Guidance 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 EPR oximetry.

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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?' Examples include

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developing 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, 3a, 3b].

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, industry typically undertakes the trials in these phases, not only shouldering the lion's share of costs but also focusing on obtaining the lion's share of profit. For example, company leaders may choose to abandon promising inventions with low yield in investment returns, independently of their relative value for society [4].

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 trials. Indeed, the overwhelming majority of new inventions begin in academia, with mostly federal dollars providing the support. 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 [3a]. The National Institutes of Health (NIH), as the major US funder, has identified several failure points in the translational path from basic science to the bedside, with the goal of improving the likelihood that more novel devices and drugs will be adopted into clinical practice. 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. NIH and other federal agencies have also expanded their vision of which sciences need to be integrated into the process, e.g., those that address how to make devices and drugs more acceptable to end-users in usual clinical practice such as sciences that inform dissemination of innovations and integrate human factors and end-use evaluations that allow the device to be welcomed into clinical workflow (by demonstrating value and minimizing disruption) [5, 6]. Some agencies such as the Food and Drug Administration (FDA) have a history of efforts focused on human factors. However, their aim was to assure safety and the adequacy of training of device end-users, rather than to develop devices that patients and clinicians will embrace [3a, 3b, 7].

2 Comparing Design Features in Drug vs. Device Studies

To explain why development costs and time differ so much between drugs and devices, many point to their differences in regulatory burdens and expectations for clinical studies, e.g., the lighter burden of evidence required for devices vs. drugs [1, 3a, 3b]. Following Grunkemeier et al. [8], this paper instead focuses on the differences 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. The first column notes the basic disciplines most needed to provide the evidence and solve any problems. Bolded text is used 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, the problems are more difficult for drugs compared to devices. For example, drugs in general are addressing a biological problem involving a chemical interaction with

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:	Studies of drugs	Studies of devices	
	Design features:		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

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 usually solve a defect using bioengineering solutions that only physically interact with the body and only at the local site of 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. However, 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 delivering a targeted drug.

In contrast, the problems become more difficult for devices than drugs when the design features focus on how to incorporate the products into clinical practice. These challenges include ergonomic, human factors or behavioural issues such as patient compliance or operator skills and training required to administer the product.

In sum, 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.

3 Case Study Examples[1] from EPR Oximetry

Based on our experience in developing an EPR spectrometer for in vivo clinical applications, especially in using EPR oximetry to assess oxygen in tumours during radiation treatment, we present four cases where we needed to significantly modify the design and uses of the EPR spectrometer in order to address very important clinical problems that arose as well as to meet practical constraints and preferences.

3.1 Clinical Issues Involving Patient[2]/User Comfort and Tolerance

We illustrate (Fig. 1 (see footnote 2)) 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 [9]. 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-min 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. [10] and Flood et al. [11]) 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 min instead of 5 min, so that patient comfort and ability to stay sufficiently still while remaining in the same region of the spectrometer's magnet was much more challenging.

Consequently, (see Fig. 1a) the original rigid resonator produced unexpected technical complications on a patient with a tumour on the neck. Namely it interfered 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 min. 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.

The revised flexible resonator (Fig. 1b) 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 tech-

[1] https://www.clin-epr.com/s/Flood-Supplementary-Material-OT-1.pdf

[2] Note: all volunteers are under IRB approved protocols.

nical 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.

Developments need to take into account large variation in sizes both of the patients and the operators; (the particular application describes the simulation stage of human factors designs for EPR tooth dosimetry; see Fig. 2 (see footnote 2)). Problems encountered include both the ergonomic difficulties in fitting some patients into the magnet and in operator fatigue when performing multiple measurements during a given day. Figure 2a shows the use of CAD software used to plan for safety issues (e.g., holding the patient's weight and the stability of the instrument if connected to the chair) as well as the feasibility of fitting obese individuals into the instrument, i.e., taking into account body dimensions other than simple height and weight. Figure 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.

3.2 Clinical Issues Involving Operator Skills and Training

The next illustration concerns the need for expertise and additional instrumentation to accurately place an implant into a tumour below the surface (Fig. 3 (see footnote 2)). 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.

The current practice for implanting 5 mm long rods of LiNc-BuO crystals suspended within a medical grade silicone elastomer (referred to as OxyChips) is illustrated in Fig. 3. 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; Fig. 3b shows the ultrasound image seen by the expert placer during placement.)

The data acquisition software interface has also progressed significantly (from ~2010 to ~ 2018 (Fig. 4 (see footnote 2))). 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 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. Figure 4a shows the graphic user interface (GUI) originally in use. Figure 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.

4 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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