Innovative Practice, Clinical Research, and the Ethical Advancement of Medicine

Jake Earl

(forthcoming in the *American Journal of Bioethics*)

INTRODUCTION

In January 2016, Paul Marik's 53-year-old patient Valerie Hobbs was dying of severe sepsis. After standard therapies failed to improve Hobbs's condition, Marik treated her with large, intravenous doses of vitamin C along with hydrocortisone and thiamine. Although this intervention was inspired by recently published, early-phase clinical research on the effects of vitamin C in septic patients, it had never before been attempted in humans or subjected to formal evaluation. Hobbs made a surprising recovery following the novel treatment, and after successfully treating two additional patients with the same intervention, Marik convinced his hospital to adopt it as the local standard of care (Simpson 2017a). A retrospective study conducted by Marik and colleagues suggests that the intervention reduced the hospital's mortality rate for patients with severe sepsis from 40.4% in late 2015 to 8.5% in early 2016 (Marik et al. 2017). This so-called "miracle cure" for sepsis has generated significant controversy among clinicians and researchers (Simpson 2017b). Some critics claim that it was unethical for Marik to provide an untested intervention to sick patients outside of a formal research study (Rezaie 2017), while others warn that clinicians should refrain from using Marik's intervention until a rigorous clinical trial establishes that it is safe and effective (Milne 2017).

Marik's sepsis intervention is an example of innovative practice, in which a clinician provides something new, untested, or nonstandard to a patient in the course of care, rather than under a formal research protocol. Like clinical research, innovative practice has the potential to benefit both the patients who receive it and the practice of medicine itself: anti-inflammatories (Wood 2015), anesthesia (Hammonds and Steinhaus 1993), laparoscopy (Hatzinger et al. 2006),

and pacemakers (Ward, Henderson, and Metcalfe 2013) were all introduced and developed in clinical practice before they were proven beneficial by clinical research. However, also like clinical research, innovative practice can increase the risk that patients will suffer harm, exploitation, or violations of their autonomy (Eaton and Kennedy 2007). Critics also worry that innovative practice allows clinicians to promote their favored innovations while avoiding the ethical and scientific restrictions that are imposed on clinical research, thereby undermining efforts to improve medicine through sound science (Chalmers and Silverman 1987; McKinlay 1981). These ethical concerns justify the control and oversight of innovative practice by medical institutions (professional societies and health care organizations), but what should such oversight look like? In particular, how should such oversight coordinate innovative practice and clinical research?

In this article, I argue that an ethical approach to innovative practice must encourage clinicians to subject their interventions to high-quality clinical research at an early stage in their development, but not by uniformly restricting clinicians' ability to engage in innovative practice. After clarifying the concept of innovative practice, I explore some key ethical issues it raises, in particular the risk that innovative practice will lead to the spread of harmful or nonbeneficial interventions in medical practice. I then consider the merits of proscriptive and permissive oversight approaches to this risk, and ultimately endorse a permissive approach that includes a requirement that clinicians justify their decision to engage in innovative practice rather than clinical research.

WHAT IS INNOVATIVE PRACTICE?

Belmont on Innovative Practice

It is important to understand what innovative practice is so as to avoid unnecessary confusion about its ethical ramifications. The influential *Belmont Report* defines clinical practice as "interventions that are designed solely to enhance the well-being of an individual patient" and

that "have a reasonable expectation of success," (National Commission 1978, 2-3). The report cautions against confusing "innovation" in clinical practice, wherein "a clinician departs in a significant way from standard or accepted practice," with clinical research, which is "an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge." On this view, therapeutic, preventive, or diagnostic (i.e., clinical) interventions are *innovative* if they deviate from standard or accepted clinical practice, and *innovative practice* is the use of innovative clinical interventions to enhance the well-being of individual patients (provided there is a reasonable expectation of that outcome).

Although *Belmont*'s definition distinguishes innovative practice from both ordinary clinical practice and clinical research, it is ambiguous in two ways. First, there can be different reasons for using a clinical intervention that deviates from standard or accepted practice, even if the ultimate point of using the intervention is to promote the patient's health. For example, a clinician might prescribe her a medication to improve her patient's health, but prescribe a nonstandard rather than a standard medication because doing so will save the patient money. The second ambiguity is that the "standard or accepted practice" from which innovative practice deviates could refer to various practical norms. A clinical intervention might be "innovative" in that it deviates from personal, institutional, local, national, or international standards of practice. Those standards themselves could be normative in different ways: statistically (what is most frequently done), legally (what the law requires), professionally (what professional societies require), morally (what morality requires), etc.

The various combinations of different norms from which innovative practice might deviate and different reasons for deviating from those norms raise interesting conceptual, ethical, and practical questions that warrant further examination. In this discussion, however, I will limit my focus to the sense of innovative practice that has been the implicit focus of the ethics literature

(Bracken-Roche et al. 2014; Eaton and Kennedy 2007; Reitsma and Moreno 2006). This kind of innovative practice involves deviating from what I call the *idealized expert-consensus standard* of medical care for the purpose of improving a patient's health.

The Idealized Expert-Consensus Standard

"Idealized expert-consensus standard" is a term of art for those practices of patient care that are best supported by the available scientific evidence, clinical experience, and expert judgment. More specifically, the idealized expert-consensus standard consists of those patient care interventions (including but not limited to clinical interventions) that would be collectively endorsed by a group of expert clinicians in the relevant fields of medicine following an impartial, rational assessment of all available clinical and scientific evidence. This is an "idealized" standard of care in that the recommendations are determined by a hypothetical procedure in which a diverse group of fair-minded, expert clinicians have adequate time to reach a consensus based on all currently available, relevant scientific and clinical data. The idealized expert-consensus standard conforms to the principles of evidence-based medicine (Sackett et al. 1996), and the extent of its recommendations set the boundaries of medicine. That is, if the idealized expert-consensus standard offers no normative guidance for a kind of activity (e.g., eating with chopsticks, parallel parking, etc.), then that activity lies outside the scope of medicine.[1]

Clinical interventions that deviate from the idealized expert-consensus standard deserve special attention among the varieties of innovative practice because that standard represents an aspirational ideal for the practice of medicine. It is helpful to think of the idealized expert-consensus standard as giving criteria for judging real-world clinical practice guidelines and, by extension, real-world clinical practice. Actual guidelines can fail in a number of ways: they can fail

[1] Intractable disagreement among the hypothetical expert clinicians about which among multiple interventions is best for a given condition yields a disjunctive standard (i.e., clinicians should use either X, or Y, or...).

to incorporate relevant evidence (including the experiences and practical knowledge of working clinicians), their authors can be financially conflicted or politically motivated, they can conflict with guidelines produced by other groups, etc. We can recognize these failures as failures because we have an intuitive understanding of how they make clinical practice guidelines fall short of the idealized expert-consensus standard for medical practice. Innovative practice that deviates from the idealized expert-consensus standard therefore pushes beyond the boundaries of medicine's most demanding current standards, and so deserves a different kind of scrutiny than interventions that deviate from mere local or institutional standards of care.

Although it will often be clear to competent clinicians whether a given intervention deviates from the idealized expert-consensus standard, it can be difficult to determine in some cases. When the idealized expert-consensus standard recommends no therapeutic, preventive, or diagnostic intervention for a patient's condition (e.g., incurable or untreatable illnesses), then offering or administering a clinical intervention to improve the patient's health rather than mere supportive care (e.g., symptom management, psychosocial support, etc.) is clearly innovative practice. However, in some cases an intervention will be contrary to the idealized expert-consensus standard despite being widely used by clinicians, or might adhere to the idealized expert-consensus standard despite diverging from common practice. For example, a surgeon who insists on performing a certain procedure in the afternoon rather than in the morning like her colleagues might deviate from local or institutional norms of care, but this deviation could be perfectly consistent with the idealized expert-consensus standard (London 2006). In harder cases, determining whether a clinical intervention counts as innovative practice will require individual judgment.

ETHICAL CONCERNS ABOUT INNOVATIVE PRACTICE

The ethical issues raised by innovative practice can be helpfully sorted into two categories. The first category includes ethical concerns about the direct impact of innovative practice on the

patients to whom it is offered or administered. The second category of ethical issues raised by innovative practice concerns its impacts on the wider community of patients and on society at large.

Patient-Focused Concerns

Deviating from the idealized expert-consensus standard usually entails significant uncertainty about an intervention's likely harms and benefits for the patient. Given that the history of medicine is littered with promising innovations that ultimately offered no benefit or were positively harmful (Prasad et al. 2013a), it is unclear whether engaging in innovative practice is consistent with clinicians' duty of beneficence (Grimmett and Sulmasy 1998). Like in clinical research, uncertainty about the associated risks can undermine a patient's ability to give informed consent to innovative practice, and this problem can be worsened by a patient's false belief that he is receiving standard clinical care (Bracken-Roche et al. 2014). However, informing especially vulnerable patients about an intervention's innovative nature could also undermine their autonomy by fostering unreasonable optimism (King 2001). Innovative practice also raises concerns about justice, as clinicians might have conflicting financial or professional interests in an intervention's success, which in turn can distort their judgment about its safety and effectiveness, making (perhaps unintentional) exploitation more likely (McKneally and Daar 2003, 932-33; Taylor 2010, 291-92).

These ethical concerns suffice to show that innovative practice should be controlled and managed to some extent, and I will assume that some combination of health care organizations, professional societies, and government entities can do so effectively with the right policies. One reason for this assumption is that there are countervailing ethical concerns about beneficence, respect for autonomy, and justice for patients that favor clinicians' engaging in innovative practice. For patients with anomalous physiologies, bizarre injuries, rare or complicated disease profiles, or terminal, incurable illnesses that make the idealized expert-consensus standard woefully

inadequate, engaging in innovative practice might be lifesaving (Caplan 2007; Walker, Rogers, and Entwistle 2014; White and Gelinas 2016). In such situations, patients in principle can both have a strong interest in receiving innovative practice and be fully capable of giving informed consent without being exploited.

Another reason for this assumption is that some health care organizations and professional societies have already begun implementing policies to address these concerns (e.g., ACOG 2006; Biffl et al. 2008; ISSCR 2016, 24-26; Jackson Health System 2011; Kornetsky 2005; Stanford University Medical Center 2011). These policies are similar to those widely thought to be necessary for the ethical conduct of research with human subjects (Emanuel, Wendler, and Grady 2000). In order to combat clinician bias and reduce risks to patients, clinicians are required to submit their plans for innovative practice to institutional reviewers or expert peer reviewers to assess whether deviating from the idealized expert-consensus standard is in the patient's best interest. An enhanced informed consent process that discloses an intervention's innovative nature and the clinician's potential conflicts of interest is mandated in order to protect patients from exploitation and to promote respect for their autonomy. Although there is disagreement about how such policies should be implemented and enforced (Karpowicz, Bell, and Racine 2016), going forward I will assume that they will be part of any ethically acceptable oversight approach to innovative practice.

Population-Focused Concerns

The history of percutaneous coronary intervention (PCI) for stable coronary artery disease offers a helpful example of population-focused ethical concerns about innovative practice. Stable coronary artery disease is characterized by consistent angina pectoris (chest pain), a history of myocardial infarction (heart attack), or confirmed artherosclerosis (plaque deposits) in the coronary arteries. In addition to pain and impaired function, stable coronary artery disease

increases the risk of acute heart problems and death (Pflieger et al. 2011). PCI procedures in which a stent is placed in a coronary artery to reduce stenosis (an abnormal narrowing of the artery) were first introduced as innovative practice in the 1980s. In the early 1990s, research studies comparing stenting with other surgical interventions led many clinicians to believe that stents were an effective treatment for stable coronary artery disease, resulting in a surge of PCI's popularity as a first-line intervention (Serruys, Kutryk, and Ong 2006). As PCI spread, however, doubts arose about its effectiveness, and these doubts were ultimately confirmed in the 2007 COURAGE study, a randomized, controlled trial (RCT) which showed that PCI with optimal medical therapy did not reduce mortality or risk of heart attack compared to optimal medical therapy alone (Boden et al. 2007). Subsequent research has led to a steady abandonment of PCI as a first-line therapy for stable coronary artery disease (Mitchell and Brown 2017), and this trend will likely accelerate due to recent RCT findings that PCI is no better than placebo even for chest pain (Al-Lamee et al. 2018).

The history of PCI shows how innovative practice can result in *runaway diffusion*, the widespread adoption of a harmful or nonbeneficial intervention by clinicians. Diffusion is the process by which an innovation is adopted by increasing proportions of a community of practice. Some innovative clinical interventions diffuse only after they have been evaluated in multiple RCTs and received formal (e.g., FDA) approval, while others diffuse only after showing promise as innovative practice. While rigorous clinical research sometimes leads to runaway diffusion, innovative practice likely poses a greater risk. Innovative practice lacks the institutional and scientific constraints that counteract various clinician and patient biases favoring the belief that an innovative intervention is beneficial, and reports of this perceived benefit can lead other clinicians, patient advocacy groups, and health care organizations to invest political and financial resources in the intervention (Bender, Flicker, and Rhodes 2007; McKinlay 1981; Prasad and Cifu 2012).

Positive results from retrospective or observational studies involving small numbers of patients can accelerate the diffusion process, even though such studies are often inadequate to determine whether innovative interventions are safe and effective (Redberg and Walsh 2008; Prasad et al. 2013b). Once an intervention is widely accepted within the medical community (perhaps even accepted as the idealized expert-consensus standard), new practical and ethical concerns arise about scientifically assessing its true risks and benefits (Kim and Miller 2015).

Population-focused ethical concerns about innovative practice are conceptually and practically distinct from patient-focused concerns. Administering an intervention as innovative practice might be a reasonable means for promoting a given patient's well-being in a way that respects her autonomy and avoids exploitation. The diffusion of that same intervention, however, could have negative effects on the broader community of patients and society as a whole. The widespread adoption of PCI for treating stable coronary artery disease led to many patients suffering the harmful side-effects of the procedure or forgoing effective alternatives for no real benefit. The widespread acceptance of PCI among cardiologists and clinicians' enthusiasm for the intervention likely led many patients to overestimate PCI's likelihood of benefit or to underestimate its risks, thereby undermining their ability to give informed consent to the procedure. Further, PCI for stable coronary artery disease wasted scarce private and public health care resources that could have been put to genuinely therapeutic purposes, and additional social harm likely accrued when the medical community made a public reversal on the intervention and slowly began to abandon its use (Prasad and Cifu 2015). Protecting the patients who initially received PCI as innovative practice might have done little to protect everyone else from its runaway diffusion.

Innovative practice increases the risk of runaway diffusion, and runaway diffusion raises serious ethical concerns. In addition to implementing policies requiring prospective review and

enhanced informed consent, it is imperative to subject all innovative clinical interventions to rigorous clinical research (perhaps especially RCTs) early in their development. Effective scientific evaluation facilitates the timely identification of harmful or nonbeneficial interventions before they can spread widely, which will help protect future patients and society from the untoward effects of runaway diffusion. The question, then, is how to coordinate innovative practice with clinical research in a way that appropriately responds to the values at stake (Frader and Caniano 1998).

THE PROSCRIPTIVE OVERSIGHT APPROACH

Some commentators have argued that innovative clinical interventions should be available only in the context of formal research studies of their safety or effectiveness, and that outside of such research clinicians should strictly follow the idealized expert-consensus standard (except in rare cases of emergency or extremity) (McKneally and Daar 2003; Prasad 2013; Prasad and Cifu 2012). On this view, the two categories of ethical issues raised by innovative practice together justify ensuring clinicians almost never engage in innovative practice.

The Case for Proscription

Vinay Prasad and Adam Cifu maintain that clinicians should offer or administer innovative interventions in practice only after rigorous clinical research (especially large RCTs with appropriate clinical endpoints) has established that they are safe and effective (Prasad 2013), except in those cases where a patient's condition is exceedingly rare or dire (Prasad and Cifu 2012, 82-83). They argue that given our current medical knowledge, deviations from the idealized expert-consensus standard outside of research are highly likely to be harmful or nonbeneficial. Combining analysis from the *British Medical Journal Clinical Evidence* project with their own assessment of studies published in the *New England Journal of Medicine*, Prasad and Cifu estimate that if all standard medical practices were subjected to rigorous scientific scrutiny, 55% would be proven beneficial while 35% would be proven harmful or nonbeneficial (Prasad and Cifu

2015, 83-87). If innovative practice follows this pattern, then we should expect that more than one of every three innovations will be nonbeneficial or harmful. The odds could be much worse for some types of intervention: only 10-15% of clinical trials of new drugs demonstrate therapeutic benefit, despite the extensive development and evaluation that goes into drugs prior to Phase I trials (Wong, Siah, and Lo 2018).

Given the significant likelihood that an innovative clinical intervention will be nonbeneficial or harmful (and therefore involve some risk of runaway diffusion), Prasad and Cifu argue that engaging in innovative practice violates clinicians' primary duty of nonmaleficence—*primum non nocere* (first, do no harm) (Prasad and Cifu 2012, 74; 2015, 188). Although clinicians should seek to benefit their patients, their primary responsibility is to keep their patients from suffering harm when there is no compensating benefit, and medicine as a whole has an analogous responsibility to the community of patients. As noted above, the runaway diffusion of an innovative intervention harms those patients who receive the intervention, their families and communities, and third-party payers. Those harms are magnified when an intervention that diffuses widely is later discovered to be flawed (a phenomenon Prasad and Cifu call "medical reversal") and people lose trust in the medicine itself. Except in extreme cases, then, deviating from the idealized expert-consensus standard should be permitted only in high-quality clinical research, as this would compel clinicians to prove whether interventions are safe and effective and thereby prevent the harms of runaway diffusion.

Problems with Proscription

One difficulty with Prasad and Cifu's argument for a proscriptive approach to overseeing innovative practice is that the empirical evidence does not clearly support their position. Prasad and Cifu claim that we should expect 35-40% of all new innovative clinical interventions to be nonbeneficial or harmful, but the ethical implications of that claim for innovative practice are

opaque. Even assuming that half of all clinical interventions introduced as innovative practice would be nonbeneficial or harmful, this entails that half would ultimately prove to be safe and effective. Whether this is a good or bad outcome for patients and for society depends on the magnitudes of harm and benefit from each innovative intervention, not on the proportion of interventions that are ultimately found to be harmful or beneficial. For example, a scenario in which an ineffective screening tool for HIV and an effective treatment for male-pattern baldness both diffuse widely in medical practice is much worse than a scenario in which the screening tool is effective and the baldness treatment is ineffective, even though the ratio of ineffective to effective interventions is the same in each scenario.

A more significant problem with Prasad and Cifu's argument is that it fails to properly weigh considerations of prospective harm against considerations of prospective benefit. On their view, clinicians' duty of nonmaleficence would require restricting innovative interventions to research even if the diffusion of interventions from innovative practice were much more likely to be beneficial than harmful. But clinicians' duty of nonmaleficence must be balanced against their duty of beneficence, otherwise it would be unethical to provide any intervention that poses any serious risk to a patient's health (Sharpe 1997). As with standard clinical practice, the risks of harm from engaging in innovative practice must be weighed against the risks of forsaken benefits from curtailing it, whether the victims of those harms are a clinician's own patients, future patients, or the larger society. After all, failing to introduce, develop, and adopt beneficial clinical interventions can have equally bad effects on morbidity and mortality as the diffusion of positively harmful interventions. This is not to say that clinicians should accept any risk of harm provided that there is a large enough prospect of benefit, but it does undermine the rationale for Prasad and Cifu's excessively precautionary position. In the absence of clear empirical evidence that the risks of

permitting innovative practice outweigh the risks of preventing it, clinicians' duty of nonmaleficence does not support a proscriptive oversight approach.

Defenders of the proscriptive approach might argue that restricting innovative interventions to clinical research would not risk forsaking beneficial interventions. We should expect that Institutional Review Boards (IRBs) would approve high-quality studies on any therapeutic, preventive, or diagnostic intervention that is reasonably likely to benefit future patients and society. However, as commentators have emphasized, many innovations go through a period of development during which it can be difficult to accurately determine whether they might be beneficial to a larger group of patients (Agich 2001; Lantos 1994; McCulloch et al. 2009). This was the case with the arterial switch procedure for congenital dextro-transposition of the major arteries, which for decades yielded inferior patient outcomes before it could be proven safer and more effective than alternative interventions and become the idealized expert-consensus standard (Broberg et al. 2017). Even if an IRB would have approved a rigorous scientific assessment of the arterial switch procedure during this period, such assessment would have produced false-negative results and could have derailed the procedure's development. The proscriptive oversight approach increases the risk that such premature evaluation will delay or thwart the development of beneficial clinical interventions.

A final problem with the proscriptive approach is that it unjustifiably burdens the autonomy of both patients and clinicians. If a competent, adult patient is informed of the risks, benefits, and uncertainties of a proposed clinical innovation that his clinician wants to provide him and because she has plausible reasons to believe it would benefit him, then preventing the patient from receiving the intervention burdens his exercise of autonomy. Of course, some burdens on patients' autonomy can be justified if they are necessary to prevent others from suffering serious harm or similar burdens on their autonomy; this is what justifies the FDA's authority to regulate the sale

and marketing of new drugs to the general public before they have been proven safe and effective. But as noted above, there is significant uncertainty about the actual risks posed by innovative practice and its diffusion, and the contribution to those general risks from any particular instance of innovative practice is likely to be quite small. Interfering with a patient's autonomous choice of an innovative intervention can be justified, but the proscriptive approach's hypersensitivity to risk of harm will require interference in far too many cases.

If the patient has an autonomy claim to noninterference in choosing innovative practice, then this supports a derivative autonomy claim for the clinician. Most people believe it can be disrespectful to interfere with the efforts of competent adults to carry out what they see as their moral obligations to provide aid to consenting others. Consider, for example, a financial advisor who makes a commitment to her client to assemble a list of potential investments that are attractive given his ethical values and long-term goals. In the absence of good evidence that the financial advisor will harm her client, other clients, or third parties, a colleague's or a supervisor's interfering with her efforts would imply that she is not a competent moral agent deserving of equal respect. As autonomous moral agents, clinicians who engage in innovative practice in a way that respects their patients' autonomy and avoids exploitation have a similar moral claim to respect for their competence.

PERMISSIVE OVERSIGHT APPROACHES

Due to the need for oversight of innovative practice and the problems inherent in the proscriptive approach, some commentators (McCulloch et al. 2009; Schwartz 2014; Taylor 2010), professional societies (ACOG 2006; Biffl et al. 2008; ISSCR 2016, 24-26), and health care organizations (Children and Women's Health Centre of British Columbia 2015; Jackson Health System 2011; Kornetsky 2005; Partners Healthcare n.d.; Stanford University Medical Center 2011) have favored policies that permit innovative practice while managing the ethical concerns it raises,

including concerns about runaway diffusion. Most permissive approaches include requirements for prospective peer review and enhanced informed consent procedures. These requirements are necessary for addressing patient-focused ethical concerns about innovative practice and might be helpful for addressing population-focused concerns. In this section, I argue that additional policies included in current permissive oversight approaches fail to adequately address the risk of runaway diffusion.

Required Learning

Some commentators (Eaton and Kennedy 2009, 112; Walker, Rogers, and Entwistle 2014) and professional societies (ACOG 2006, 1594) have noted that the risks of runaway diffusion could be mitigated if clinicians did more to collect and share information about innovative practice. Recommendations range from requiring clinicians to collect and submit clinical outcomes data to anonymized patient registries (Biffl et al. 2008) to publishing about innovative interventions in peer-reviewed journals (ISSCR 2016, 26). Requiring clinicians to gather and share additional information in the course of innovative practice would directly address the risk of runaway diffusion. But one might worry that this requirement would transform innovative practice into clinical research, or at least lead to confusion about the distinction (Margo 2001), which would be at odds with favoring a permissive over a proscriptive oversight approach.

The worry that requiring clinicians to gather and share information would transform innovative practice into clinical research is exaggerated. The proposal is to require that clinicians engage in *learning activities*, clinical interventions or manipulations of health information aimed at gathering information to help improve clinical practice (Faden et al. 2013, S19). Clinical research is one kind of learning activity that might warrant a distinctive kind of oversight, but other kinds of learning are a necessary and commonplace strategy for improving the quality medical care. Learning activities such as gathering and sharing anonymized clinical outcomes from innovative

practice will often not impose additional risks on patients or burden their autonomy, and so prospective IRB review and research-specific consent are neither necessary nor appropriate. There are certainly questions about the ethical limits of learning activities (e.g., should patients be required to provide information as a condition of receiving innovative interventions?), but policies requiring learning in innovative practice do not intrinsically risk transforming it into clinical research and should be included as part of a permissive oversight approach.[2]

The real issue with required learning activities is that while they are likely necessary for mitigating the risk of runaway diffusion, they are also likely insufficient. These policies might even increase the risk of runaway diffusion for some interventions: for example, publishing innovative practice protocols and outcomes might lead other clinicians to adopt an innovative intervention before rigorous scientific testing. The core problem is that learning activities such as collecting and sharing outcomes information cannot provide the same kind of evidence as early, high-quality clinical research. Several institutions explicitly articulate in guidance documents that clinicians have an ethical, professional, or organizational responsibility to conduct such research (e.g., Stanford University Medical Center 2011, 4), but merely affirming such a responsibility and demanding compliance goes only so far in motivating clinicians to conduct potentially time-consuming and expensive research on their clinical innovations.

Patient Caps

Short of taking a proscriptive approach to innovative practice, what should institutions do to encourage clinicians to subject their innovations to timely, high-quality clinical research? Some commentators and professional societies have favored capping the number of patients who may

[2] Questions about the ethics of learning activities in innovative practice are part and parcel to larger debates about the ethics of learning health care systems and quality assurance/quality improvement initiatives. See Faden et al. 2013.

receive an innovative intervention outside of a formal research study. Patient caps are endorsed by the International Society for Stem Cell Research (ISSCR), which recommends that clinicians "may provide unproven stem cell-based interventions to at most a very small number of patients outside of the context of a formal clinical trial" (ISSCR 2016, 25). The aim of the cap appears to be to facilitate "moving to a formal clinical trial in a timely manner after experience with at most a few patients," and to avoid "unnecessarily delay[ing] rigorous clinical trials" (26). Several health care organizations have implemented such caps on the number of patients who can receive an innovative intervention in the context of practice (Children and Women's Health Centre of British Columbia 2015; Jackson Health System 2011, 1; Partners Healthcare n.d., 2; Stanford University Medical Center 2011, 4), with specified caps ranging from three to ten total patients. If a clinician in one of these organizations wants to offer or administer an innovative intervention to additional patients after reaching the cap, then the intervention must be provided as part of an IRB-approved research protocol (unless the organization adopts the intervention as the local standard of care).

Although patient caps are likely effective tools for encouraging an early transition to clinical research, their significant practical and ethical problems make them unsuitable for a permissive oversight approach. First, there is no "universal cap" that will ultimately screen out only harmful or nonbeneficial interventions while allowing for the sometimes fitful development of beneficial interventions. The earliest appropriate time for subjecting an innovation to rigorous scientific evaluation will vary according to a number of factors, such as the health condition to be addressed, the technology involved in the intervention, the clinician's experience with the intervention, etc. (Agich 2001). This means that there is no single number of patients that will allow a clinician to identify a testable hypothesis about her innovation or to make a responsible judgment about how it might compare to the idealized expert-consensus standard. Engaging in innovative practice even while a research study on the intervention is in progress can be a crucial source of insight for future

research (Dobbs 2018). Raising the cap, say to one hundred patients, might avert some of these concerns about premature evaluation, but would significantly undermine the goal of encouraging an early transition to clinical research, and perhaps still not entirely resolve the problem of premature evaluation (e.g., in the case of a novel screening intervention).

Second, capping the number of patients who can receive an innovative intervention outside of research threatens patients' well-being and autonomy. As noted earlier, many patients rationally and autonomously value receiving innovative practice rather than the idealized expert-consensus standard. These patients could be denied innovative interventions under a research protocol because they do not meet the inclusion criteria (which for scientific reasons might be more stringent than the inclusion criteria for innovative practice) or because elements of the protocol introduce unacceptable risks to the patient (e.g., constrained dosing rules or invasive data collection interventions). Practical obstacles could also impede a patient's participation in a study, such as an inability to attend study appointments (e.g., the patient spends most of the year in the Alaskan wilderness) or the study's enrollment limit being met before the patient knew about the intervention. These concerns about access to innovative clinical interventions could be mitigated if the caps required only that clinicians transition to *some* form of clinical research (even those that lack rigorous inclusion/exclusion criteria, dosing or interventional constraints, invasive data collection interventions, etc.), but this would seriously undermine the utility of caps for preventing runaway diffusion.

Finally, capping innovative practice threatens the autonomy and professional integrity of clinicians. In those cases in which a patient is a good candidate for receiving the innovative intervention but not a good candidate for a research study on that intervention, a clinician will not be able to offer what she has good reason to believe is the best option for her patient. This restriction burdens the clinician's ability to carry out her moral and professional obligations, and it

is far from clear that the restriction's uncertain benefits for future patients or society justify those burdens. Further, there might be legitimate justifications for a clinician's unwillingness to engage in high-quality clinical research: a lack of funding or technical resources for research, institutional or professional skepticism about an innovation's prospects for success, expert judgment that the intervention is not sufficiently developed for meaningful evaluation in a controlled study, etc. (ACOG 2006, 1592). While clinicians have an ethical and professional responsibility to contribute to the advancement of medicine through research (ABIM Foundation 2002; McCullough 2006), this responsibility has to be appropriately balanced against the ethical and professional responsibility to promote the well-being and autonomy of one's patients. Patient caps on innovative practice do not appropriately balance these ethical concerns, and so should not be part of a permissive oversight approach.

DUAL-DEVIATION REVIEW

I have argued professional societies, health care organizations, and government entities tasked with managing and overseeing innovative practice should take a permissive approach instead of restricting all uses of innovative interventions to clinical research. In addition to policies aimed at protecting patients who receive innovative interventions, a permissive oversight approach should include policies aimed at mitigating the risk of runaway diffusion. Requiring clinicians to engage in learning activities in the course of innovative practice is ethically justified but insufficient to address that risk. Capping the number of patients in innovative practice might be more effective, but patient caps are ethically unjustified for a number of reasons. In this section, I outline a policy for overseeing innovative practice that, unlike the proscriptive approach or patient caps, encourages an early transition to clinical research, allows for the early development of beneficial interventions, and respects the autonomy of patients and clinicians.

Prospective Review and the Research Standard

As mentioned earlier, one of the widely endorsed recommendations for overseeing innovative practice is to require clinicians to submit their plans for prospective review and approval by expert peers and/or institutional officials. These recommendations conceive of prospective review as a means of protecting patients who receive innovative clinical interventions by requiring clinicians to provide evidence that they are protecting patients' rights and promoting their well-being. As part of this effort, prospective reviewers require clinicians to justify their plans to deviate from the idealized expert-consensus standard. Because the idealized expert-consensus standard is normative for the practice of medicine, it is reasonable to demand that clinicians provide convincing reasons for deviating from that norm. If clinicians' justifications for engaging in innovative practice are judged inadequate by reviewers, then oversight bodies (which might be a professional society, health care organization, or government entity) will withhold support and protection for clinicians if they proceed with their plans. Clinicians who engage in innovative practice without prior approval may be liable for retrospective evaluation and institutional penalties.

Prospective review by expert peers and institutional officials is crucial to ethically overseeing innovative practice, but current recommendations and extant policies demand only that clinicians justify engaging in innovative practice *rather than following the idealized expert-consensus standard*. I propose that prospective review policies should also require clinicians to justify engaging in innovative practice *rather than clinical research*. That is, reviewers should demand that clinicians provide convincing reasons for administering an innovative clinical intervention outside of a research study as a condition of receiving support or protection. There is an emerging consensus among professional societies (ABIM Foundation 2002; ISSCR 2016) and commentators (McCullough 2006; Faden et al. 2013) that there is a *research standard* for ethical

medical practice, that clinicians have a positive duty to improve medicine by engaging in and supporting learning activities, including clinical research when appropriate. Engaging in innovative practice therefore deviates from two norms of medical care, the idealized expert-consensus standard and the research standard, and both of these deviations should be justified in prospective review.

Enhancing prospective review of innovative practice by requiring clinicians to justify their plans to deviate from the research standard would significantly reduce the risk of runaway diffusion. It would incentivize clinical research in cases where clinicians are unable to provide compelling reasons to expert peers and institutional officials for engaging in innovative practice instead. Paired with institutional resources to promote high-quality research, this sort of policy would also facilitate the identification, evaluation, and rapid diffusion of beneficial interventions that are introduced in innovative practice. Call this kind of enhanced prospective review a *dual-deviation review policy* for innovative practice, since it requires clinicians to justify deviating from two different standards. Dual-deviation review can help permissive oversight approaches to innovative practice deal effectively and ethically with the risk of runaway diffusion.

Guidelines for Dual-Deviation Review

What should a dual-deviation review policy look like? While it is beyond the scope of this discussion to determine which institutions or officials should implement and enforce such a policy, we can identify some general guidelines for how dual-deviation review should operate. Since guidelines for evaluating clinicians' justifications for deviating from the idealized expert-consensus standard have been described at length elsewhere (e.g., Reitsma and Moreno 2006; Eaton and Kennedy 2009), in this section I will focus on how expert peers and institutional officials should evaluate justifications for deviating from the research standard.

Reviewers should be aware that different considerations will apply to innovative practice depending on whether it occurs before or after the initiation of clinical research on the innovation in question. Before the initiation of clinical research, reviewers need to evaluate the appropriateness of subjecting the proposed innovative intervention to scientific evaluation, especially to rigorous evaluations such as RCTs. Depending on the nature of the innovation, an initial review could be performed before the clinician engages in innovative practice followed by a subsequent review after a few patients have received the intervention, which would allow early results to inform the reviewers' judgments. Even if the innovation appears to be successful in the first few patients, the clinician might have weighty scientific or practical reasons for not engaging in clinical research that reviewers should consider: the intervention might be too underdeveloped or risky for a study to gain IRB approval, the clinician might need more experience for any research to be well-controlled, there might be insufficient technical or financial resources for conducting research, etc. Reviewers should incorporate these reasons into their assessment and issue recommendations to both clinicians and other institutional actors for overcoming these obstacles to rigorous clinical research.

After the initiation of high-quality scientific assessment of an innovation, whether conducted by the clinician seeking approval or by another party, reviewers need to ensure that innovative practice would not undermine ongoing research. As with engaging in innovative practice before any research has begun, clinicians might have excellent reasons for administering an innovative intervention outside of an extant research protocol: the patient might not meet inclusion criteria for a research study despite being a good candidate for the intervention, participating in the study might impose significant nonmedical burdens on the patient, the patient could benefit from a modification to the intervention not allowed by the ongoing study, etc. Reviewers should incorporate these reasons into their judgment of whether engaging in innovative practice in the

given case would pose excessive risks to ongoing research and whether there are ways to mitigate those risks.

Conscientious reviewers who apply these sorts of considerations would readily identify clinicians who delay transitioning from innovative practice to clinical research due to financial or professional conflicts of interest, research-related inconvenience, or personal bias in favor of their intervention. But one might worry that dual-deviation review policies would be ineffective and burdensome in more complicated cases because they leave it up to the reviewers' own judgment of whether clinicians have adequately justified deviating from the research standard. Strict patient caps for innovative practice are ethically flawed, but at least they provide a clear, consistent boundary for clinicians and reviewers. This objection is correct that reviewers' idiosyncratic judgments should not wholly determine whether a clinician gets approval to deviate from the research standard, but this merely demonstrates the need for guidelines on how to assess clinicians' justifications.

While it is beyond the scope of this discussion to fully specify such guidelines, some reasons that could justify engaging in innovative practice rather than clinical research include:

- The health condition addressed by the intervention occurs sufficiently infrequently that research is unnecessary or infeasible.
- The intervention is in a relatively "early" stage of development, such that the clinician is likely to make significant changes depending on patient outcomes.
- The clinician's IRB would not approve a research study on the intervention due to issues that could be resolved with additional innovative practice.[3]
- The clinician is unable to acquire the financial and technical resources needed to conduct a research study on the intervention.

[3] This reason suggests that if an institution's dual-deviation review is not carried out by an IRB, then reviewers would need support and assistance from the local IRB in evaluating plans for innovative practice.

- There are no other clinicians or institutions with whom the clinician could collaborate to conduct a research study on the intervention.
- Administering the intervention to the patient would not interfere with subject recruitment or other aspects of ongoing research.
- The patient is ineligible to enroll as a subject in ongoing research on the intervention.
- The patient would be unduly burdened by receiving the intervention within a research study rather than as innovative practice.

Another objection to a dual-deviation review policy that it offers too little protection against the risks posed by runaway diffusion. Exempting clinicians from the research standard whenever they are concerned for their own patients leaves the door wide open for innovative practice leading to runaway diffusion. Two responses to this objection are in order: First, recall that we lack firm empirical evidence about the magnitude of the risk that innovative practice will lead to runaway diffusion and how harmful that outcome would be. For all we currently know, premature evaluation of innovative practice might be more harmful than runaway diffusion. Second, provided that deviating from the idealized expert-consensus standard in a given case is consistent with concern for patient well-being and nonexploitation, respect for patients' and clinicians' autonomy gives us weighty moral reasons for permitting innovative practice. That these reasons can in some cases outweigh serious population-focused ethical concerns is fairly uncontroversial. One reason it is thought to be unethical to enroll competent adults in clinical research against their will is that doing so disrespects their autonomous choices about their medical care in order to promote the interests of others (Lowry 2014). Similar reasoning favors allowing patients to autonomously choose innovative practice in the face of empirically underdetermined worries about runaway diffusion.

CONCLUSION

I have argued that in response to population-focused ethical concerns about innovative practice, medical institutions should take a permissive approach to management and oversight that includes a dual-deviation review policy to hold clinicians accountable for subjecting their innovations to timely, rigorous scientific evaluation. The full set of considerations that could justify deviating from the research standard will need to be worked out in practice, but patients' well-being and autonomy and the integrity of medical practice will be important. Although this discussion began by articulating the conceptual differences between innovative practice and clinical research, it should be noted that they share a fundamental ethical commitment. Clinicians engage in innovative practice and research because the idealized expert-consensus standard is in many ways inadequate, and because more people will suffer disease and early death unless clinicians deviate from that standard. Since our current best is not enough, we are ethically required to innovate in medicine. Clinical research responds to this imperative by subjecting some people to the risk of harm in order to benefit other people. Innovative practice responds to this imperative by responsibly subjecting some people to risk of harm in order to benefit them, with the foreseeable possibility that others could subsequently be harmed or benefited. Innovative practice and clinical research require different kinds of oversight, but they each have a role to play in the ethical advancement of medicine.[4]

[4] The author thanks Dave Wendler, Christine Grady, two anonymous reviewers, and audiences at the University of Texas at Dallas and the National Institutes of Health for their invaluable assistance with this article. The views expressed here are the author's own and do not reflect the policies or positions of the National Institutes of Health, the U.S. Public Health Service, or the U.S. Department of Health and Human Services. This research was supported by the Intramural Research Program of the National Institutes of Health Clinical Center.

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