a medical setting. However, as we added different types of oxygen sensors—especially because of the clinical interest in assessing tumours deeper than 5 mm—the skill needed to ensure correct placement into the tumour, as well as to locate it for measurements and for removal, has become more important.

Fig. 3 also illustrates the current practice for implanting 5 mm long rods of LiNc-BuO crystals suspended within a medical grade silicone elastomer (referred to as OxyChips). It is important both to know that the sensor is accurately placed within the tumour and to be able to locate the sensor for repeated measurements. Repeated measurements can also be challenging because the tumour may shrink in response to cancer treatments. To address these issues, and because we currently need to remove the OxyChip at the time of tumour resection for usual care, we have opted to utilize radiologists who are expert at using ultrasound to implant fiducial markers in tumours, e.g., in the breast. These experts place our oxygen sensor into the tumour, utilizing the same ultrasound technology. Fig. 3A shows placement in a breast tumour during ultrasound, and 3B shows the ultrasound image seen by the expert placer during placement.

Fig. 4 shows the progression of the data acquisition software interface from 2010 to the intended endpoint ~ 2018. The original software display had all of the parameters that were being developed and assessed in the real-time use of the spectrometer by engineers. Both EPR dosimetry and oximetry were being developed at this time, and the software available to control the various components of the spectrometer (e.g., the RF bridge, power supply, amplifiers, etc.) was a work in-progress. Data needed to be gathered about the instrument components that were evolving, e.g., the resonators and RF bridge. There was also a need to automate calibrations and provide adjustments for signal-to-noise problems, as well as to develop techniques for automatic tuning.

The early data acquisition software provided flexibility to the developing engineers to handle all the instrument interfaces reliably and produce accurate results. At the same time, the team evaluating the human factors deliberately included ‘novice’ users of the equipment to understand how novice users would use the equipment (e.g., to observe common mistakes and problems that may compromise data collection) and to gather data needed to more fully automate the use of the machine *and* to provide the data that the end-user really needs. For the latter, we sought to provide online results and analysis of the quality of the data, instead of requiring these to be done post-measurement, and to remove clinically irrelevant information and parameters from the data acquisition interface in order to reduce end-user confusion and minimize mistakes in operation. Fig. 4A shows the graphic user interface (GUI) originally in use. Fig. 4B shows the ultimate GUI with a completely simplified set of actions that an operator can make and displays of data in a user-friendly form that clinicians can readily use and adapt as needed.

Conclusions

Not highlighted in these examples are the immeasurable efforts of the technical staff to insure the safety, accuracy, and usability of these devices and data. The overall goal is to make the inventions—in this case devices—both technically and scientifically as accurate, efficient, effective and safe as possible while also attending to the needs and preferences of the end users. These were achieved in great part by working in concert with the end-users (operators and clinicians) to help ensure that the instrument is useful and feasible to be incorporated into actual clinical practice as intended. This strategy enables the developments to tackle real clinical needs by providing novel strategies to improve patient care while using solutions that fit into clinical practice and that are welcomed by patients and clinical staff. Academics need to pay greater attention to these latter goals—to incorporate the human factors and human use considerations into the innovations being developed in academia—in order to be more successful in advancing their inventions into and through the long regulatory processes that must be followed to bring innovative improvements into standard care.

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Figure 1. Practical considerations when using resonators in tumor measurements

A: Rigid resonator shown with loop against neck of cancer patient (shown using a breathing mask to deliver oxygen-enriched air). The resonator is held by a positioning arm that allows complete rotation during placement, for optimizing angle against the skin and optimizing EPR signals, but is then locked in place from above during the ~30 min session.

B: The flexible resonator is held in place with a fixation ring and an adhesive, reducing pressure (thereby minimizing oxygen changes induced by pressing surface vessels) and allowing the resonator to move with small voluntary and involuntary movements, e.g., breathing (thereby reducing noise associated with motion). When the skin becomes friable, e.g., due to radiation dermatitis, the fixation ring is held using medical grade honey, easily removed with water.

Figure 2. Accommodating EPR tooth dosimetry to variations in size of patients and operators

A: CAD drawing of 95% height male, with photo of a male weighing 182 kilos superimposed; used to assess stability and distances needed to swing chair from entry at side to facing the instrument and to allow access of resonator extension to head without hitting chest. Note: post (containing RF bridge, computer and power sweep and supply) adjusts platform up and down to fit patient. Small box on platform allows operator to adjust the resonator at x, y, and z angles for fit to tooth.

B. CAD drawing of a 5% female and 95% male (not shown to same scale as in A); CADs are used to evaluate ergonomics and access for operators performing tasks during measurements.

Figure 3. Complexity of implantation of Oxygen Sensor into Tumor

A: Experienced radiologist using XXX Ultrasound (probe in left hand) while inserting needle with stylus containing the 5mm oxygen probe into breast tumor ~ 1.2 cm deep.

B: Needle (diagonal line on upper right) shown on ultrasound, just before implanting oxygen sensor into the tumor.

Figure 4. Simplifying software graphic user interfaces (GUI): Reducing errors and unwanted variation in use

A: Actual GUI in use in 2010 for EPR dosimetry and oximetry showing multiple operator-adjustable spectrometer parameters and actionable buttons and displaying output as: 1) in and out of phase scans/spectra; 2) calculated median of spectra and Lorentzian fit to median; 3) unconverted spectral parameters, e.g., amplitudes (used to estimate dose), linewidths (used to calculate oxygen levels) and signal-to-noise (used to evaluate parameters).

B: Proposed GUI for Oximetry, displaying 4 simple actions for operator and exhibiting continuously collected data that show calibrated conversion of EPR spectra to absolute oxygen levels. Example data illustrate the changes in tissue oxygen at the culmination of a patient's 30-min tripartite measurement period, i.e., while patient breathes: 1) room air (baseline), 2) hyperoxic gas mixture, and 3) return to room air.

Table 1

Comparing the Ease of Design Features for Clinical Studies based on Drugs or Devices: Bold text indicates greater difficulty

SCIENTIFIC DISCIPLINE:	TYPE OF STUDY: DESIGN FEATURES:	DRUGS	DEVICES	
			IMPLANTED	EXTERNAL USE ONLY
Basic Science	Purpose	Solve a biological problem	Solve a biological or engineering problem	Solve an engineering problem
	Intended mechanism of action	Chemical	May include chemical; mostly physical	Physical
	Impact on person	Systemic	Local (for physical)	Same as implanted
Clinical Science	Clinical outcomes	Difficult to observe Long term effects directly	Easily observed directly, i.e., effect is immediate	Same as implanted
	Clinical process of effect	Sometimes not well understood	Measured objectively	Same as implanted
Ergonomic or Human Factors	Compliance	Problematic	None; determined	Problematic
	Change in design	Unknown impact	Modest or no impact	Same as implanted
	Provider skill to use	Unimportant	Very important	May be important
	Recruitment	Easier to get large #s	Usually few cases	Easier to get large #s
	Time in person	Temporary (<30 days)	Permanent	Not applicable
	Ease of change	Easy to change dose e.g., escalation trials or stop	Must be explanted to change or stop	Easy to stop; can change design