Legal and Regulatory Responses to Innovative Treatment

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I. INTRODUCTION

Patients suffering from illness that has no standard medical therapy,¹ or who have exhausted all current therapeutic options are often in a desperate situation. They press their doctors in search of something new in the hope that it can offer them some chance of recovery. Their doctors, in turn, are thus motivated to experiment or innovate in order to develop alternative treatments. This therapeutic motivation, however, comesling in modern healthcare with other professional and commercial considerations such as enhanced reputation and profit. In addition, there is the potential for innovative therapy to generate knowledge that will spur its development and eventual adoption by the profession. However, this desire to benefit future patients may be at odds with the interests of the particular patient offered innovative treatment.

Innovative medical therapy has thus been a matter of increasing concern internationally in health care, particularly where market forces are at play in the health care system. The concern stems both from the particular features of innovative therapy and its differential regulatory treatment – as part of the traditional therapeutic pathway in healthcare rather than the research ethics pathway.² If innovative therapy continues to fall within the therapeutic paradigm, as it traditionally has, decision-making would remain subject to the confines of the physician-patient relationship and certain post hoc review processes such as medical negligence. Substantial faith is therefore placed on professional judgment and the informed consent process. Patients in such situations may, however, not be in the best position to size up the medical complexities and uncertain risks, and are thus more vulnerable to false hopes and overly optimistic assessments of the worth of innovative therapy. In contrast, activity that is classified as research stands on a significantly different ethical, legal and regulatory footing, where the need for prior ethical review is the current international best practice.

Ongoing developments in medical technology, health care delivery and commercial interests in medicine have increased both the potential for conflicts of interest on the part of physicians, and doubts over the sufficiency of patient autonomy as a justification for administering innovative therapy. The legal and regulatory treatment of innovative therapy therefore becomes an important question, on which there is a current lack of consensus on a number of issues. This paper proceeds as follows. Part II discusses the recent pertinent developments in Singapore and uses them as a springboard to flesh out basic regulatory issues that arise from the deployment of innovative treatment. Part III examines the question of how we should distinguish innovative treatment from research, and the significance of appropriate classification. Part IV examines the adequacy of the current post

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¹ A working definition of “standard medical therapy” can be found in the U.S. National Commission, The Belmont Report: Ethical Principles and Guidelines for Protection of Human Subjects of Research (18 April 1979), Part A, para 2; online: <http://ohsr.od.nih.gov/guidelines/belmont.html#goa>: “interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable chance of success.”

hoc scrutiny of innovative therapy under existing legal principles, on the basis that it possesses a distinctive status notwithstanding its legitimate use within the realm of medical practice. Part V then considers if specialized regulatory measures are warranted given the deficiencies of a purely post hoc system, and how existing regulatory systems could be developed in order to best meet the challenges presented by innovative treatment.

II. RECENT ENCOUNTERS WITH INNOVATIVE TREATMENT IN SINGAPORE

A. What is Innovative Treatment?

As a preliminary, it is necessary to specify what we mean by innovative treatment or practice. Generally, this phrase refers to significant departures from standard medical therapy which have not been validated by reliable research methods, or where there is simply insufficient evidence to support the safety and efficacy of the innovative procedure, method or device. The adjective significant emphasizes a distinction from variations or adaptations of existing standard therapy to suit individual patient circumstances. Thus, in offering innovative treatment, the physician is working on a hunch or scientific theory that has not been adequately investigated or researched. Such medical procedures that are administered for the benefit of a specific patient but have uncertain outcomes. Conceptually, a more comprehensive definition has been offered as follows:

Innovative therapies generally represent uncontrolled, often single, interventions intended to manage or solve particular problems. They are not ordinarily designed to test hypotheses. Additionally, they are not undertaken in order to gain new knowledge beyond the needs of the patient. Although the use of innovative therapies may lead to new knowledge, this consequence is secondary to their primary purpose of benefiting patients.

B. Innovative Treatment as a Legitimate Aspect of Medical Practice

Between August 2009 and November 2010, the Disciplinary Committee of the Singapore Medical Council (SMC) convicted several physicians for offering various forms of novel treatment that were not adequately supported by sufficient clinical or scientific evidence. In addition these cases seemed to suggest that there was a sharp dichotomy between standard and innovative therapy. The latter should only be administered under the auspices of a clinical trial. The legitimate place of innovative therapy within in the context of medical practice was, however, recognized in Gobinathan Devathasan v. Singapore Medical Council. A neurologist’s appeal against a Disciplinary Committee (DC) of the SMC’s conviction of inappropriate administration of therapeutic ultrasound was allowed by a High

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7 [2010] 2 SLR 926 (Sing. HC)
Court of three judges. The novelty in Dr. Devathasan’s treatment of a patient’s complicated neurological condition was actually in the combination of therapeutic ultrasound with repetitive transcranial magnetic stimulation (rTMS). However, as the court noted, the two charges proffered against him for inappropriate treatment did not allude to this novel combination, but rather focused discretely on the two forms of treatment. In this respect, the SMC’s Ethical Code and Ethical Guidelines (Ethical Code) provides that:

4.1.4 Untested practices and clinical trials

A doctor shall treat patients according to generally accepted methods and use only licensed drugs for appropriate indications. A doctor shall not offer to patients management plans or remedies that are not generally accepted by the profession, except in the context of a formal and approved clinical trial.

The DC had acquitted him in respect of rTMS even though it was not generally accepted by his peers in Singapore. It reasoned that:

... Whilst the use of rTMS is not generally accepted in our local practice, Dr Devathasan’s work may represent novel treatment and may aid the progress and innovation in medicine... In our view, these above stated studies and other studies do support the basis of the application of rTMS as an extended indication or auxiliary treatment for a patient with PD [i.e., Parkinson’s Disease], especially one who has failed other treatment options.

However, the DC convicted him on the second charge related to therapeutic ultrasound as an inappropriate “extension from its normal use into clinical neurology practice” that was not supported by any “experimental evidence or physical proof of the safety of [therapeutic ultrasound] on the human brain.” Neither had the appellant specialist “verified his assumptions or conclusions through expert consultation, in-vitro or in-vivo experimentation or test of any form.” Devathasan’s case was that therapeutic ultrasound was administered, not for an established use to treat acute stroke, but rather to augment the effects of rTMS through increased cerebral blood flow. He justified its use by extrapolation from such combined use in relation to patients with gait apraxia, which was described in a paper he co-authored on the subject.

The High Court overturned this conviction on a number of grounds, the majority of which related to procedural and evidential deficiencies in the DC’s conduct of the proceedings and grounds of decision. The substantive ground relevant to the present discussion related to the professional ethical requirements for appropriate extension of existing treatments such as

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8 Repetitive transcranial magnetic stimulation is a form of brain stimulation that uses a magnet instead of an electrical current to activate the brain. Unlike electroconvulsive therapy, in which electrical stimulation is more generalized, rTMS can be targeted to a specific site in the brain: U.S. National Institutes of Mental Health, Brain Stimulation Therapies, online: <http://nimh.nih.gov/health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml>.
9 Ibid. at para. 32
11 Supra note 7 at para. 21 [emphasis added]
12 Ibid. at para. 24
ultrasound into novel uses. After reviewing the expert evidence, the court surmised that the test for ‘general acceptance’ (i.e. standard therapy) required the following critical factors to be satisfied:

(a) there had to be at least “one good study”;
(b) the results of the study can be replicated and reproduced under the same sort of like treatment parameters and conditions;
(c) the study had been written up in publications and presented at meetings;
(d) the study had received peer review;
(e) the study had to have “clear-cut results” and the sample had to be “statistically significant”; and
(f) the study had to have some form of controls, such as randomised double-blind trials.

However, it was only in respect of “off-label” treatment for unapproved indications that specific questions of patient safety and adequate scientific rationale became pertinent. As Dr. Devathasan was charged with administering treatment that was not generally accepted in accordance with para. 4.1.4 of the Ethical Code, the court reasoned that the DC had thus applied the incorrect test. Questions of safety and the presence of scientific rationales for extrapolation to present use had a closer “nexus” to when “off-label” use of a particular treatment is allowed, rather than whether they were indicated and generally accepted.

C. Legal and Regulatory Issues

Counsel for the SMC in Devathasan had argued that the neurologist ought to have administered the novel combination in the context of a formal clinical trial. This unfortunately collapsed two distinct issues – whether innovative treatments have any place in clinical practice, and whether what Dr. Devathasan was doing nevertheless amounted to clinical research. The court only answered the former question, accepting the legitimacy of the activity as off-label (or innovative) treatment for a patient who did not respond to standard therapy. In fact, the broader context in Devathasan suggested the presence of some form of informal study. Dr. Devathasan had in fact treated 200 other patients in a similar way prior to the complainant, a number that had risen to 700 by the time of the DC

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13 Ibid. at paras. 42-60
14 Ibid. at para. 46
15 The court accepted expert evidence that “off-label” use (i.e. innovative treatment) refers to the use of a therapeutic modality “which is not mentioned in the literature, or … is not approved by any of the [regulatory] agencies...”: Ibid. at para. 49
16 Ibid. at para. 60
17 With respect, the soundness of this reasoning may be questioned. There was no doubt that both rTMS and therapeutic ultrasound were not generally accepted treatments for the patient’s condition. However, as the DC accepted that innovative treatment was a recognised exception to the general standard of care required under para. 4.1.4 of the Ethical Code, the ethical requirements for off-label or innovative treatment became relevant for the purposes of determining an ethical breach of para. 4.1.4 read in its entirety (see infra note 24 and accompanying text). In addition, it is difficult to see why patient safety is only relevant in determining the ethical propriety of innovative treatments, but not its passage into the realm of standard therapy. The quality of the clinical studies supporting adoption as standard therapy must surely encompass the basic clinical requirement of acceptable patient safety.
18 Devathasan, supra note 7 at para. 40
hearing. He had accumulated sufficient clinical data to assert to the Singapore Ministry of Health and the Agency for Science Technology and Research that his novel combination would benefit patients generally. Acknowledging that a double-blinded clinical trial might be desired, he thought that this was not necessary. The first issue therefore relates to how we determine the boundary between innovative treatment and research. The implications of classification are serious – it determines which of the existing two regulatory pathways apply. If an activity constitutes research, this confers on it significantly different regulatory paradigm where the physician no longer has primary influence over whether the ‘treatment’ is offered to a patient. In fact, her status as physician is said to morph into an investigator or researcher. Prospective control intervenes in the form of peer review by institutional review boards (IRBs) or research ethics committees (RECs). Heightened informed consent requirements, often statutorily supplemented, also apply.

However, if a practice is safely within the boundary of medical therapy, then the decision to administer it is primarily one for the usual, internal dynamics of the physician-patient relationship. Freedman et al observe:

> Ordinary therapeutic practice is managed within the health provider-patient relationship however dangerous the intervention or ambiguous the indication. The doctrines of patient consent to care and of professional autonomy are intended to ensure that the intervention in question is the product of joint deliberation and agreement between patient and doctor – moreover of sole agreement between them. No outsiders need be consulted. ... Any third party involvement will come retrospectively. ...  

External scrutiny of its merits is then largely post hoc via a medical negligence action or disciplinary proceedings (as was the case in Devathasan). At best, there might also be external peer review in the form of quality assurance reviews within institutional health care systems that are put in place to systematically review the outcomes of therapeutic interventions. Generally, none of these quality assurance or safety systems kick-in prospectively to protect the interests of patients in determining if the risks of innovative therapy are worth the potential benefits, particularly where there is insufficient evidence of either. It therefore becomes important for physicians to know when they will cross the regulatory line between therapy and research.

Second, assuming an activity is not research but innovative therapy, what legal or ethical requirements should apply? Devathasan provides a good indication of what the professional ethical expectations are, but the court also observes that the current professional ethical framework is lacking. Should innovative therapy be subsequently challenged in court, how would the medical negligence analytical framework apply to treatment that, by definition, is not supported by a responsible body of medical opinion because it is innovative in nature? These questions were not addressed in Devathasan.

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19 Ibid. at para. 64
20 Ibid. at para 73
23 Supra note 7 at para. 53
Finally, in the wake of such analysis, a larger regulatory question looms: is the current *post hoc* review of innovative therapy via tort law and the medical disciplinary system adequate in the interests of patient safety and the public health? The efficacy and safety of any proposed innovative therapy is not only the concern of the particular patient asked to receive it, but also that of the larger public health interest in ensuring that innovative therapies are adequately investigated and evaluated before they move into mainstream medicine.

### III. THE ELUSIVE BOUNDARY BETWEEN INNOVATIVE TREATMENT AND RESEARCH

#### A. ‘Intention’ as a Classificatory Device

The SMC’s *Ethical Code* unfortunately does not provide sufficient clarity on the boundary between therapy and research. Para 4.1.4, clause 1 appears to draw a blunt dichotomy between generally accepted methods and “untested practices”, stipulating that the latter should only be offered in the context of a formal and approved clinical trial. However, clause 3 of the same paragraph elaborates further:

> It is not acceptable to experiment or authorise experiments or research which are not part of a formal clinical trial and which are not primarily part of treatment or in the best interest of the patient, or which could cause undue suffering or threat to the life of a patient.24

The conjunctive and alternate clauses confuse the meaning of the paragraph, but a contextual reading suggests two distinct situations when “experiments” or “research” are ethical: (a) if they are part of a formal clinical trial conducted in accordance with prevailing legal and ethical standards; (b) if they are *primarily* part of treatment administered in the best interests of the patient. If this interpretation is accepted, this clause amounts to a qualification of the first in that it expands the reach of medical practice to encompass instances of experimentation if these serve the patient’s best interests. It would also be consistent with the recommendations of the *Declaration of Helsinki*.25 Nonetheless, the *Ethical Code* does not offer a definition of “experiment” or “research” in order to determine when a particular medical activity crosses the threshold.

Experimentation seeks to resolve unknowns in relation to a particular patient. It may also involve testing hypotheses and generate new information about *that* patient. But it does not, by itself, elevate an activity to ‘research’ unless the information is sought for its general, as opposed to particularized, value.26 The US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in its *Belmont Report* (1979) was candid about this conceptual confusion:

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24 *Supra* note 10. This particular clause in paragraph 4.1.4 was quoted but not analysed by the court in Devathasan, *supra* note 7.


The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called “experimental” when the terms “experimental” and “research” are not carefully defined.  

More elaborate guidance is found in the Singapore National Medical Ethics Committee’s Ethical Guidelines on Research Involving Human Subjects (1997). Paragraph 2.2.1 defines ‘research’ as follows:

> ... **Research.** Human research can be broadly defined as studies which generate data about human subjects which go beyond what is needed for the individual’s well-being. The primary purpose of research activity is the generation of new information or the testing of a hypothesis. The individual patient may or may not benefit directly. The fact that some benefit may result from the activity does not alter its status as “research”. ...  

In contrast, medical “therapy” without a research function is defined by the NMEC in a similar fashion to that adopted the *Belmont Report*:

> ...When an activity is undertaken with **the sole intention of benefiting the patient**, the activity may be considered to be part of “therapy”. The progressive modification of methods of diagnosis and treatment in the light of experience is a normal feature of medical practice and should not be considered as research. There could be conflicts between research (intended to generate new information) and therapy (intended to benefit the individual patient directly). Their resolution rests on the integrity of the physician/investigator. The patient is always entitled to the best clinical management, and research considerations must never override this.  

These definitions of research and therapy were endorsed in the subsequent Bioethics Advisory Committee Report, *Research Involving Human Subjects: Guidelines for IRBs*. Therefore, the BAC’s recommendations in respect of human biomedical research do not apply to “therapeutic activities undertaken with the sole intention of benefitting the patient”.

Several observations are warranted here. The main distinction between research and therapy seems to be the **purpose** or **intent** with which an activity is undertaken. Activity is properly

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27 Supra note 1 at Part A, para 1  
29 The Belmont Report’s definition of medical “practice” is found in Part A, para. 2: “For the most part, the term “practice” refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.”  
30 Supra note 28 [emphasis added].  
31 Singapore: BAC, 2004 at paras. 3.21-3.23  
categorized as treatment only where its sole purpose is to serve the interests of the patient for whom it is administered. In contrast, the term ‘research’ seeks to demarcate activity that, additionally, serves to generate ‘new’ information that is not necessary for the treatment of a patient. This seems a rather narrow definition of research from the perspective of outcomes, for it would suggest that if scientific methods such as randomization and controls were used in an activity, it would not amount to research unless additional data was collected in excess of what was needed for the clinical treatment of the patient. Thus, it is suggested that it is more likely that the purpose of deriving or developing generalisable knowledge captures the intended object of research – information that will serve not only the patient’s interests, but that of future patients.

This is consistent with the earliest recommendations floated before the US National Commission in 1978 that centred around the use of ‘intent’ as a device to draw boundaries between research and medical practice (and innovative treatment in particular). The device of intent is also used in the Royal College of Surgeons’ Guidelines on the practice of ethics committees in medical research with human participants. However, the NMEC’s ultimate recourse to the ‘integrity of the physician/investigator’ to resolve any difficulty in determining which is the operative intent suggests that this is a subjective phenomenon. Without further specification of criteria from which intent is to be inferred, its utility as a regulatory sorting device is the subject of much reservation. Without clearer objective criteria, a subjective state of mind raises validation difficulties and thus the potential for inconsistent results. Furthermore, regulatory reliance on the ‘integrity’ of the physician/researcher to identify relevant research intent is unrealistically optimistic, especially where the consequences of increased regulatory scrutiny may conflict with the individual’s professional and personal interests.

Secondly, exclusive therapeutic intent may be an unduly stringent standard. Administering innovative therapy has the inherent capacity to generate, at the least, anecdotal evidence which could ground future pilot studies or clinical trials. It is thus always possible to infer some secondary research intent in deploying innovative therapy, even if the primary purpose is therapeutic. Similarly, by referring to ‘primary purpose of research’, the NMEC definition acknowledges that much professional activity in health care can possess more than one purpose, whether to benefit the patient, test a hypothesis and/or generate new information in the progressive development and improvement of therapy. The true difficulty then posed by these definitions above is that there are no criteria specified to determine when there is a primary research purpose, or in what proportions these must be to transform activity into research.

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33 See R. Levine, “The Boundaries between Biomedical or Behavioral Research and the Accepted or Routine Practice of Medicine” (14 July 1975), in the Belmont Report, supra note 1, Appendix A, Section 1 at 5
34 4th ed. (London: RCP, 2007) at paras. 3.4-3.5
36 See also Levine, supra note 33 at 11-12
Thirdly, even if by ‘new’ the NMEC meant ‘generalisable’ knowledge, what does this mean? Scientific knowledge requires a certain methodological rigour for general acceptance, with the randomized controlled trial (RCT) representing the gold standard. Knowledge that physicians are prepared to act on in adopting novel treatments does not always meet this standard. In the realm of innovative treatment, where new modalities or combinations of diagnosis or treatment are administered without sufficient validating evidence to support their use, the medical information thereby generated often confers clinical value both in particular and general fashion. This, it is argued, is the true source of the difficulty in distinguishing between innovative treatment and research, not simply a reliance on research intent.

Finally, there is one criterion from which research intent can be readily inferred: the presence of procedures that impose burdens or risks on the individual patient without any compensating medical benefit. For example, RCTs typically include additional interventions to measure study outcomes – such as blood draws, biopsies, lumbar punctures and imaging procedures – which are not required for the purpose of providing any diagnostic or therapeutic value to the individual. These are procedures where it may be properly inferred that the sole purpose is research. Some difficulty of application arises, however, in identifying the presence of non-beneficial procedures (in the absence of a formal written protocol). This depends on the level of uncertainty about what the standard practice is, against which the presence of additional non-beneficial procedures can be identified. However, this criterion alone will not suffice in classifying a broad range of activity where procedures used may correspond with what is clinically indicated, for reasons which will be apparent shortly.

B. Alternatives to ‘Intention’

Accepting the shortcomings of a subjective approach to research classification based on an ambiguous concept of new or generalisable knowledge, alternative approaches have been proposed that seek to identify more objective features of any clinical activity that would constitute research.

1. The deviation approach

In a pilot paper for the US National Commission, Levine proposed to include innovative therapy within the definition of research, being activity which differs in any way from customary medical practice. He argued that, in general, innovative therapy should be

41 Supra note 33 at 6-7, 32.
conducted and reviewed as if it were research. However, given the inherent uncertainties even in standard therapy, there is always some element of ‘experimentation’ even in customary practice. Levine was probably alluding to the experiential modifications to existing therapies noted by the NMEC above, and he thus sought to confine research categorization to ‘substantive’ innovative therapy in order to keep research review manageable. His primary reason for doing so was to minimize the informal incorporation of ‘bad’ innovations into standard therapy which have not been tested adequately, by subjecting such activity to IRB or more specialist regulatory review in order to ensure they are systematic and properly designed trials.

This more expansive approach to research classification thus focuses on significant deviations from standard therapy, and not the quality of the information generated. However, it was ultimately not accepted in *Belmont Report*, which decided that:

> When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is “experimental,” in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

A couple of arguments against such an expansive approach would explain this position. First, including innovative therapy within the sphere of research would probably introduce an undue burden on the practice of medicine, and hinder patient’s access to timely medical treatment, albeit of an experimental nature. This would arise from the inherent bureaucracy and delay of the IRB review process. Second, there was likely to be a concomitant burden on medical innovation if this could only proceed on the basis of formal research. The latter would be dependent on factors not within the immediate control of the practitioner, such as funding and institutional support, in addition to important ethical constraints on clinical trials.

2. **Systematic design generating scientific knowledge**

A stricter approach to demarcating research from medical practice focuses on the presence of systematic design. The U.S. Common Rule adopts this definition of research:

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42 *Ibid.* at 35 [emphasis added]
43 *Ibid.* at 37; 41
44 *Supra* note 1, Part A, para 3 [emphasis added].
Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.\textsuperscript{48}

The emphasis on design suggests the use of methodology that would generate information or knowledge that meets stipulated standards. The Common Rule however does not elaborate on what it means by generalizable knowledge, or what specific scientific or professional standards were envisaged.\textsuperscript{49} In respect of design, Miller argues that the distinctive purpose of clinical research is revealed by its “characteristic methods that are foreign to medical care”.\textsuperscript{50} These include:

(a) random assignment of treatments
(b) the use of placebo controls
(c) techniques to mask treatments so that investigators and patients do not know what treatment they are receiving [blinding]
(d) restrictions on the flexibility in adjusting doses of study drugs and use of concomitant treatments

These methods are drawn from the characteristic features of the RCT. It is the RCT that is the core fount of conflicting moral demands made of a physician/investigator conducting it – routinely asking them to sacrifice the interests of their particular patients for the sake of the trial and the quality of information it will generate.\textsuperscript{51} Thus, implicit in the reliance on relevant RCT methodological features is the narrower reading of generalizable as representing knowledge that bears the acceptable hallmarks of scientific methodological rigour.\textsuperscript{52}

An emphasis on systematic design also suggests an affinity for more formalized activity that involves written documentation that can be scrutinized as a research ‘plan’ or ‘protocol’.\textsuperscript{53} It was envisaged by the Belmont Report that the common practice when an investigator formed a research intent was to formulate a written research protocol outlining this intent, which could then be used for seeking IRB approval.\textsuperscript{54} Indeed, for the most part, the clear cases of research relate to activity that is formally organized and reduced into a written protocol designed to test a hypothesis.

\textsuperscript{48} 45 C.F.R. ¶46.102(d)
\textsuperscript{49} See National Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants (Bethesda, August 2001), c.2 at 35
\textsuperscript{50} Miller, supra note 40; S. Strasberg & P. Ludbrook, “Who Oversees Innovative Practice? Is There a Structure that Meets the Monitoring Needs of New Techniques?” (2003) 196(6) Journal of the American College of Surgeons 938 at 942. There is some support for this approach in Ancheff v. Hartford Hospital 799 A.2d 1067 at 1071-72 (Conn. 2002), but it was framed as a factual question to be answered with the assistance of expert evidence.
\textsuperscript{52} See Miller, supra note 40. Similarly, Lewens considers research to refer to activity designed to answer questions that the “medical research community would generally regard as scientifically important”: supra note 26 at 426.
\textsuperscript{53} J.K. Mason & G.T. Laurie, Law and Medical Ethics 8th ed. (Oxford: OUP, 2010) at 612, seem to prefer this definitional approach: “Research implies a pre-determined protocol with a clearly defined end-point. Experimentation, by contrast, involves a more speculative, ad hoc, approach to an individual subject.”
\textsuperscript{54} Supra note 1, Part A, para. 2.
However, confining research to formalized activity overlooks other less formal activities could also harbour a research purpose—whether wittingly or unwittingly—and which are practically influential in moving innovative treatments into the mainstream (whatever the scientific methodological flaws). A clear example of such activity is what Margo terms ‘investigational studies’ (particularly in respect of surgery) with the following characteristic features:

(a) they consist of a series of patients  
(b) outcomes measures are common clinical parameters, the type usually obtained during routine clinical follow up  
(c) effectiveness is determined by comparison with historical controls  
(d) formal written protocols do not exist; and  
(e) because the activities are viewed as clinical care, they are invisible to institutional review boards.

Such informal studies, at least in a surgical context, serve a transitional role between the development of new surgical models in the laboratory and the conduct of formal clinical trials by developing preliminary data and allowing refinements and modifications through testing in humans. The underlying imperative in such informal studies is nonetheless the testing of a hypothesis that is hoped will benefit future patients by improving on conventional surgical practice. However, if we adopt a definition based on scientific methodological rigour, ‘investigational studies’ would not amount to research.

3. Reiteration of treatment and dissemination of clinical data

In response to the challenges posed by ‘investigational studies’ of innovative treatment, Gladstein argues that the boundary between treatment and research is crossed when a physician offers a reiteration of innovative treatment, collects patient data on clinical outcomes and subsequently presents or publishes this data publicly. However, it is not clear what the rationale for these proposed criteria is. The collection and public dissemination of clinical information by a physician (suitably anonymised) is equally consistent with good clinical practice, and it would seem to create a perverse incentive against the sharing of useful data with the medical community if public dissemination per se could transform innovative treatment into research. Similarly, the notion of reiteration of treatment is inherently ambiguous since innovative treatment could justifiably be offered to more than one patient if they happen to be in a similar situation where, for example, standard medical practice does not avail any beneficial treatments. If reiteration involves restrictions on the flexibility of treatment parameters in order to standardize the innovative treatment across the series, then this would seem to coincide with the fourth scientific method outlined by Miller above.

55 See McKinlay, supra note 38  
56 C. Margo, “When is surgery research? Towards an operational definition of human research” (2001) 27(1) Journal of Medical Ethics 40 [emphasis added]  
59 Gladstein, ibid., argues that these criteria were supported by the Belmont Report, but a perusal of the relevant Part A of the Report does not support such a reading, unless he assumes that these are commonly taken as the essential elements of a formal research project.
Consequently, Margo offers an operational variation on this approach by focusing on the reiteration of innovative treatment after a scientific hypothesis has been made public by the physician:

After a case series has been formally presented or submitted for publication, there can be no turning back. Any addition of new patients to enlarge an existing clinical database is a clear departure from just clinical practice to clinical research. After a scientific hypothesis is a matter of record, the physician who enters more patients into the same series needs to regard the work as research as well as himself or herself as a researcher.\(^{60}\)

The discernable rationale underlying this operational approach is that whatever the ambiguities of a prior case series of innovative treatment, the collection of further clinical data on the innovation (after a hypothesis about its safety and efficacy has been formulated) would generate relevant clinical data in support of it and thus operates for the benefit of future patients as well. This arguably amounts to an implicit, broader interpretation of generalisable knowledge that encompasses any data that could have clinical, and not just scientific, influence on the merits of the innovative treatment in question.

C. A proposed way forward

The choice of more objective criteria to demarcate the zone of clinical research activity essentially involves a policy choice that balances competing concerns. There is the common thread of protecting vulnerable patients from unknown risks and sub-optimal treatment, which has to be balanced against the need for preserving a healthy amount of flexibility in clinical practice to encourage innovation, and the practical competencies and resources of the research ethics oversight system. Working from dictionary definitions is unlikely to be helpful, as different quarters define the term ‘research’ according to their needs and priorities,\(^{61}\) and proffered definitions may not have taken into consideration the underlying rationales for the burdens imposed by research oversight that would follow.\(^{62}\)

In this respect, the objective of regulatory guidelines demarcating research should be grounded in the history of research ethics and regulation – the experiential lessons learnt from historical research abuses that occurred not only under the ideological conditions of war, but also in everyday medical practice by well-meaning physician/researchers.\(^{63}\) At the core was a realization that abuses were possible because of the blurring of duties created by the inherent conflict of interests held by a physician who was also conducting research.\(^{64}\) Regulatory definition of research should be guided by an objective of identifying activity where there is a deviation between serving the best interests of the patient and the interests in developing generalisable knowledge. Lewens puts it well:

\[^{60}\text{Supra note 56 at 42 [emphasis added].}\]
\[^{61}\text{See e.g., E. Ahrens, The Crisis in Clinical Research (New York: OUP, 1992), c.3}\]
\[^{62}\text{See N. Fost, “Ethical Dilemmas in Medical Innovation and Research: Distinguishing Experimentation From Practice” (1998) 22(3) Seminars in Perinatology 223 at 224-225}\]
\[^{63}\text{See Eaton & Kennedy, supra note 45, c.2, for a brief review of the modern history of human research ethics.}\]
\[^{64}\text{J. Katz, “The Regulation of Human Research – Reflections and Proposals” (1973) Clinical Research 785 at 787}\]
If we define treatment not merely as a series of events designed to promote the health of the patient, but as a series of events optimized solely for the promotion of health of the patient, then anything that is not optimized solely for the promotion of the health of the patient does not count as treatment. Some research does aim partially at the promotion of health of those who participate in the study. In refusing to label it treatment, we ensure that patients will be made aware of the ways in which health promotion may have been partially sacrificed for other ends, and we encourage a careful scrutiny of whether the promotion of health has not been unduly sacrificed in experimental design.65

The focus on methodology, it is submitted, provides the clearest way forward in identifying objective features of any activity that would bear the relevant hallmarks of research, and would benefit from the distinct ethical analysis that the research ethics pathway has been developed to provide answers for.66 Reliance on more diffuse criteria such as greater uncertainty of risks and benefits, or professional conflict of interest,67 would likely extend oversight across large swathes of medical practice that current processes are not optimally designed for.68 However, confining ourselves to the strict methodological features of the RCT would be unduly restrictive if there are other types of methodology that are practically influential, even if not scientifically rigorous.69 Any single recognized method or combination of methods that has the potential to compromise the individualized, optimal clinical management of the patient should count as research. Thus the use of any control, not just a placebo, could affect the optimal choice of treatment modality for a particular patient, and thus constitute a research purpose.70 A more purposive test for research should thus encompass any methodology with a real potential to place the best interests of the patient in tension with the physician-researcher’s need to satisfy the rubric of the relevant methodology (and hence the expectations of the relevant professional or scientific audience).

Therefore, turning to the ‘investigational study’ example, the use of historical controls (comparisons with a prior cohort of patients who received standard therapy) would raise a regulatory concern if that standard therapy was indicated for patients in the informal study, but they were offered the innovative treatment instead. This does not amount to randomization, but it still puts the physician in a clear situation of conflict between his desire to help the patient, and his desire to acquire sufficient data to formulate and test a hypothesis.71 Where, however, the criteria for offering innovative treatment stipulate the absence of standard therapy for such patients, there is less of a concern that their care is not optimized since they have no other existing options. Further, there is no relevant conflict.

65 Lewens, supra note 26 at 427 [emphasis added]. See also Belmont Report, supra note 1 at Part A, para. 4.
66 Innovative treatment raises distinct ethical issues within the realm of medical practice that would arguably require a different form of regulatory oversight: see the discussion below under Part V.B.
67 See e.g. Noah, supra note 39 at 370-371.
68 See Part V.B.1 below.
69 Cf. E. H. Morriem, “Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve” (2003) 4 Houston Journal of Health Law and Policy 1 at 15-16: “If facts are not gathered in a consistent fashion according to specified rules, then they cannot add up to scientifically credible generalizations--and the project is unworthy of the name ‘clinical research.’”
70 Freedman et al., supra note 21 at 658.
71 This was first suggested in basic terms by B. Dickens, “What is a Medical Experiment” (1975) 113 Canadian Medical Association Journal 635 at 637.
between the needs of the patient and the expectations of the audience the physician might later address.

Thus, on the particular facts in *Devathasan*, at least in relation to the subject of the complaint, the patient was offered the innovative combination of rTMS and therapeutic ultrasound only because she had failed to respond to standard therapy and had requested alternative forms of therapy. If the series of cases in an informal study were enrolled on the same basis, then it is submitted that the exercise should remain within the realm of medical practice rather than research – notwithstanding the subsequent retrospective analysis of clinical data to support its continued use in future patients (which might itself constitute research under the absence of therapeutic benefit test).

IV. THE LEGAL CONSTRUCTION OF INNOVATIVE THERAPY: *POST HOC* REVIEW

Based on the foregoing analysis, there remains a distinct category of innovative treatment that rightly remains outside the research paradigm. In the absence of a definitive regulatory regime for such innovative treatment, legal or professional reviews of complaints concerning the administration of such therapy are generally *ex post* where compensation is sought for injury or loss suffered as a result, or a complaint is made in respect of professional misconduct. Medical negligence law offers the most obvious cause of action with which to hold a medical professional to account, and innovative therapy is therefore likely to raise issues relating to a breach of the requisite standard of care and informed consent. The focus here is on these, although similar issues are likely to be raised in a disciplinary review.

A. The Applicable Standard of Care

By definition, innovative treatment departs in some significant way from standard therapy. Historically, such deviation was treated as proof of negligence itself, or at least put the defendant medical practitioner under strict liability for untoward consequences by reason of attempting it. That conservative approach has since changed with the legal recognition that deviations are part and parcel of innovation in medicine, a crucial aspect of medical development and progress. Thus, as early as 1935, US courts recognized that some departures from standard therapy should not automatically be faulted by the law:

> We recognize the fact that, if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on; but such experiments must be done with the knowledge and consent of the patient or those responsible for him, and must not vary too radically from the accepted method of procedure.

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72 *Devathasan*, supra note 7 at paras. 14 and 72
73 See Ryan & Swanson, *infra* note 134 at 748
74 The exception being prospective legal review by a court where innovative therapy is offered to a patient who lacks decision making capacity and the court is asked to authorize it or confirm that the therapy is in the patient’s best interests: see e.g. *Simms v. Simms* [2003] Fam 83.
75 *Slater v. Baker & Stapleton* (1797) 95 ER 860
76 *Fortner v. Koch* 261 N.W. 762 (1935) at 765 (S.C. Michigan) [emphasis added]
Critics of US case law however point out that it has yet to develop any distinctive set of principles to evaluate innovative treatments, given that traditional malpractice standards have been formulated principally with customary practices in mind. While similar sentiments in support of medical innovation were made across the Atlantic in Hunter v. Hanley, the court took an arguably more innovation-friendly stance:

... To establish liability by a doctor where deviation from normal practice is alleged, three facts require to be established. First of all it must be proved that there is a usual and normal practice; secondly it must be proved that the defender has not adopted that practice; and thirdly (and this is of crucial importance) it must be established that the course the doctor adopted is one which no professional man of ordinary skill would have taken if he had been acting with ordinary care. There is clearly a heavy onus on a pursuer to establish these three facts, and without all three his case will fail. If this is the test, then it matters nothing how far or how little he deviates from the ordinary practice. For the extent of deviation is not the test. The deviation must be of a kind which satisfies the third of the requirements just stated.

Mason & Laurie interpret this to represent a general reasonableness test to be applied in the particular circumstances of the case, albeit that the court must be assisted by expert evidence ‘as it thinks fit’. However, this seems to ignore the emphasis on the onerous burden that the pursuer bears in establishing all three elements, and in particular, demonstrating that no medical professional would have adopted the innovative course.

In Singapore, the courts have also encountered innovative treatments through the lens of medical negligence, but have not fully appreciated the status of innovative treatment and its dissonance with professional custom. The Court of Appeal decision in James Khoo v. Gunapathy Muniandy involved the evaluation of the “unproven, experimental or controversial” application of stereotactic radiosurgery to treat the plaintiff’s neurocytoma. Nonetheless, the court reaffirmed and applied the traditional Bolam standard of care to evaluate, inter alia, the appropriateness of the radiation treatment parameters. It went further by offering a more restrictive gloss to the Bolitho clarification of Bolam, emphasizing that the court should restrict itself to analyzing “the process and not the result

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77 M. Greenberg, “Medical Malpractice and New Devices: Defining an Elusive Standard of Care” (2009) 19 Health Matrix 423 at 433
78 1955 SC 200 at 206
79 Ibid. [emphasis added]; Cf. D. Giesen “Civil Liability Of Physicians for New Methods of Treatment and Experimentation: A Comparative Examination” (1995) 3 Med. Law Rev. 22 at 32: “The degree of knowledge and skill a doctor owes his patients increases, the further he departs from well established practice by applying new methods of treatment...” This seems to suggest a stricter standard of care based on the extent of deviation, which seems contrary to the more recent jurisprudence on standards of care in respect of innovative therapy.
80 Mason & Laurie, supra note 53 at 627.
82 [2002] 2 SLR 414 (Sing. CA)
83 Ibid. at para. 99
84 Bolitho v. City and Hackney Health Authority [1998] AC 232 at 242 (HL): “In determining what represents a responsible body of medical opinion, the court is not bound to follow expert evidence led by the defendant physician. It must be satisfied that that respectable body of medical evidence has a ‘logical basis’, which requires the court to ensure that the experts had ‘directed their minds to the question of comparative risks and benefits and reached a defensible conclusion on the matter.”
of the [medical] expert’s reasoning...”85 In particular, the court restricted its interpretation of ‘a defensible conclusion’ in Bolitho to two factors: internal consistency of reasoning and external consistency with ‘proven extrinsic facts’.86 The ‘defensible conclusion’ referred to in Bolitho should not be understood as a reasonable one. This clearly prevents a court from preferring one expert opinion over another in determining what ought to be reasonable professional conduct even in respect of innovative treatment.

From a policy perspective, the constraints of the Bolam/Bolitho test are perhaps rightly self imposed in respect of standards that have move into the mainstream of medical practice, supported by adequate empirical research, peer review or collective medical experience. In this context, the persistence of competing or ‘minority’ practice standards should be treated with greater judicial caution. In contrast, innovative therapy by definition would not have been subject to the same level of professional medical or scientific assessment under the various developmental pathways in medical science. The courts should therefore not unduly constrain themselves in evaluating the reasonableness of the physician in offering and administering such treatment by confining themselves solely to process-oriented evaluations of expert testimony in respect of innovations.87 Recognising the challenges created for medicine by a patient who does not respond, or is not amenable, to standard therapy, they may make generous allowance for the challenges and uncertainties involved in serving the patient’s best interests when standard medical therapy falls short.88 This should not, however, prevent them from criticizing as unreasonable innovative treatment that presents inordinate risks and questionable benefit when compared with the circumstances and interests of the particular patient. Such an approach, it is argued, should go beyond interference confined to logical flaws within the internal reasoning of the innovating physician.

This particular restrictive approach to expert testimony and judicial oversight of medical standards of care does not seem to have been taken in both the UK and US in respect of innovative therapy.89 Nonetheless, although a general reasonableness standard reinforces a professional ethical requirement that innovative treatment must offer a “reasonable medical alternative”,90 it still leaves much uncertainty as to how it will be evaluated. The decision in Devathasan arguably draws out three broad criteria that courts reviewing innovative treatments for negligence would find useful structuring a review of innovative treatments: (a) the presence of some scientific rationale for the innovative therapy, (b) pre-clinical evidential support for the safety and efficacy of the treatment and (c) the lack or

85 Supra note 82 at para. 64
86 Ibid. at para. 65
87 A good illustration of the court’s willingness to reject defence expert testimony in the situation of innovative therapy is Hepworth v. Kerr [1995] 6 Med LR 139
88 See e.g. Baldor v. Rogers 81 So.2d 658 at 660 (S.C. Florida, 1954)
89 See e.g. Heppworth v. Kerr, supra note 87 at 164-165 (QBD Sheffield); Hood v. Philips 554 S.W. 2d. 160 at 165 (1977) (S.C. Texas). See also J. Robertson, “Legal Implications of the Boundaries between Biomedical Research involving Human Subjects and the Accepted or Routine Practice of Medicine,” (31 December 1975), in the Belmont Report, supra note 1, Appendix B at 4-6; Mastroianni, supra note 2 at 384.
ineffectiveness of any available standard therapy. At the same time, one can discern a
countervailing judicial trend towards leniency in reviewing unsuccessful innovations (as
compared to historical reprobation) which probably stems from a particular concern with
hindsight bias and the implications that would have on medical progress. This limits the
utility of a medical negligence action in providing adequate *ex ante* incentives for innovating
physicians to carefully investigate and weigh the risks and benefits in offering innovative
treatment.

B. *Patient Informed Consent*

An equally important aspect of *post hoc* review is whether a patient has given informed
consent to receive innovative therapy. Informed consent is a well established requirement in
medical treatment, but the question of the nature and scope of disclosure acquires greater
importance given the feature of greater uncertainty regarding the risks and benefits of
proposed innovative therapy, and the possibility of a greater divergence of interests on the
part of the physician when compared to the administration of standard therapy. In particular
it has been recognized by common law courts that interests related to reputational prestige
and increasing direct or indirect commercial interests in the administration of innovative
therapy are important considerations in formulating disclosure standards.

There are three possible approaches to the scope of informed consent in the context of
innovative treatment: the first treats it no differently from informed consent in a clinical
setting, and the scope of disclosure remains on of professional judgment to be determined by
a responsible body of medical opinion. This was first indicated in the important case relating
to the first artificial heart transplant in *Karp v. Cooley*, where the US Fifth Circuit Court of
Appeals ruled that notwithstanding the experimental, laboratory tested nature of the device,
the question of what should be disclosed was a medical one to be determined by what “what
a reasonable practitioner of the same school of practice and the same or similar locality
would have advised a patient under similar circumstances.” This non-distinguishing,
profession-centred approach was also endorsed by the Singapore Court of Appeal in 2002,
which affirmed in *Gunapathy* the profession-centred approach in *Sidaway* without taking
into account the innovative application of X-Knife surgery in the circumstances. The court
was content to accept professional testimony that disclosure of the typical risks inherent in
radiosurgery was adequate, without any mention of the complete absence of empirical data
of the appropriate radiation dosages applicable to the patient’s type of tumour, nor what
uncertainties were created by this lack of evidence. Thus in that case, evidence that the
patient was informed of the main (known) risks associated with the procedure was sufficient
to exonerate the medical team from liability for inadequate disclosure.

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91 See *supra* note 82 at paras. 53-57 (endorsing guidance issued by the U.K General Medical Council and the U.S. Food and Drug Administration on the off-label use of ‘medicines’ and ‘drugs, biologics and devices’ respectively); 62-67 and 72.
92 See e.g. *Brown v. Hughes* 30 P.2d 259 at 262-263 (1934) (SC, Colorado)
94 493 F.2d 408 (1974) at 419 (C.A. 5th Cir.)
95 *Sidaway v. Bethlem Royal Hospital Governors* [1985] AC 871 (HL)
96 *Supra* note 82 at para. 143
97 *Ibid.* at para. 131
98 *Ibid.* at paras. 99-105
The second approach adopts a patient-centred analysis of reasonable disclosure based on materiality is adopted. Courts endorsing this approach have specified that at the least, patients must be informed of the experimental nature of the surgery. This is a basic, material feature of innovative therapy that needs to be communicated irrespective of the particular nature of the therapy. Some courts have gone on to include the particular physician’s individual experience with the procedure, given its relative novelty, on the grounds that this constitutes a material risk factor in the patient’s evaluation of the desirability of undergoing the innovative procedure.

However, apart from the contextual significance of material risks and alternative standard procedures (if any), these courts have not gone further to indicate that any higher standard of disclosure extending to all reasonably foreseeable risks applies. This third, more onerous approach has not yet been accepted by a common law court in relation to innovative treatment. Where one is clearly within the realm of research, various courts have indeed imposed a distinctly higher threshold of disclosure just mentioned. On top of that, they have weaved this requirement into consent to battery as well. One clear underlying concern motivating this higher standard relates to the similarities that innovative treatment has with formal research – a greater uncertainty as to risks and benefits, and the influence of developing new knowledge concerning the innovative treatment or procedure on the motivations of the physician. Thus, some commentators read the Helsinki Declaration as requiring just such a standard even in respect of innovative therapy, or support such a principle on the basis of the altered nature of innovative therapy and greater risks accompanying them.

If the distinction between research and treatment argued for earlier is accepted, it would seem to suggest that the primary therapeutic motivation in innovative therapy unconstrained by an imperative scientific or professional methodology would render a full and complete disclosure under the third approach a bit of overkill. Furthermore, such disclosure might be counterproductive if the patient (often already in a vulnerable situation without standard therapeutic alternatives) is overwhelmed by the minutiae of reasonably possible risks, and suspicions might be unduly heightened by perceived defensive posturing given such full and frank disclosure. In research, this is considered a good thing as it highlights to the patient that a different paradigm is involved. This is provided that the innovative, untested option does indeed present a reasonable alternative in the patient’s circumstances. As the court in Zimmer v. Ringrose observed:

In the case of a truly “experimental” procedure,... no therapeutic benefit is intended

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99 See supra note 93
100 See e.g. Hales v. Pittman 576 P.2d 493 at 500; See also P. Healey & A. Samantha, “When Does the ’Learning Curve’ of Innovative Interventions Become Questionable Practice?” (2008) 36 Eur J Vasc Endovasc Surg 253 at 256
101 See Noah, supra note 39 at 375-379.
103 Halushka, ibid.
105 Supra note 25 at para. 32 read with para. 22
106 Healey & Samantha, supra note 100.
107 Giesen, supra note 79 at 35; Cf. Noah, supra note 39 at 407-408.
to accrue to the participant. The subject is simply part of a scientific investigation designed to enhance human knowledge. ...To hold that every new development in medical methodology was “experimental” in the sense outlined in Halushka v. Univ. of Sask. would be to discourage advances in the field of medicine. ...

There may however be specific concerns about a direct conflict of interest where the physician also holds a financial interest in demonstrating the success of an innovative therapy. 108 In such situations, it might be more pertinent to recognize a fiduciary duty to disclose the interest and allow the patient to seek a second opinion, rather than impose a blanket requirement of full and frank disclosure. 109

Therefore, if we properly remain within the realm of treatment, the focus of informed consent should be on disclosure of material risks that would influence the judgment of a reasonable patient in those particular circumstances. If appropriately framed to focus on the needs and interests of a reasonable patient in the relevant circumstances, then this would necessarily entail a fuller disclosure than if the subject matter pertained to standard therapy. There is ample common law authority to indicate that materiality in these circumstances must at the least encompass ensuring patient appreciation that the therapy is experimental and has not been sufficiently tested and evaluated in order for it to enter within the bounds of standard therapy. 110 By reason of its experimental nature, informed consent for innovative therapy would necessarily involve the disclosure and discussion of a wider range of potential risks simply because their likelihood or severity would not be known or fully understood. Nevertheless, it should be noted that a patient-centred materiality test will more likely require a higher level of disclosure and patient engagement in practice. Uncertainty of benefit and increased risks associated with innovative therapy would require a more involved disclosure and discussion when compared with validated standard therapy where a clearer profile of the risk/benefit analysis is available.

What the present analysis highlights more acutely is the uncertainty over whether a profession-centred standard of disclosure will adequately capture the rationale underlying informed consent to innovative therapy. This is particularly a concern where, apart from the physician-patient communication dynamic, there is no other independent evaluation of the innovation proposed. This paper does not attempt to revisit the general debate over physician and patient-centred standards of disclosure. 111 However, in the particular context of innovative therapy, it becomes even more imperative that the physician actively engage a patient and her values at a level she is prepared for –her personal goals of care and acceptable risk thresholds. Respect for patient autonomy in the face of uncertainty aside, informed consent also forces the physician into a process of self-scrutiny in carefully

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109 See e.g. Moore v. Regents of the University of California 793 P.2d 479 (1990) (S.C. Cal.)

110 See e.g. Estrada v Jacques, supra note 93 at 254: “...With experimental procedures the “most frequent risks and hazards” will remain unknown until the procedure becomes established. If the health care provider has a duty to inform of known risks for established procedures, common sense and the purposes of the statute equally require that the health care provider inform the patient of any uncertainty regarding the risks associated with experimental procedures. This includes the experimental nature of the procedure and the known or projected most likely risks.” [emphasis in original]

111 See e.g. P. Schuck, “Rethinking Informed Consent” (1994) 103 Yale Law Journal 899.
investigating potential risks and articulating her case for the proposed innovation. This becomes a default, protective mechanism in a situation where no other regulatory mechanism is triggered and the decision is essentially a private one made in the confidential context of the physician-patient relationship. Giesen observes that physicians may also have a bias in favour of experimenting in order to advance medical development. Such medical ‘adventurism’ needs to be balanced by ensuring that individual patient’s concerns and interests are not ignored or downplayed in that decision making process, particularly when all the uncertain risks associated with the innovation will unequivocally be borne by the patient, not the physician. Finally, given that innovative therapy is more likely to be offered in situations where there are is no standard therapy available, failure to appropriately disclose and advise patients of the experimental nature of proposed therapy would essentially deprive them of a meaningful choice on the misimpression that the option was effective and appropriate. Thus, whatever the merits of the profession-centred standard of disclosure, at least in respect of innovative therapy, its desirability is questionable given the interests at stake.

V. FURTHER REGULATORY IMPLICATIONS

A. Persisting Concerns over Innovative Treatment

Left to current processes, innovative treatment that is not classified as ‘research’ escapes any external review and is dealt with by the internal dynamics of the physician-patient relationship and possible post hoc review in a medical negligence action or disciplinary proceeding. The latter are generally not considered sufficiently robust to provide adequate oversight for innovative treatment: patients may only sue if they suffer injury, may not actually bring a suit or complaint, and even when they do, face considerable hurdles in obtaining recovery. The question therefore is whether this generally hands-off approach is satisfactory. Several features of innovative treatment within the domain of professional discretion raise serious doubts over the status quo.

First, the decision to offer innovative therapy is subject to increasing potential for conflicts between the patient’s best interests and the physician’s personal and professional interests in profit and advancement. The potential intellectual property and commercial spin-offs related to the development of new medical technologies hold great potential for influencing professional judgments concerning innovative treatments, given their nascent stage of development and inherent capacity, once administered, to generate potentially valuable information in advancing the physician’s interests. Concerns over conflicts of interest are heightened in a system where healthcare is principally delivered through privately operated institutions and cost recovery (if not profit) is an overriding concern.

Secondly, quite apart from financial considerations, there may also be an evaluative bias in favour of the soundness of self-produced innovation, with the risk of an overestimation of

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113 Giesen, supra note 79 at 35.
114 See also King & Henderson, supra note 39 at 1032; 1044-1045.
115 Ibid. at 1044, 1048.
116 Robertson, supra note 89 at 20.
117 Taylor, supra note 108 at 291-292.
the potential benefits and underestimation of the risks. This may be difficult to determine particularly in an area where there is a lack of supporting data.\textsuperscript{118}

Thirdly, pressure to innovate comes not only from professional quarters, but also from patients themselves. Patients without existing alternatives, and their families, may place strong pressure on doctors to try something new in the hope of a miracle cure.\textsuperscript{119} They are increasingly well informed and may point physicians to the latest media-informed developments across the globe. The burden of providing a detached, objective evaluation of the innovative option currently falls on the shoulders of the individual attending physician or surgeon, which may often be an unrealistic aspiration.\textsuperscript{120}

Finally, a different interest hovers over every decision to deploy innovative therapy – the public health interest in the development of safe, efficacious new therapies. The public health interest reflects the interests of future patients who are affected by the precipitous introduction of new therapies before they are sufficiently tested. There is currently no general mechanism to inject such considerations into decision making at the stage of casuistic innovation, as the decision to deploy innovative therapy is made ostensibly solely on the patient’s best interests, irrespective of the interests of future patients in having such therapy systematically investigated for safety and efficacy.\textsuperscript{121} Thus it has been observed that a large majority of therapeutic interventions in medicine have not been subjected to the gold standard of scientific proof represented by the RCT.\textsuperscript{122} These considerations point towards a need to introduce some form of upstream regulation in order to preserve the integrity of the physician-patient relationship and promote better processes for the development and mainstreaming of innovative therapies.

B. Appropriate Regulatory Responses

1. Protecting vulnerable patients through independent peer review

There are several broad regulatory strategies that have been adopted or recommended as responses to the concerns raised by innovative treatment. The first and foremost is the recommendation or requirement for prior independent peer review of the proposed innovative therapy.\textsuperscript{123} This is seen as a means for review and oversight of the individualized professional decision whether to offer innovative therapy, and draws obvious inspiration from the requirement for ethics review in the case of research. A key rationale underlying this approach is perhaps the impetus such review creates for any medical professional to

\textsuperscript{118} Ibid. at 296; P. MacNeil, “Regulating Experimentation in Research and Medical Practice”, in H. Kuhse & P. Singer, \textit{A Companion to Bioethics}, 2d. (Blackwell, 2009), c.39 at 471


\textsuperscript{121} This was a major concern of Levine in his report to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research; see \textit{supra} note 33 at 37


\textsuperscript{123} See e.g. Eaton & Kennedy, \textit{supra} note 45 at 104, reporting the consensus at the Lasker Foundation Forum on Innovation in Medical Technology.
reflect upon the proposal for innovative therapy, and a more impartial evaluation of the evidence supporting it and the personal needs of the patient.\textsuperscript{124}

However, there is a broad variation on the specifics of independent peer review of innovative therapy, such as the appropriate forum and thresholds for ethical review. For example, in New Zealand, the Ministry of Health’s \textit{Operational Standard for Ethics Committees} provides guidelines and ethical standards for committees to review both health/disability research and innovative practice in seamless fashion.\textsuperscript{125} The recommendations require that innovative practice be subject to the same systematic evaluation, ethical review and informed consent requirements as with other health research.\textsuperscript{126} In particular, like research, the innovative practice’s justifiability must be demonstrated in terms of both contribution to medical knowledge and its potential to be of direct benefit to individual consumers.\textsuperscript{127} This is in part explicable on the particular conception of innovative practice adopted: “a planned deviation from currently accepted practice ... involving an untested or unproven clinical intervention \textit{intended to be used on an ongoing basis},”\textsuperscript{128} ‘This definition is akin to the classificatory approaches based on intention and reiteration of treatments used to identify research activity.\textsuperscript{129} The New Zealand approach thus appears to reflect the philosophy that innovative practice is substantially akin to research, and should be governed by similar ethical review processes and documentation.

The Final Bristol Royal Infirmary Inquiry Report in the UK similarly recommended that any clinician undertaking a “new and hitherto untried invasive clinical procedure” should satisfy a local REC that it is justified in the patient’s best interests. This expansion of REC jurisdiction nevertheless recognizes that the REC should be “re-formed” as necessary so that they are capable of undertaking the requirements of ethical review for innovative therapy.\textsuperscript{130} However, RECs were not given jurisdiction over all new interventional procedures.\textsuperscript{131} Rather, medical practitioners intending to undertake “new interventional procedures” should also seek approval from their NHS Trust’s Clinical Governance Committee – which focuses on scientific safety and efficacy appraisal – before proceeding.\textsuperscript{132} Price thus observes that a regulatory gap exists within the parallel clinical governance and research ethics pathways in that no one is specifically tasked to undertake an ethical review of the innovative therapy offered.\textsuperscript{133}

\textsuperscript{124} Edgar, \textit{supra} note 120 at 128 and 132; MacNeil, \textit{supra} note 118 at 483
\textsuperscript{126} \textit{Ibid.} at 25, para. 123
\textsuperscript{127} \textit{Ibid.} at 25, para 123(iii), 26, paras. 127, 129, 131 and 132
\textsuperscript{128} \textit{Ibid.} at 24, para. 121; which resonates with the ‘reiterative’ definition of research considered above: See Part III.B.3 above.
\textsuperscript{129} See parts III.A and III.B.3 above.
\textsuperscript{131} D. Price, “Remodelling the regulation of postmodern innovation in medicine” (2005) 1 International Journal of Law in Context 121 at 135
\textsuperscript{133} \textit{Supra} note 131 at 136.
Other jurisdictions and institutions deploy adapted processes to cater to the specific needs of innovative therapy, rather than streamlining review within the research ethics paradigm. For example, various U.S. hospitals such as the University of Pittsburgh Medical Centre and Boston Children’s Hospital have created specific review processes to accommodate innovative practice. In the former, the Innovative Practices subcommittee of the UPMC’s Technology and Assessment Committee (distinct from the University’s IRB) was established to systematically evaluate innovative practice. It focuses on whether the proposed innovative therapy possesses a favourable risk-benefit ratio suitable for patient care, and its composition is carefully chosen to reflect this emphasis. In comparison, the Boston Children’s Hospital divides review between unaffiliated departmental members (for assurance of patient safety) and administrative IRB review (for informed consent) in respect of innovative surgery. The oversight model also provides mechanisms for resolving ambiguities of classification between research and innovation. This preference for alternative models of review has also been the approach of various professional bodies such as the Surgical Innovations Team of the Society of University Surgeons, and the International Society for Stem Cell Research in their respective fields of innovation.

Should existing research ethics review processes be expanded to accommodate innovative treatment, or are bespoke oversight mechanisms preferable? The optimal form of regulatory supervision should follow its specific function. Innovative therapy, unlike research, is focused on the care of a specific patient and not generalisable knowledge. Although the nature of the risks imposed and uncertainties involved are more akin to that experienced in the conduct of research, the ethical issues raised are different. Innovative therapy raises issues more focused on the needs and interests of the patient in electing for an innovative option. This is largely a clinically oriented issue which weighs the risks and uncertainties against the specific individual needs of the patient, and the clinical systems available to manage and mitigate those risks. Thus, Taylor argues that it requires “oversight tailored to the risks and patient implications actually presented by specific therapeutic innovations.” In particular, emphasis should be placed on (a) a review of the available data and scientific rationale support for the innovation proposed in the light of the patients needs and interests, (b) adequate coordination and follow-up by the relevant clinical services involved in the particular patient’s care, (c) a rigorous, patient-specific informed consent process that conveys to the patient not only the uncertain risks and available options, but also the financial implications of innovative therapy, and (d) an ethical review of the offer of innovative therapy given the risk-benefit analysis to ensure that it is not clearly inappropriate.

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135 Ibid. at 749.  
136 Mastroianni, supra note 2 at 440-441  
137 Ibid.  
139 ISSCR, Guidelines for the Clinical Translation of Stem Cells (2008) at 15-16; online: <http://www.isscr.org/GuidelinesforClinicalTranslation/2480.htm>  
140 Taylor, supra note 108 at 293.  
141 Ibid. at 295.  
142 Ibid. at 296-298.
In comparison, research ethics analysis performs a different sort of risk-benefit analysis that weighs the additional risks posed to the participants against the value of the knowledge to be derived from the research (in the light of its scientific design and on the assumption that clinical equipoise is satisfied where appropriate). Although research oversight may also focus on underlying scientific plausibility, this is for the different purpose of assessing the suitability of the proposed scientific methodology. The acceptable evidential thresholds may thus depend on whether the object is to develop generalisable data or to help a particular patient who has no other available options.

The capacity of IRBs or RECs to review innovative therapies might be further limited in so far as their authority to undertake scientific review is restricted by the relevant regulations or ethical guidelines. For example, under the UK Department of Health Governance Framework for NHS Research Ethics Committees, RECs are not expected to, nor are they appropriately composed, to review scientific aspects of a research protocol. Likewise, in Singapore, under the Ministry of Health’s Operational Guidelines for IRBs, review boards are not responsible for the scientific review of research projects. These limitations do not suggest that IRBs or RECs, at least with their current mandates, are eminently suited to review innovative practice as well.

Furthermore, Agich has observed that there is a lack of fit between the research regulatory oversight methods and the typical circumstances of innovative practice:

> The typical [research ethics paradigm] review is conducted by committee relying on the submitted application, protocol, and informed consent documents. The complex processes characteristic of clinical innovation are often not reducible to a scientific protocol. They typically involve intuition, experience, and an evolving knowledge about the treatment and disease processes and the interaction between treatment and pathology.

An insistence on conformance to the practices and expectations of the existing research ethics paradigm, or interposing multiple gatekeepers in the oversight process, may thus impede innovation in a rapidly evolving field of medicine.

It is thus submitted that, consistent with more recent scholarship mentioned above, the form and routine in existing research ethics processes can inhibit appropriate understanding and review of the particular clinical and ethical questions raised by innovative treatment. In this respect, given the greater clinical ‘character’ of innovative therapy and the needs of the particular patient, a process more akin to clinical ethics peer review is necessary, with

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143 Freedman et al, supra note 21 at 656
144 Taylor, supra note 108 at 296
appropriate expertise drawn (whether internal or external to the institution in question) to address the underlying characterization, scientific and ethical issues. The quality of peer scrutiny on the underlying rationale and supporting evidence of innovative therapy would necessarily be influenced by the urgency of the patient’s situation. Such a process would also have to be more flexible in terms of the necessary documentation and response times needed to make it viable in the context of innovative therapy. Informed consent review would also need to be more personalized, and should even consider independent peer involvement in communicating and explaining the necessary information, so as to obtain more meaningful informed consent.¹⁴⁸

On this score, a related issue arises concerning the appropriate threshold for independent professional review. This is necessitated because of the wide ranging scope of potentially innovative practice within the practice of medicine, such that too low a threshold would likely overwhelm regulatory oversight and unduly impede access to innovative therapy to the detriment of patients. The Lasker Foundation Forum on Innovation in Medical Technology thus recommended that a high threshold be set in respect of the degree of deviation and potential risks involved.¹⁴⁹ Indeed, the Belmont Report originally flagged out “significant innovations” for possible research as soon as practicable.¹⁵⁰ Useful starting points of reference are “innovations that provide diagnosis or treatment for a condition that previously had none,... that claim to provide a different stratum of effectiveness over standard treatments... or whose rationale is novel... signify a degree of novelty that is associated with uncertainty and the potential for significant risk.”¹⁵¹ Where this threshold is set may partly be addressed by professional guidelines, but should ultimately be left to the particular institutions implementing a system that should continue to follow an enforced self-regulation model.¹⁵² This context specific classification would better adapt to the particular activities conducted by an institution, and its experience and capacity to manage different levels of risk associated with innovative practices.

2. Protecting the public health interest

Prescriptions are far less forthcoming in respect of regulatory measures needed to serve the public interest in the responsible development of new therapies. First, the ability of independent peer and ethical review of innovative therapy to regulate proper development is necessarily limited. The responsibility of such committees is conceived of as first and foremost protecting the interests of the patient in need. Innovative practice may thus be responsibly approved under such oversight even if it will not lead to generalisable (as opposed to anecdotal) knowledge that will accrue to the benefit of future patients under the RCT standard.¹⁵³ If there is a sufficiently sound rationale for the innovation when balanced against the patient’s medical need and lack of available therapeutic alternatives, then it could be unethical to deny the patient the choice solely because insufficiently rigorous knowledge would be generated. Certainly, prior ethical peer review would serve a useful function in screening out of instances of quackery or unacceptable innovative risks in comparison with

¹⁴⁸ See King, supra note 39 at 13; MacNeil, supra note 118 at 483-484
¹⁴⁹ Eaton & Kennedy, supra note 45 at 104
¹⁵⁰ Supra note 44
¹⁵¹ Strasberg & Ludbrook, supra note 50 at 944
¹⁵² I. Ayres & J. Braithwaite, Responsive Regulation (NY: OUP, 1992), c.4. 102-6. See also, Cowan, supra note 22 at 250.
¹⁵³ See Taylor, supra note 108 at 295-296.
available standard therapy, and could encourage the physician or institution to undertake suitably designed research to compare the innovation with existing standard therapy. Independent peer review of innovative practice nevertheless cannot mandate the additional funding needed for, nor ethical propriety of, such research, let alone the professional desire to do so.154 A couple of regulatory mechanisms have thus far been used to complement independent peer review in improving the assessment of innovative practice in the process of development into standard therapy.

The first is the use of clinical registries to improve the collection of data concerning the deployment of innovative therapy, thereby facilitating outcomes research in general and the deliberation of peer committees reviewing innovative practice in particular.155 This has most often been used on the field of innovative surgery, with examples of registries created by professional societies156 and the state agencies.157 They are not without their shortcomings, however, which range from the substantial cost of implementing them on sufficient scale, to difficulties ensuring inclusiveness and validity, and ensuring respect for patient privacy.158

The need for careful selection and implementation of registries for innovative treatment points also to the need for some coordinating agency or professional society to provide a coherent strategy to protect both patients and the larger public health interest. This leads naturally to the second mechanism, which involves placing responsibility for oversight of the development process with a suitably equipped regulatory agency or institution. In respect of the systematic review of such therapies, various jurisdictions have agencies tasked accordingly. For example, the UK’s National Institute for Clinical Excellence (NICE) maintains a compulsory register of interventional procedures. Its Interventional Procedures Advisory Committee assesses the available evidence on their safety and efficacy, and issues guidance on them.159 The NICE programme dovetails with the UK Department of Health’s Interventional Procedures Programme mentioned above,160 which responds to notifications of new procedures with either fresh guidance or the commissioning of a systematic review of research on the procedure.161 A similar function is performed at the federal level by the U.S. Agency for Healthcare Research and Quality in respect of new or as yet-unproven medical technologies that are being considered for coverage under Medicare and Medicaid.162 Such systematic review, however, also does occur at the institutional level: Witness the Massachusetts General Hospital Innovative Diagnostics and Therapeutics Committee, which

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154 See Noah, supra note 39 at 406-407
155 Strasberg & Ludbrook, supra note 50 at 946.
156 E.g. the registry established by the American College of Surgeons in respect of surgical innovations: Biffl, supra note 138 at 1208.
157 In the UK, a voluntary register, Safety and Efficacy Register for New Interventionsal Procedures (SERNIP), was initially set up by the royal colleges. Australia followed suit with its own ASERNIP for surgical procedures: B. Campbell & G. Madden, “Safety and efficacy of interventional procedures: Scrutinising the evidence and issuing guidelines without stifling innovation” (2003) 326 BMJ 347-348. SERNIP’s functions were subsequently taken over by the National Institute for Clinical Excellence (NICE) in February 2003: Price, supra note 131 at 135.
158 Strasberg & Ludbrook, supra note 50 at 946.
159 Price, supra note 131 at 135-136
160 See supra note 132 and accompanying text.
161 Ibid. at 2
162 Eaton & Kennedy, supra note 45 at 103; AHRQ online:<http://www.ahrq.gov/about/profile.htm>.
reviews new medical technologies and determines whether they need formal research examination or can be introduced into practice without it.\textsuperscript{163}

A substantial part of the regulatory complexity is rooted in the ongoing debate as to the proper conception of medical epistemology – whether medicine is essentially science or treatment.\textsuperscript{164} Adopting the former view would require the proper scientific assessment of innovative therapy before diffusion, while the latter would accommodate less formal and scientifically rigorous assessment in the development process.\textsuperscript{165} Add to this ethical and resource constraints on research and one is left with the impression that there is unlikely to be any standard form regulatory solution to the challenge of protecting the public interest in the proper passage of innovative treatments into standard medical practice. A systematic resolution of this depends largely on the health care system in question, the profile of innovative practice within its institutions and healthcare professions, and the existing systems already in place that could be adapted to regulate innovative therapy. This larger discussion is beyond the scope of this paper; the point made here is that this regulatory interest cannot be adequately served simply by implementing an independent peer review mechanism for innovative treatments.

VI. CONCLUSION

In summary, innovative therapy is increasingly, and rightly, seen as a distinct category of medical activity that possesses features in common with both the therapeutic paradigm of the physician-patient relationship and the clinical research paradigm. It is most effectively distinguished from research by using both a methodological analysis (which searches for methodological constraints on the physician’s judgment in serving the patient’s best interests), or the absence of therapeutic benefit analysis (which complements the former by identifying research purpose from the presence of procedures that are unnecessary for treatment). Streaming of innovative practice into the research ethics regulatory pathway would thus be put on a clearer footing.

Legal oversight over innovative therapy exists in both medical negligence law and disciplinary proceedings, but greater analytical clarity is needed in first recognizing the unique features of innovative therapy that distinguish it from standard therapy, and the appropriate standards of care in treatment and advice that should accompany it. Informed consent for innovative therapy needs to be more rigorously evaluated to respect the particular importance of patient autonomy in appreciating and accepting the uncertain risks and benefits associated with such therapy.

Finally, post hoc legal scrutiny often comes too late, or not at all, in aid of vulnerable patients. It is also limited in its ability to systematically protect the public health interest in the development of safe and effective new therapies. Additional regulatory measures are necessary, which include, in particular, an adaptive peer oversight process that properly balances the interests of the individual patient and responsible innovation in medicine. The latter interest needs to be supported by other complementary regulatory mechanisms such

\textsuperscript{163} Ibid. See also Cowan, \textit{supra} note 22 at 246, 248-251.
\textsuperscript{164} King & Henderson, \textit{supra} note 39 at 1023-1024
\textsuperscript{165} See Noah, \textit{supra} note 39 at 400-407
as clinical registries and dedicated institutional oversight of the development process, because peer review itself cannot do this alone effectively.