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New non-validated practice: an enhanced definition of innovative practice for medicine

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ABSTRACT

A significant part of the literature on innovative practice in medicine relates to seizing opportunities and curbing harms for patients in desperate situations. Unfortunately, the term innovation has multiple meanings and a rich rhetorical flourish that adds confusion and misunderstanding to an already difficult debate. This paper aims to enhance the current definition of innovative practice for medicine. First, we replace the term 'innovation' with the more literal 'new non-validated practice'. To identify this meaning, we analyse the traditional research ethics' distinction between research, validated practice, and innovation in the Belmont Report. Second, we propose the following explicit definition of new non-validated practice: the first or recent use of diagnostic, therapeutic or preventive interventions that introduce a significant change, with an insufficient level of evidence of safety or efficacy for regular healthcare, and with the main aim to benefit individual patients. This definition is a promising conceptual tool to inform empirical research, ethicists, and the harmonisation of regulation and legislation (e.g. right-to-try laws).

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KEYWORDS Right to try; innovation in medicine; innovative care; innovative practice; distinction between research and practice

1. Introduction

The activity of innovative practice and the concept of innovation have gained importance in medical ethics guidelines,[1] ethical

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[1]Alex J London, 'Cutting Surgical Practice at the Joints: Individuating and Assessing Surgical Procedures' in Angelique M Rietsma and Jonathan D Moreno (eds), *Ethical Guidelines for Innovative Surgery* (University Publishing Group, 2006); The American College of Obstetricians and Gynecologists' Committee on Ethics (ACOG Committee on Ethics), 'ACOG Committee Opinion No. 352: Innovative Practice: Ethical Guidelines' (2006, reaffirmed 2015) 108 *Obstetrics and Gynecology* 1589; International Society for Stem Cell Research

literature[2] and current discussions of different 'right-to-try' regulations in various countries.[3] The main background concern of this literature is seizing opportunity and curbing harm for patients in desperate situations and the dilemmas around it. However, the term innovation has multiple meanings and a rhetorical flourish that generates confusion and problems of communication in an already difficult debate.[4] Hence, recent literature suggests avoiding the term innovation for study and regulation, or if it cannot be avoided, defining it explicitly.[5] Therefore, this paper aims to enhance the definition of innovative practice in two ways. First, we propose to curb the problem of rhetoric and multiple meanings of innovation by replacing it with the more literal term of 'new non-validated practice' and by distinguishing the specific meaning of innovation in medicine. To identify this specific meaning, we analyse the traditional research ethics distinction between research, validated practice, and innovation. Second, we propose

(ISSCR), *Guidelines for Stem Cell Research and Clinical Translation* (2016) www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2 (accessed 28 July 2020); Vic Larcher, Helen Turnham and Joe Brierley, 'Medical Innovation in a Children's Hospital: "Diseases Desperate Grown by Desperate Appliance Are Relieved, or Not at All"' (2018) 32 *Bioethics* 36.

[2]Patrick L Taylor, 'Overseeing Innovative Therapy without Mistaking It for Research: A Function-Based Model Based on Old Truths, New Capacities, and Lessons from Stem Cells' (2010) 38 *The Journal of Law, Medicine & Ethics* 286; Jeremy Sugarman, 'Questions Concerning the Clinical Translation of Cell-Based Interventions under an Innovation Pathway' (2012) 40 *The Journal of Law, Medicine & Ethics* 945; Steven Joffe, 'Evaluating Novel Therapies During the Ebola Epidemic' (2014) 312 *JAMA* 1299; Dominic Wilkinson and Julian Savulescu, 'After Charlie Gard: Ethically Ensuring Access to Innovative Treatment' (2017) 390 *The Lancet* 540; Udo Schuklenk and Ricardo Smalling, 'The Moral Case for Granting Catastrophically Ill Patients the Right to Access Unregistered Medical Interventions' (2017) 45 *The Journal of Law, Medicine & Ethics* 382; Alex J London, 'Social Value, Clinical Equipoise, and Research in a Public Health Emergency' (2019) 33 *Bioethics* 326; Felicitas Holzer and Ignacio Mastroleo, 'Innovative Care in Latin America: Definition, Justification and Ethical Principles' in Eduardo Rivera-López and Martin Hevia (eds), *Controversies in Latin American Bioethics* (Springer International Publishing, 2019) https://doi.org/10.1007/978-3-030-17963-2_9 (accessed 25 June 2019); Felicitas Holzer and Ignacio Mastroleo, 'Innovative Practice in Latin America: Medical Tourism and the Crowding Out of Research' (2019) 19 *The American Journal of Bioethics* 42; Jake Earl, 'Innovative Practice, Clinical Research, and the Ethical Advancement of Medicine' (2019) 19 *The American Journal of Bioethics* 7.

[3]Anna Mastroianni, 'Liability, Regulation and Policy in Surgical Innovation: The Cutting Edge of Research and Therapy' (2006) 16 *Health Matrix: The Journal of Law-Medicine* 351; José Miola, 'Bye-Bye Bolitho? The Curious Case of the Medical Innovation Bill' (2015) 15 *Medical Law International* 124; Joseph J Fins, 'In Reply: Commentary: Deep Brain Stimulation as Clinical Innovation: An Ethical and Organizational Framework to Sustain Deliberations About Psychiatric Deep Brain Stimulation' (2017) 80 *Neurosurgery* E271; Julian Savulescu, 'Press Release "Vale Charlie"' (*Practical ethics*, 2017) http://blog.practicalethics.ox.ac.uk/2017/07/press-release-vale-charlie-prof-julian-savulescu/ (accessed 28 July 2020); Steven Joffe and Holly Fernandez Lynch, 'Federal Right-to-Try Legislation – Threatening the FDA's Public Health Mission' (2018) 378 *New England Journal of Medicine* 695; Tina Cockburn and Michael Fay, 'Consent to Innovative Treatment' (2019) 11 *Law, Innovation and Technology* 34; Jonathan Montgomery, 'The "Tragedy" of Charlie Gard: A Case Study for Regulation of Innovation?' (2019) 11 *Law, Innovation and Technology* 155; José Miola, 'Postscript to the Medical Innovation Bill: Clearing up Loose Ends' (2019) 11 *Law, Innovation and Technology* 17.

[4]Anahita Baregheh, Jennifer Rowley and Sally Sambrook, 'Towards a Multidisciplinary Definition of Innovation' (2009) 47 *Management Decision* 1323.

[5]Richard Lilford, 'Health Service and Delivery Research – a Subject of Multiple Meanings' (*NIHR CLAHRC West Midlands News Blog* 2018) https://clahrcwmblog.wordpress.com/2018/11/30/hsdr-subject-of-multiple-meanings/ (accessed 28 July 2020); Giles Birchley and others, 'Have We Made Progress in Identifying (Surgical) Innovation?' (2019) 19 *The American Journal of Bioethics* 25.

Table 1. Concise comparison of definitions of innovation in medicine and other fields.

Term	Field	Author	Definition
Innovation	Economy	Schumpeter (1947)	Innovation is 'the doing of new things or the doing of things that are already being done in a new way'[6]
Technological innovation	Technology	OECD (2002)	'Technological innovations comprise new products and processes and significant technological changes of products and processes. An innovation has been implemented if it has been introduced on the market (product innovation)'[7]
Innovative therapy	Medicine	Taylor (2010)	'Innovative therapy is the name we give to novel medical interventions, radically different from the standard of care, provided in order to benefit a patient, rather than to acquire new knowledge'[8]
Innovation as liminality	Medicine	Sethi (2019)	'A liminal approach … helps us acknowledge that medical innovation is a space within which both aims of individual benefit and contributing to the wider stock of knowledge can co-exist'[9]
Innovation as new non-validated practice	Medicine	Mastroleo and Holzer	'New non-validated practice is the first or recent use of diagnostic, therapeutic or preventive interventions that introduce a significant change, with an insufficient level of evidence of safety or efficacy for regular healthcare, and with the main aim to benefit individual patients'[10]

the following unified definition of 'new non-validated practice', that is, the first or recent use of diagnostic, therapeutic or preventive interventions that introduce a significant change ('new'); with an insufficient level of evidence of safety or efficacy for regular healthcare ('non-validated'); and with the main aim to benefit individual patients ('practice').

One easy way to show that the term innovation and its derivatives have a specific meaning in medicine, is to compare it with other widely used definitions of innovation in other fields (see Table 1).

In economy, Schumpeter defines innovation broadly as 'the doing of new things or the doing of things that are already being done in a new way'.[11] A more specific definition of technological innovation refers to new products and processes or significant changes and their introduction in the market ('product innovation').[12] However, despite the family resemblance, the

[6]Joseph A Schumpeter, 'The creative response in economic history' (1947) 7 *The journal of economic history* 151.
[7]Organisation for Economic Co-operation and Development (OECD), *Technological Innovations* (2002) https://stats.oecd.org/glossary/detail.asp?ID=2688 (accessed 28 July 2020).
[8]Taylor (n 2) 286.
[9]Nayha Sethi, 'Regulating for Uncertainty: Bridging Blurred Boundaries in Medical Innovation, Research and Treatment' (2019) 11 *Law, Innovation and Technology* 123.
[10]Ignacio Mastroleo and Felicitas Holzer, this paper.
[11]Schumpeter (n 6) 151.
[12]OECD (n 7).

meaning of innovation in medicine we want to capture refers to an activity that has as its main aim the wellbeing of patients. For instance, Taylor states that 'innovative therapy is the name we give to novel medical interventions, radically different from the standard of care, provided to benefit a patient, rather than to acquire new knowledge.'[13] What will strike some readers is that the term innovation at stake refers to a special form of medical practice, rather than to a research activity.[14] Neither the economic nor the technological definition considers the main aim or intention of the innovative activity. Hence, they cannot capture this specific meaning of innovation in medicine. This is important because medical practice and medical research have different legal and ethical regulations that include different economic, administrative, and judicial consequences.[15] Taylor's definition of innovative therapy does capture the main aim of innovative practice and distinguish it from the main aim of research ('acquire new knowledge'). It should be mentioned there are also tendencies to blur the research-practice distinction regarding the term innovation as a medical activity. Lately, Sethi[16] has argued that a context-sensitive 'liminal approach' enables us to see that in innovative medical spaces there can be features of both research and practice. While Taylor's term 'innovative therapy' is too narrowly tailored to therapies (as innovative practice applies also to diagnostic and preventive measures, not only therapies), Sethi's account seems to refer to more general 'terrains' or new innovative medical fields.

As we will argue, a unified definition such as *new non-validated practice* avoids the ambiguous term 'innovation' and captures both the main aim and appropriate scope of innovative practice as diagnostic, therapeutic, or preventive interventions. Furthermore, if sound, our enhanced definition of new non-validated practice allows comparing activities in different fields of medicine that previously have been considered unconnected (e.g. compassionate use of investigational drugs, humanitarian uses of devices, novel off-label uses, etc.). In turn, since the definition of innovative practice is logically prior to its justification and regulation, it also provides a promising conceptual tool to inform empirical research, to discuss responsible access to innovative care and evaluate the regulation of innovative practice (e.g. right-to-try laws).

However, before proceeding, we would like to make two clarifications. First, that new non-validated practice is a neutral definition of innovative practice. We understand that a definition is neutral if it can capture all

[13]Taylor (n 2) 286.
[14]National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission), *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US Government Printing Office 1979) www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html (accessed 28 July 2020); Taylor (n 2) 286; Sugarman (n 2) 945.
[15]Mastroianni (n 3) 351; Taylor (n 2) 286.
[16]Sethi (n 9) 123.

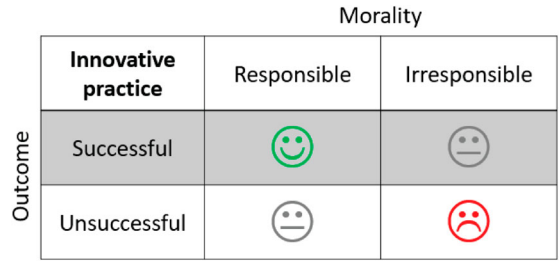

Figure 1. Neutrality of the definition of innovative practice

relevant cases of innovation, whether successful or failed (outcome neutrality), responsible or irresponsible (moral neutrality) (see Figure 1). Here, we agree with Lipworth et al. that neutrality regarding ethical justification and regulation is an essential feature of an adequate definition of innovative practice because we want to have room for reasonable disagreement and avoid using the definition as a rhetorical wand that can compromise critical evaluation.[17]

Second, we want to clearly state that a systematic analysis of the ethical justification and regulation of innovative practice is outside the scope of this paper. The ethical problem of innovative practice can be broken down into three interrelated questions. First, what is innovation in medicine? (definition). Second, is innovation ethically permissible? (justification). Third, if permissible, what are the ethical principles and appropriate governance of innovation? (regulation). In view of our aim, in this paper, we will mainly focus on the first question. However, we will sometimes need to present substantive positions to show how our definition works. When we do this, we will explicitly present these positions as maintained either by the defenders or detractors of innovation and rely on most commonly held ethical principles and frameworks of responsible innovative practice when needed.[18]

To defend our proposal, we will proceed in three stages as follows. First (in section 2), we analyse the definition of innovation in traditional research ethics. We revisit the distinction between research, validated practice, and innovation in the Belmont Report. Finally, we reconstruct Levine's definition of *non-validated practice*.[19] Secondly (in section 3), we present a selection of

[17]Wendy Lipworth, Cameron Stewart and Ian Kerridge, 'The Need for Beneficence and Prudence in Clinical Innovation with Autologous Stem Cells' (2018) 61 *Perspectives in Biology and Medicine* 101.

[18]World Medical Association (WMA), *Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects* (1964) www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/l (accessed 28 July 2020); Taylor (n 2) 286; ACOG Committee on Ethics (n 1) 1589; ISSCR (n 1); Larcher, Turnham and Brierley (n 1) 36.

[19]To the best of our knowledge, this is the first attempt in the literature to eliminate the term innovation from the definition of innovative practice, a path that we and other authors have followed (Birchley and others [n 5] 25).

exemplary cases to show why innovative practice is usually considered a valuable medical activity that is different from both validated practice and research. This preliminary conceptual analysis and the exemplary cases help us to develop the conceptual core of our proposal. Readers familiar with this discussion may want to skip ahead to the next section. Thirdly (in section 4), we introduce our definition of *new non-validated practice* and critically analyse its components. To avoid confusion with related activities, we also introduce a four-category classification of interventions used in medical practice that logically follows from our proposal.

2. The definition of innovation in traditional research ethics

2.1. The Belmont Report's definitions of validated practice, research, and innovation

According to Beauchamp and Saghai,[20] the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (hereinafter the Commission) established two classes of activities labelled 'research' and 'practice' as categories for medical activities that are logically distinguishable from each other (although they may coexist in complex activities). The practical aim of this distinction in the Belmont Report is to establish what kinds of activities must undergo special regulations and ethical review by institutional review boards. However, the distinction is not drawn between research and practice as such, but between research and validated practice.[21] Hence, the Commission defines validated practice as follows:

> [F]or the most part, the term [validated] 'practice' refers to interventions where: (P1) the purpose of an intervention is 'to provide diagnosis, preventive treatment, or therapy'; (P2) the intervention is 'designed solely to enhance the well-being of an individual patient or client' (though benefit to other persons is sometimes the goal); (P3) the intervention has 'a reasonable expectation of success'.[22]

In our interpretation of the scope condition (P1), the term 'practice' refers to preventive, diagnostic, or therapeutic uses of medical interventions, as well as – we will include as a logical addition – their combination. However, the necessary condition that defines practice is the design condition (P2); that is, if a medical intervention's main aim is to enhance the well-being of an individual patient. Hereinafter, we will drop the 'solely' in the formulation of (P2).

[20]Tom L Beauchamp and Yashar Saghai, 'The Historical Foundations of the Research-Practice Distinction in Bioethics' (2012) 33 *Theoretical Medicine and Bioethics* 45.

[21]Here, we interpret standard practice in the prescriptive sense that it has a sufficient level of evidence of safety and efficacy for regular healthcare use. As we will later discuss, we are aware that the term 'accepted or standard practice' used in a descriptive sense may not always refer to validated practice (London, 'Cutting Surgical Practice at the Joints' [n 1] 28–29).

[22]Beauchamp and Saghai (n 20) 52.

This does not present a particular problem for traditional research ethics, since the Belmont Report includes both a wide and a narrow formulation of the practice condition. Practice, in a narrow sense, refers to paradigmatic cases of the doctor–patient relationship.[23] However, the Belmont Report also formulates design condition (P2) in a broad sense as 'an intervention designed to enhance the well-being of a particular individual or groups of individuals'.[24] This broad formulation logically captures the narrow paradigmatic sense of practice, as well as non-paradigmatic cases of practice, for example, interventions designed only to enhance the well-being of others (e.g. blood donation and organ transplant) and interventions designed to enhance the well-being of an individual and others (e.g. vaccination).[25]

The remaining question is how to interpret the validation condition (P3) of 'a reasonable expectation of success'. Reasonable expectations of success vary in different contexts. Here, we wish to distinguish between two different contexts, that is, the use of an intervention in regular healthcare and the use of an intervention for patients with unmet health needs and no reasonable alternatives. We will argue that, for validated practice, the validation condition (P3) should be interpreted as referring to the use of interventions in regular healthcare contexts. If this is the case, all exemplary cases of innovation fail, by definition, to meet the evidence threshold of sufficient validated practice at the time they were first used.

The Commission also defines research as follows:

> To qualify as research two conditions are central. The first is not a necessary condition for all forms of research, but the second is a necessary condition: (R1) there is (in pertinent research methods) a formal protocol-controlled design to test a hypothesis; (R2) there is an organized design 'to develop or contribute to generalizable [scientific] knowledge'.[26]

The design condition (R2) of 'generalizable [scientific] knowledge' defines research according to the traditional view. The Commission differentiates 'generalizable knowledge' gained through research from other forms of knowledge gained through medical learning activities.[27] They recommend that if an activity has an organised design 'to develop or contribute to generalizable knowledge,' it should undergo a research review to protect human subjects, irrespective of the fact that the intervention is also intended to provide a direct health benefit for an individual patient.[28] Thus, the Belmont report

[23]Ibid, 54.
[24]National Commission (n 14) note 1.
[25]Robert J Levine, 'Clarifying the Concepts of Research Ethics' (1979) 9 *Hastings Center Report* 22; National Commission (n 14) note 1.
[26]Beauchamp and Saghai (n 20) 52.
[27]'[…] knowledge gained through research must be oriented toward the types of generalizations found in scientific theories, scientific laws, and statements of relationships, in contrast to the learning that occurs in particular cases through astute clinical observations or diagnostic tests' (Beauchamp and Saghai [n 20] 52).
[28]Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 23.

established a precautionary measure to prevent researchers from taking advantage of a loophole in the oversight system by presenting research with components of care under the label of 'practice' to avoid the review process.[29] However, this measure does not apply to uses of interventions with the main aim to benefit an individual patient but with an insufficient level of evidence of safety or efficacy for regular healthcare, if they do not have evident research components.

Finally, the Commission introduces a further distinction they call innovation and that cannot be regarded as validated practice or research:

> 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.[30]

In the Belmont Report, innovation is defined mainly in terms of novel interventions that significantly depart from validated practice, but retain their main aim to benefit patients. The Commission refers less clearly to non-validation ('untested' procedures). Innovation does not constitute research even if it entails a relevant change in the benefit-harm profile of an intervention in comparison with standard practice. As we will discuss, this implies that the practice-research distinction in traditional research ethics is not related to the harm-benefit profile or soundness of evidence of a medical activity. Whether an activity is research or practice depends on what the activity is designed to do, that is, its main aim or intention (and the appropriate means used to pursue them). The Commission neither considers innovation to be a grey zone between research and practice,[31] nor introduces a third *sui generis* category of activities for innovation.[32] Instead, as we will argue following Levine, the Commission considers innovation as practice because its main aim is to benefit individual patients.

As a result, commissioners and staff were concerned about underprotection of patients. Toulmin and others even hypothesised that certain medical practices, such as innovative therapies, were potentially more risky than well-designed research.[33] Hence, the Commission went beyond defining innovation in the Belmont Report. They supported the view that the oversight of

[29]Beauchamp and Saghai (n 20) 43.
[30]National Commission (n 14), emphasis added.
[31]Nancy King, 'The Line Between Clinical Innovation and Human Experimentation' (2002) 32 *Seton Hall Law Review* 573.
[32]Mianna Lotz, 'Surgical Innovation as Sui Generis Surgical Research' (2013) 34 *Theoretical Medicine and Bioethics* 447.
[33]Beauchamp and Saghai (n 20) 50; Fins (n 3) E271.

innovation should be improved and advised that 'medical practice committees' (not IRBs or research ethics committees) should be responsible for seeing that innovation should be made the object of formal research at some point. But eventually the Commission fell short of proposing regulations for innovation. They made that decision because the National Research Act was about research and the politics of institutional forces in medicine would not allow any venture into the regulation of practice.[34]

2.2. Levine's definition of non-validated practice

Levine[35] offers a thorough analysis regarding the concept of innovation based on the Commission's different reports. According to Levine,[36] the purpose of the Commission in introducing the term innovation has been to avoid common confusion with research because they share the attribute of significant change from accepted or standard practice. However, Levine suggests abandoning the term innovation for a better term and defines this subclass of practice as follows:

> *Nonvalidated practices [sic.]*. A class of procedures performed by physicians conforms to the definition of 'practice' to the extent that these procedures are [P2] 'designed solely to enhance the well-being of an individual patient or client.' However, [not P3] they may not have been tested sufficiently often or sufficiently well to meet the standard of having 'a reasonable expectation of success.' The Commission uses various terms to describe these procedures: [e.g.] 'innovative therapies' […]. In my opinion, the best designation for this class of procedures is 'nonvalidated practices' [sic.]. Novelty is not the attribute that defines this class of practices; rather, it is the lack of suitable validation of the safety or efficacy of the practice.[37]

First, although here the scope condition (P1) is not mentioned it is implied. In later work, Levine clarifies that 'the Commission's reasoning about how to deal with such practices applies to diagnostic and preventive measures, not only therapies'.[38] Hence, 'innovative therapy'[39] and its derivatives does not capture the full extension of the term innovation in research ethics or is confusing. This is the case because if taken literally, it restricts the scope to just one of the three possible uses of a medical intervention. Second, Levine disregards novelty as a defining attribute of innovation. In section 4.1, we argue this is a mistake and try to amend it. Third, for Levine, what makes practice non-validated is the failure to meet 'a reasonable expectation of

[34]Beauchamp and Saghai (n 20) 45–50; Fins (n 3) E271.
[35]Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 21.
[36]Ibid.
[37]Ibid 22, edited.
[38]Robert J Levine, 'The Nature, Scope, and Justification of Clinical Research' in Ezekiel J Emanuel and others (eds), *The Oxford Textbook of Clinical Research Ethics* (Oxford University Press, 2008) 218.
[39]Taylor (n 2) 286.

success' condition (not P3). In section 4.2, we contend that both the Commission and Levine understand 'a reasonable expectation of success' as referring to the level of evidence an intervention should meet to be used as regular healthcare. Finally, Levine considers an intervention as practice if it meets the design condition of 'enhancing the well-being of individuals' (P2). Although Levine quotes the narrow ('solely') formulation of design condition (P2), we will interpret it in the wider sense, as discussed above. Levine's conceptual analysis sheds light on the fact that the Commission considers innovation as a form of practice, not research or other *sui generis* category. In section 4.3, we will further inquire what it means for an intervention to be considered practice in the Commission's sense. But before developing our proposal in full, it will be useful to firstly flesh out to the concept of innovation to make it more comprehensible to the general reader.

3. Exemplary cases of innovative practice

Before developing our proposal, we outline three exemplary cases of what we consider innovation in medicine, already within the definition of traditional research ethics. Our aim here is to give the reader an intuitive grasp of the circumstances where innovation occurs. To save space, we have imposed two restrictions: first, we only provide exemplary cases of therapeutic and diagnostic uses, but not preventive interventions;[40] second, we skip classic examples of innovation in surgery in favour of cases with drugs, biologicals and devices where the discussion is less well-developed.[41]

Our first exemplary case of innovation refers to the successful therapeutic use of an intervention:

> *The Farrows: stem cell transplantation of umbilical cord blood.* In 1988, Matthew Farrow, a 5-year-old patient with Fanconi's anemia who had no reasonable medical alternatives for treatment, received the first successful umbilical cord blood transplant from his baby sister, Alison Farrow, based on sound scientific evidence, including animal studies.[42] Since this first successful transplantation,

[40]For instance, preventive uses of interventions for Ebola Virus Disease under the Monitored Emergency Use of Unregistered Interventions (MEURI) framework could be regarded as an exemplary case of preventive new non-validated practice as in World Health Organization [WHO], 'Consultation on Monitored Emergency Use of Unregistered and Investigational Interventions [MEURI] for Ebola Virus Disease' (2018) www.who.int/ebola/drc-2018/notes-for-the-record-meuri-ebola.pdf (accessed 28 July 2020); for a brief introduction to the WHO MEURI ethical framework see Ignacio Mastroleo and others, 'Allocating Scarce Unproven Interventions during Public Health Emergencies: Insights from the WHO MEURI Framework' *American Journal of Bioethics* https://doi.org/10.1080/15265161.2020.1795539 (accepted for publication June 2020).

[41]Here we follow the authors that consider innovative practice can be applied to both technologies and surgery in medicine (Taylor [n 2] 286, table 1).

[42]Eliane Gluckman and others, 'Hematopoietic Reconstitution in a Patient with Fanconi's Anemia by Means of Umbilical-Cord Blood from an HLA-Identical Sibling' (1989) 321 *New England Journal of Medicine* 1174; BBC Staff, 'Children's 'lifeblood' Hope' (*BBC*, 10 October 2001) http://news.bbc.co.uk/2/hi/health/1591933.stm (accessed 28 July 2020).

cord blood is now widely used as a treatment with hematopoietic stem cells for a wide range of malignant and non-malignant conditions.[43]

Intuitively, we argue that successful cases such as Matthew Farrow illustrate the potential benefits of innovative practice, which serves as a basis for defending it in frameworks of responsible innovation for patients with unmet health needs, serious conditions and no reasonable medical alternatives.

Nevertheless, the use of new non-validated interventions that aim to benefit individual patients does not always attain the desirable results for patients deprived of alternative validated options. Therefore, consider the following case of a failed therapeutic use of an intervention:

Jim Gass: stem cell therapies. The case of Jim Gass caused an outcry in international media that illustrated a growing concern about the number of 'stem cell tourists' worldwide. He had several stem cell interventions at private clinics in Mexico, China, and Argentina, paying tens of thousands of dollars each time for injections to recover from a stroke. The total cost, including travel expenses, reached 300,000 US dollars. Eventually, Jim Gass developed a tumor in his lower spinal column. The subsequent tests showed that the tumor mass was made up of abnormal, primitive cells that were growing aggressively.[44]

Someone may claim that the case of Jim Gass is not an exemplary case of responsible innovation but one of potentially inappropriate or futile use of cell therapy. This is a reasonable claim, and it will be discussed in section 4.2. However, this case is useful to remind us that our proposal is neutral and captures all cases of innovation, whether successful or unsuccessful, responsible or irresponsible.

As implied in the scope condition (P1), examples of using new and unproven interventions outside of sound research are not limited to therapeutic and preventive procedures and can also be exemplified by diagnostic use of interventions.

Genome sequencing for rare diseases. Two siblings in the United Kingdom with an unusual muscle wasting disease had to wait 20 years until they were diagnosed at a cost of more than 14,000 pounds sterling. Whole exome sequencing, costing approximately 1,000 pounds at this time, revealed that a heterozygous mutation was likely disease causing.[45]

[43]Gluckman and others (n 42) 373; Taylor (n 2) 286; Sugarman (n 2) 945.

[44]Gina Kolata, 'A Cautionary Tale of 'Stem Cell Tourism' (2016) *The New York Times* (New York, 22 June 2016) www.nytimes.com/2016/06/23/health/a-cautionary-tale-of-stem-cell-tourism.html (accessed 28 July 2020).

[45]Lizzie Perdeaux, 'The Rare Diseases Genomes Project and Genomics England: By the NHS, for the NHS' (*BHD Foundation*, 25 October 2013) www.bhdsyndrome.org/forum/bhd-research-blog/the-rare-diseases-genomes-project-and-genomics-england-by-the-nhs-for-the-nhs/ (accessed 28 July 2020); Heidi L Rehm and others, 'ClinGen — The Clinical Genome Resource' (2015) 372 *New England Journal of Medicine* 2235.

Although, unlike gene editing, genomic sequencing does not 'intervene' in the sense that it can change the patient's genome, new diagnostic tools are interventions in the sense that they have the potential to change a given patient's life prospect. Patients who suffer from rare diseases are usually in this situation. They often face unsuccessful and burdensome diagnostic procedures over several decades. Despite the uncertainties of our genetic knowledge, rapidly diagnosing a rare disease could be crucial to avoid distress, and unnecessary potentially harmful therapeutic interventions. Moreover, in some cases, molecular diagnosis of rare diseases may lead to improved treatment or preventive decisions. In the defenders' view of responsible innovation, considerations of this kind make the benefit-harm profile of new non-validated diagnostic interventions positive for the use in a limited number of patients, despite their inherent risks. Therefore, some uses of genome sequencing technologies, including whole genome and whole exome sequencing for patients with rare diseases, are recent exemplary cases of innovative practice, precisely when they are not sufficiently validated for regular healthcare.

Finally, innovative practice can be the result of combining different interventions with different purposes for the main aim to benefit an individual patient:

> *The Nashes case: IVF, cord blood transplant, and PGD*. Molly Nash was born in 1994 with type-C Fanconi's anemia, a more aggressive type than that affecting Matthew Farrow. Lacking a suitable match for a bone marrow transplant, the Nashes conceived a baby they named Adam to be a suitable umbilical cord blood donor that possibly matched with Molly. However, due to their low probability of having a baby without Fanconi's anemia, the parents had to use three different interventions – namely, in vitro fertilization (IVF), pre-implantation genetic diagnosis (PGD), and umbilical cord blood transplantation – to have an acceptable donor. The PGD was used twice, first to select an embryo without Fanconi's anemia and then to find a match for Molly.[46]

As Kahn and Mastroianni[47] note, the chosen interventions in the Nashes' case had sufficient level of evidence of safety and efficacy to be used in regular healthcare for their intended indications in 2000 when Adam was born, so they were separately considered validated practices. However, the combination of these interventions –necessary to attain a more promising treatment for Molly[48] – was still considered an innovation ('experimental procedure') at that time and was not covered by insurers.[49]

[46]Amanda Faison, 'The Miracle of Molly' (*5280 Magazine* 2005) www.5280.com/2005/08/the-miracle-of-molly/ (accessed 28 July 2018).

[47]Jeffrey P Kahn and Anna C Mastroianni, 'Creating a Stem Cell Donor: A Case Study in Reproductive Genetics' (2004) 14 *Kennedy Institute of Ethics Journal* 81.

[48]As Faison states 'A bone marrow transplant, in which diseased cells are killed off and replaced with new donor cells, is the only cure for progressive bone marrow failure. But the procedure is risky at best. When Molly Nash was born, the success rate of a transplant from an unrelated donor was a dismal 18 percent. However, under the right circumstances, the success rate for transplants from a brother or sister was as high as 65 percent' (Faison [n 46]).

As Taylor notes, exemplary cases of innovative practice do not follow the linear model of basic research, to translation, to clinical research, and eventually to its application. Instead, innovative practice comes from thinking backward from a patient's perspective and forward from deep knowledge of how the body functions and interacts with the disease to challenge the limits of current therapeutic, preventive, and diagnostic interventions.[50] For those who believe innovative practice is ethically justified, novel and as yet untested interventions can be an option for patients who lack reasonable medical alternatives for their health conditions despite the uncertainty of such interventions in terms of risks and potential benefits.

Having introduced some exemplary cases of innovation, we now introduce our proposal of a refined definition of innovation for research ethics.

4. New non-validated practice

We propose to define innovative practice as *new non-validated practice*, that is, the first or recent use of diagnostic, therapeutic or preventive interventions that introduce a significant change, with an insufficient level of evidence of safety or efficacy for regular healthcare and with the main aim to benefit individual patients. Levine's definition of non-validated practice focuses only on non-validation (insufficient evidence of safety or efficacy) and leaves out the characteristic of novelty. We suggest that it is the conjunction of both novelty and non-validation that defines innovation in traditional research ethics. However, we agree with Levine and the Commission that innovation is a subclass of practice and not of research. Hence, we see our definition as a continuation and refinement of what we call the traditional research ethics view.

But before proceeding, we would like to explain the rationale for grounding our proposal on this view. Essentially, we think the traditional research ethics analysis of innovation harmonises with most of the current discussion in the literature of justification and regulation of innovation and yields a greater practical impact than other alternatives such as innovation as 'a grey zone' between research and practice or as a *sui generis* activity.[51] First, the defenders of innovation consider responsible innovation in certain circumstances not only ethically permissible medical practice for patients, but sometimes also an obligation on the part of doctors.[52] However, this does not mean uncritically defending the current way of regulating innovative care. For instance, Taylor[53] proposes to improve the current regulatory landscape with an

[49]Kahn and Mastroianni (n 47) 81.
[50]Taylor (n 2) 286.
[51]King (n 31) 573; Lotz (n 32) 447.
[52]London identifies this as a special category within a wider spectrum of innovation and names it 'innovation as emergent problem-solving' (London, 'Cutting Surgical Practice at the Joints' [n 1] 45–46).

independent oversight mechanism, which does not mistake innovative practice for research. Also, Sugarman argues that doctors have an obligation to incorporate innovation into sound research in a timely manner after experience with, at most, a few patients.[54] These authors also defend the position that innovation cannot be reduced to research, due to its complex nature.[55] Second, authors who meaningfully disagree with innovation's defenders also use the same meaning of innovative practice. These detractors argue that innovative practice should be prohibited on ethical grounds, and usually propose standard research protections as appropriate regulation for all non-validated interventions.[56] For instance, they claim that 'last chance' unproven interventions should only be accessible through research studies designed to evaluate the safety or efficacy of new interventions.[57] Third, the concept of innovation is used even under learning healthcare systems, in which the sharp distinction between research and practice of the current system is allegedly 'blurred'.[58] For instance, Faden et al.[59] explicitly use a similar definition of innovation or non-validated practice, as do the Commission and Levine.[60] Similar to Taylor,[61] they propose regulatory measures, such as oversight and systematic assessment of innovative practice and other practice that has not been rigorously evaluated. Moreover, they explicitly state that they will not simply expand the current review system for research to solve the problem of patients' underprotection from insufficient validated practice.[62]

[53]Taylor (n 2) 286.
[54]Sugarman (n 2) 945; ISSCR (n 1).
[55]George J Agich, 'Ethics and Innovation in Medicine' (2001) 27 *Journal of Medical Ethics* 295; Taylor (n 2) 286.
[56]Agich (n 55) 295.
[57]'6. Research of Unproven, "Last Ditch" Treatments: In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention to promote the patient's health or well-being, *but only if it is undertaken as a research study designed to evaluate its safety and efficacy*. *Repeated uses of an unproven intervention can only be justified as part of a research study* that fulfils all the protections in this Declaration' (Ezekiel J Emanuel, 'Reconsidering the Declaration of Helsinki' [2013] 381 *The Lancet* 1532, emphasis added). See also, Annette Rid and Ezekiel J Emanuel, 'Ethical Considerations of Experimental Interventions in the Ebola Outbreak' (2014) 384 *The Lancet* 1896.
[58]Nancy E Kass and others, 'The Research-Treatment Distinction: A Problematic Approach for Determining Which Activities Should Have Ethical Oversight' (2013) 43 *Hastings Center Report* s4.
[59]Ruth R Faden and others, 'An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics' (2013) 43 *Hastings Center Report* s16.
[60]'Health care institutions and clinicians are constantly adopting new practices, ranging from platforms to support clinical decision-making built on electronic health systems to minimally invasive and robotic surgery. These innovations are often introduced without systematic assessment of their impact, perhaps to avoid crossing the unwelcome and curious divide between practice and research. Our framework makes this distinction irrelevant to questions of oversight and provides reasons why health care institutions and professionals are obligated to accompany the introduction of such innovations – as well as practices that have never been rigorously evaluated – with a commitment to systematically learn about their effects on clinical outcomes, health care value, patients' experience, and heath disparities' (ibid s24–25).
[61]Taylor (n 2) 286.
[62]Faden and others (n 59) s24.

This brief summary of the literature shows that despite the differences on matters of justification and regulation, all the authors referred to above share the Commission's and Levine's concept of innovation.

Hence, to introduce our proposal of new non-validated practice, we now analyse its three core elements.

4.1. First or recent significant change ('new')

In Levine's analysis, the defining attribute of innovation is '[…] the lack of suitable validation of the safety or efficacy of the practice'.[63] However, we suggest that it is the conjunction of both novelty and non-validation that captures the specific meaning of the term innovation in traditional research ethics. Hence we first need to delineate the concept of novelty.

We stipulate that in the attribute we call 'novelty,' the term 'new' refers to the recent or first use of an intervention that introduces a significant change in the context of medical practice. Here, it is useful to differentiate 'significant change' from 'mere variation' or non-significant change[64] to avoid including meaningless changes in practice under the label of innovation. For example, medical powdered gloves have been extensively used since the 1990s due to concerns with HIV.[65] Replacing blue with indigo gloves would probably not be considered a significant change in most cases. However, a change from powdered latex gloves to nitrile or non-powdered latex gloves could be a significant change, and hence an innovation, given that latex allergies are a major concern.[66] More formally, one criterion proposed to distinguish between innovation and mere variation is that a change is significant if it entails a relevant modification in the benefit-harm profile of the use of an intervention, given a specified context.[67]

Furthermore, we use the term 'long-standing' as the logical opposite to 'new' in the sense that it does not refer to the recent or first use of an intervention that introduces a significant change. In our analysis, we mainly use 'new' and 'long-standing' as terms that refer to continuous time properties of objects (segments of time), not discrete time properties (points of time). We define novelty as the 'first or recent uses of an intervention' because something is new even if it has been used a few times. We cannot offer a precise limit to the use of the term 'new' and say how many uses it implies for something to become 'long-standing'. However, we believe this is a positive feature of our definition because it does not settle matters corresponding to

[63]Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 22.
[64]London, 'Cutting Surgical Practice at the Joints' (n 1) 31; ACOG Committee on Ethics (n 1) 1593.
[65]Timo Palosuo and others, 'Latex Medical Gloves: Time for a Reappraisal' (2011) 156 *International Archives of Allergy and Immunology* 234.
[66]Ibid.
[67]London, 'Cutting Surgical Practice at the Joints' (n 1) 31.

Table 2. 2D classification of medical practice characterised by validation and novelty.

Validation	Novelty New practice	Long-standing practice
Non-validated practice	*New insufficiently validated interventions* (***innovative practice***). *Examples*: The Farrows, Jim Gass, genomic sequencing for rare diseases, and the Nashes.	*Long-standing insufficiently validated interventions. Example*: routine episiotomy for vaginal birth in 2009[68]
Validated practice	*New sufficiently validated interventions*. *Example*: imatinib for chronic myeloid leukemia in early 2000s[69]	*Long-standing sufficiently validated interventions*. *Example*: amoxicillin for infectious diseases as of 2018[70]

justification and regulation *a priori*. Also, in our definition of new non-validated practice, we take as the ideal meaning of novelty uses of interventions that have not been used before anywhere at any time. In principle, this implies that 'new' or 'long-standing' are not a country, hospital, or department-specific concept. For instance, if a long-standing validated intervention is used for the first time in Argentina (even though it has been used for 30 years in the US), it may not constitute an innovation according to our definition of new non-validated practice. It could be rather an implementation of a long-standing validated intervention. Time, country or other specific uses of the concept of novelty might be useful for practical purposes, such as for regulation or evidence extrapolation from one specific context to another. However, they do not replace the ideal meaning of novelty.

Consequently, once we introduce novelty and non-validation as two necessary attributes of the definition of innovation, we obtain a classification of four different categories of 'practice' – still in the traditional research ethics sense – that is, the use of an intervention with the main aim to enhance patients' well-being (see Table 2). Within this classification, innovation refers to 'new insufficiently validated interventions.' The rest of the exemplary cases quoted in the table illustrate the remaining categories as we understand them.

Our first argument for an enhanced definition of innovative practice is that conflating novelty and validation is a semantic confusion that can lead to false implications. An example of conflating novelty and validation is the following statement by King: '[…] how does innovation differ from standard medical practice? By virtue of its novelty it lacks reasonable expectation of success'.[71] Admittedly, both concepts correlate in many interventions, just

[68]Guillermo Carroli and Luciano Mignini, 'Episiotomy for Vaginal Birth' (2009) 1 *The Cochrane Database of Systematic Reviews* CD000081.
[69]Brian J Druker, 'Perspectives on the Development of Imatinib and the Future of Cancer Research' (2009) 15 *Nature Medicine* 1149.
[70]R Sutherland, EAP Croydon and GN Rolinson, 'Amoxycillin: A New Semi-Synthetic Penicillin' (1972) 3 *British Medical Journal* 13.
[71]King (n 31) 574.

like the concepts of 'swan' and 'white' do in many cases of birds, but not in all. Hence, if we conflate the novelty of an intervention with its insufficient evidence, we incorrectly imply that either all new interventions used in practice are non-validated or all long-standing interventions are validated.

Second, even if novelty and non-validation are appropriately distinguished, defining innovative practice only in terms of 'non-validation' is still confusing. If Levine's 'non-validated practice' proposal is taken as equivalent to the definition of innovation in the Commission's sense, then cases of long-standing non-validated interventions, such as routine episiotomy – an incision of the perineum to facilitate the baby's birth – would fall under the category of innovation. However, no one would call routine episiotomy an innovation today, although it was introduced as such in the first half of the twentieth century.[72] Christine Grady puts forward a similar objection to long-standing 'off-label' uses of drugs.[73]

Third, we argue that our definition, and the classification for interventions used in practice that it implies (Table 2), help to avoid confusion and misunderstandings. On the one hand, it is crucial to distinguish new non-validated practice (innovative practice) from long-standing non-validated practice. Typically, the real-world problems of innovative practice are related to whether they should be used or not at all,[74] and if this is the case, when and how they should be made an object of sound clinical research. However, cases of long-standing non-validated practice, like the current use of routine episiotomy or long-standing 'off-label' uses, are different. The real-world problem is rather how to gather sufficient scientific evidence to establish a sufficiently validated harm-benefit profile of the intervention. Moreover, in the case of routine episiotomy, the relevant question is how to stop doctors from using accepted long-standing interventions when there is sound evidence that a practice lacks net clinical benefits.[75] These concerns can be extrapolated from routine episiotomy to other long-standing non-validated interventions, such as the off-label use of drugs or devices in reproductive and maternal health.[76] If this extrapolation is sound, it makes a distinction between new and long-standing non-validated practices even more useful.

On the other hand, it is also useful to distinguish between new and long-standing validated interventions to better understand the specific meaning of innovative practice for medicine. For instance, the drug imatinib for

[72]Carroli and Mignini (n 68) CD000081.
[73]Jeremy Sugarman, 'Ethics Rounds: Offering Patients Innovative Therapy: When Is It a Good Idea?' (*NIH VideoCast*, 1 February 2017) https://videocast.nih.gov/summary.asp?Live=21779&bhcp=1 (accessed 28 July 2018).
[74]Larcher, Turnham, and Brierley (n 1) 36.
[75]Carroli and Mignini (n 68) CD000081.
[76]Margaret O Little and Marisha N Wickremsinhe, 'Research with Pregnant Women: A Call to Action' (2017) 14 *Reproductive Health* 156.

chronic myeloid leukemia is an exemplary case of new validated practice in the early 2000s after rational drug design and sufficient validation from expedited multiphase randomised controlled trials.[77] Unlike the exemplary cases of innovation, imatinib did follow the linear model of basic research to clinical research and eventually to practice.[78] Therefore, it makes sense to talk about new validated interventions and distinguish them from exemplary cases of innovative practice such as the Farrows, Jim Gass, genomic sequencing for rare diseases, and the Nashes. In turn, we also argue that even though imatinib has been validated and has thus shown sufficient evidence for its regular use in healthcare for chronic myeloid leukemia in the early 2000s, its harm-benefit profile had not yet been fully established at that time. For instance, some rare adverse events are only known after long-standing use because they occur after thousands (or tens of thousands) of uses. Hence, long-standing validated interventions, such as amoxicillin for infectious diseases, usually have the advantage of a better-known harm-benefit profile than new validated practice.

Finally, with our classification we do not lose, but rather integrate and clarify, the insights of previous definitions of innovative practice. We resuscitate the Commission's intuition according to which it is important to highlight the attribute of novelty as the recent or first use of an intervention that introduces a significant change, since this is why new non-validated practice gets commonly confused with research. But we keep Levine's intuition that non-validation is a central attribute to distinguish in practice whether it is new or long-standing.

4.2. Insufficient evidence for regular healthcare ('non-validated')

Although 'validation' is an epistemic concept, 'insufficient validation for' is an ethical concept. Sufficient validation presupposes that an intervention has a sound level of scientific evidence of safety or efficacy for a certain use in certain contexts. Insufficient validation lacks this level of evidence. The proper task of ethics does not consist in establishing what this level of evidence is, but rather in justifying what reasonable agents can or are required to do given different levels of evidence, uses, and circumstances. Lastly, the preposition 'for' is a reminder of the contextual nature of validation, that is, an intervention can be sufficiently validated for certain uses and contexts, but not for others.

In our present analysis, we take as a working hypothesis the defender's position that restricts the term innovation to interventions that are insufficiently

[77]Druker (n 69) 1149; Krishnan V Chary, 'Expedited Drug Review Process: Fast, but Flawed' (2016) 7 *Journal of Pharmacology & Pharmacotherapeutics* 57.
[78]Taylor (n 2) 286.

Table 3. Evidence-based upper and lower conceptual bounds of innovative practice in medicine.

Type of practice	Level of evidence	Exemplary cases
Validated practice	• Sufficient level of evidence of safety and efficacy for regular healthcare.	• imatinib for CML from early 2000s to date.[80]
Upper bound: reasonable expectation of success for regular healthcare		
Innovation,[81] Non-validated practice,[82] New non-validated practice,[83] Innovative practice.[84]	• Insufficient level of evidence of safety and efficacy for regular healthcare. • Sufficient level of evidence of safety and efficacy for 'last chance' interventions.	• Successful: The Farrows, the Nashes (section 2). • Non-Successful: Jim Gass (section 2), bone marrow transplants for breast cancer.[85]
Lower bound: reasonable expectation of success for 'last chance' interventions		
Futile practice	• Sufficient level of evidence of no safety or efficacy for its use.	• Antifungals for myocardial infarction; CPR on a dead patient[86]

validated for regular healthcare, but sufficiently validated as 'last chance' interventions. Therefore, it is necessary to distinguish between regular healthcare and 'last chance' contexts. Most notably, the literature on regulation of innovation[79] characterises innovation as interventions with 'reasonable chances of success.' Here, they refer to a reasonable level of scientific evidence for the use of innovative care for individual patients with few or no acceptable medical alternatives. Note that, as Table 3 shows, both standards of reasonable expectations of success for regular healthcare and 'last chance' interventions set the conceptual upper and lower bounds of innovation. Conceptually, as soon as the upper bound is surpassed, an intervention is validated practice. In turn, when the lower bound is surpassed, an intervention is futile. To keep our definition of innovation as neutral as possible, we will distinguish futility in a narrow sense from potentially inappropriate practice as we explain below.

Table 3 only provides a rudimentary outline of possible conceptual upper and lower bounds of evidence levels for innovation in cases of 'last chance' interventions. This table represents the semantic fact that innovation is a relational or comparative concept,[87] that is, a concept that needs a fixed point or

[79]Sugarman (n 2) 945; ISSCR (n 1); Earl (n 2) 7.
[80]Druker (n 69) 1149.
[81]National Commission (n 14).
[82]Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 21.
[83]Mastroleo and Holzer, this paper.
[84]Earl (n 2) 7.
[85]ACOG Committee on Ethics (n 1) 1591.
[86]Gabriel T Bosslet and others, 'An Official ATS/AACN/ACCP/ESICM/SCCM Policy Statement: Responding to Requests for Potentially Inappropriate Treatments in Intensive Care Units' (2015) 191 *American Journal of Respiratory and Critical Care Medicine* 1325.
[87]London, 'Cutting Surgical Practice at the Joints' (n 1) 26.

baseline to be meaningful. In this case, the baseline of the concept 'innovation' is the relevant level of evidence of safety or efficacy of certain use of an intervention in a certain real-world context (validation). In what follows, we want to explore this characteristic in more depth. We will discuss three substantive basic questions regarding 'validation'. To do this, we will present the defenders' position that at least certain cases of new non-validated practice are ethically permissible. Nevertheless, our aim is not to give an original justification, but to show that our definition harmonises with this dominant view in the literature on innovation.

Our first question is about the appropriate level of evidence for regular healthcare use of interventions. Here, we want to explore the upper bound of innovation, that is, 'reasonable expectation of success' for regular healthcare. Interventions accepted in medical practice may fall short of an appropriate scientific validation.[88] That is, although they are regularly used, their harm-benefit profile remains underdetermined as to whether it provides net clinical benefit or not. However, this informed judgment can vary depending on what we consider adequate scientific methods of validation. Beauchamp and Saghai[89] conclude that the commissioners of the Belmont Report never specifically addressed under which conditions a medical intervention or a hypothesis is validated. The Commission knew that there is no universal gold standard of validation. Multi-phase randomised controlled trials seek to systematically identify risks and adverse effects and assure that treatments that are to be approved are shown to be safe and effective.[90] However, the scientific community usually accepts that sufficient validation of an intervention is not obtained only through the multi-phase trials system.[91] In fact, from a point of view of evidence-based medicine, 'RCTs have never monopolized medical knowledge production'.[92] Hence, there seem to be good reasons not to consider randomised controlled trials as a *universal* gold standard, but rather to adopt a case-by-case approach applying different research methods and methodologies to appropriate circumstances.[93] This latter position does not deny that in many cases, multi-phase randomised controlled trials are the appropriate standard of scientific validation. However, even if reasonable agents disagree about the appropriate level of evidence for validated practice or the methods of validation for the context of regular

[88]Beauchamp and Saghai (n 20) 49–50.
[89]Ibid 45.
[90]Achim Rosemann, Gabriela Bortz and Federico Vasen, 'Regulatory Developments for Nonhematopoietic Stem Cell Therapeutics: Perspectives From the EU, the USA, Japan, China, India, Argentina, and Brazil' in Xiao-Dong Chen (ed), *A Roadmap to Non-Hematopoietic Stem Cell-Based Therapeutics* (Academic Press 2019).
[91]M Diaz and D Neuhauser, 'Pasteur and Parachutes: When Statistical Process Control is Better Than a Randomized Controlled Trial' (2005) 14 *BMJ Quality & Safety* 140.
[92]Laura E Bothwell and others, 'Assessing the Gold Standard — Lessons from the History of RCTs' (2016) 374 *New England Journal of Medicine* 2175.
[93]Nancy Cartwright, 'Are RCTs the Gold Standard?' (2007) 1 *Biosocieties* 11.

healthcare, they must agree if they rationally accept our definition, that innovative practice refers to the category of interventions that fail to reach that level.[94]

Our second question concerns the appropriate level of evidence for 'last chance' uses of interventions in medical practice. In the literature, the term 'last chance' refers to interventions for patients with serious conditions and unmet health needs. But 'last chance' is not a synonym of a particular regulatory pathway of accessing innovative practice. Here, we want to examine the lower bound of evidence of innovation identified by the principle of 'reasonable expectation of success'. Translated into more contemporary research ethics language, this refers to an appropriate evidence level regarding the harm-benefit profile of an intervention for individuals who lack other reasonable alternatives. From the point of view of justification and regulation, this is a substantive issue. As stated by Sugarman,[95] the lack of reasonable medical alternatives for an individual goes along with a changed evaluation of the harm-benefit profile of an insufficient validated intervention compared to its use in regular healthcare. For the defenders, the fact that an individual has no alternative intervention can make a 'last chance' intervention *ex ante* a reasonable choice provided certain conditions are met, among them scientific validity. As in the case of validated practice for regular healthcare, the question about the sound level of evidence for 'last chance' interventions remains open. Authors engaged in the 'the right to try' debate, argue that for terminally ill patients, it should be the successful preliminary prospect of an intervention or, e.g. the successful approval of a phase I trial, or in some exceptional cases, just a reasonable scientific rationale and some relevant evidence.[96] According to the ISSCR guidelines, the assessment of the expected success of a stem cell intervention should include any preclinical evidence of safety and efficacy.[97] Furthermore, Sugarman[98] and the ISSCR[99] guidelines put forward that this should be complemented by a justification of why an innovative intervention is used instead of other existing alternatives. Behind this multiplicity of epistemic standards and proposed regulations, most defenders of innovation seem to agree that all reasonable agents should accept that innovative practice must be evaluated by informed judgments, based on detailed literature knowledge and reasonable peer agreement, about the merits of the interventions.[100]

[94]London, 'Cutting Surgical Practice at the Joints' (n 1) 19.
[95]Sugarman (n 2) 945.
[96]Rebecca Dresser, *Silent Partners: Human Subjects and Research Ethics* (Oxford University Press, 2016) Ch 6 ('Terminally Ill Patients and the "Right to Try" Experimental Drugs'); Julian Savulescu, 'Press Release "Vale Charlie"' (n 3).
[97]ISSCR (n 1), recommendation 3.4.
[98]Sugarman, 'Questions Concerning the Clinical Translation of Cell-Based Interventions under an Innovation Pathway' (n 2) 945.
[99]ISSCR (n 1).

Finally, we wish to distinguish between futile and potentially inappropriate interventions. Following Bosslet et al., an intervention is futile in a narrow sense if it cannot accomplish the intended physiological goals, for example, administering antifungals as treatment for an acute myocardial infarction or cardiopulmonary resuscitation (CPR) on a patient with signs of irreversible death (rigour mortis, dependent lividity).[101] This narrow definition of futility precludes reasonable disagreement, but doctors should still care about patients and family perceptions if non-reasonable disagreement remains. This justifies the fact that, in general, responsible doctors should not administer futile interventions in this narrow sense for ethical reasons of non-maleficence, stewardship of social resources, and integrity.[102] However, there may be room for ethically permissible use of futile intervention in very limited situations, such as futile CPR for reasons of care towards the patient's family or other patients.[103] Hence, our use of futile interventions in a narrow sense is morally neutral, which is consistent with the neutrality of the definition of innovative practice (see Figure 1). In turn, an intervention is potentially inappropriate if it has at least some chance of accomplishing the effect sought, but competing ethical considerations may justify refusing to provide the intervention. For example, it is potentially inappropriate to initiate dialysis in a patient in a persistent vegetative state.[104] Competing ethical considerations may be summarised in harm for patients *or* for others.[105] As Bosslet et al.[106] clarify, whether an intervention is potentially inappropriate is not only a technical judgment but a value judgment. Appropriate evidence and technical facts are necessary conditions for informed and reasonable judgment, but they have to be interpreted in relation to the patients' best interest, the patients' (or surrogates) values, and society's rules of fairness. Therefore, reasonable disagreement among the parties is possible and should be managed by a 'fair process' of conflict resolution that could either favour the doctors' or the patients' (or surrogates') perspective.

If our exemplary cases are true cases of innovation, then their harm-benefit profiles show, in our definition, an insufficient level of evidence for their regular use in healthcare at or over a specific time period. However, even if the harm-benefit profile of an intervention shows insufficient level of evidence

[100]London, 'Cutting Surgical Practice at the Joints' (n 1) 30.
[101]Bosslet and others (n 86) 1325.
[102]Ibid 1327.
[103]Robert D Truog, 'Is It Always Wrong to Perform Futile CPR?' (2010) 362 *New England Journal of Medicine* 477; David Choma, Kerri Cavanaugh and Jamie Dwyer, 'Is It Always Wrong to Perform Futile CPR? [Replies to Truog]' (2010) 362 *New England Journal of Medicine* 2034.
[104]Bosslet and others (n 86) 1324.
[105]Dominic Wilkinson, Stavros Petrou, and Julian Savulescu, 'Expensive Care? Resource-Based Thresholds for Potentially Inappropriate Treatment in Intensive Care' (*Monash Bioethics Review*, January 2018) https://doi.org/10.1007/s40592-017-0075-5 (accessed 28 July 2020).
[106]Bosslet and others (n 86) 1318.

regarding safety and efficacy for regular use, such interventions may or may not show sufficient level of evidence to be used as a 'last chance' intervention. If responsible innovation is ethically permissible as the defenders argue, then new non-validated practice can still be a *reasonable* option in a limited number of cases if they have a sound scientific rationale and meet other appropriate conditions. The cases of Matthew Farrow or Molly Nash may meet such rationale. Refining the concept of innovation with explicit upper and lower bounds of evidence and introducing the category of potentially inappropriate practice allows us to deal with hard cases such as Jim Gass. In table 3, we suggest that, from a morally neutral point of view, the case of Jim Gass is neither a futile intervention nor validated practice. From a moral stance, Jim Gass seems to be a paradigmatic case of potentially inappropriate practice because it did not comply with relevant ethical principles for use of innovative care.[107] Unfortunately, we cannot explore the details of the case at this point. However, interpreted as an exemplary case of innovation, the case of Jim Gass shows why a good definition of innovation should be morally neutral. We want to evaluate the ethical status of cases such as Jim Gass, but we first need a definition that captures what it is a case of, since different activities have different ethical principles, as we shall argue in the next section. In turn, our proposal also harmonises with the literature that counts first or recent uses of unsuccessful interventions such as bed rest, bone marrow transplants for breast cancer, and diethylstilbestrol to prevent miscarriages, as exemplary cases of failed innovation.[108] Here, we depart from the view that 'improvement' should be considered a definitional attribute of 'genuine' innovation.[109] Our neutral definition captures all responsible or irresponsible and successful or failed cases of new non-validated interventions.

4.3. Intention to benefit individual patients ('practice')

In the last part of our analysis, we state that if the use of new insufficiently validated interventions is regarded as innovative practice, then the intention or main aim of such activity should be to benefit individual patients. This formulation is roughly equal to others in the literature such as the promotion of 'patients' well-being'[110] or patients' best interests.[111] In traditional research ethics this means that innovation is practice, not research.

[107]ISSCR (n 1); Holzer and Mastroleo, 'Innovative Care in Latin America' (n 2) 145.
[108]ACOG Committee on Ethics (n 1) 1591.
[109]London, 'Cutting Surgical Practice at the Joints' (n 1) 19.
[110]National Commission (n 14).
[111]Julian Savulescu, 'Appendix 2, Savulescu's View' in Dominic Wilkinson and Julian Savulescu (eds), *Ethics, Conflict and Medical Treatment for Children: From Disagreement to Dissensus* (Elsevier 2018) www.ncbi.nlm.nih.gov/books/NBK537986/ (accessed 28 July 2020).

Here 'intention' refers to a goal or aim to which an action is directed, that is, the intention with which someone acts.[112] Intentional action neither presupposes success in achieving its aim, nor always is based on conscious reflective judgments at the time of acting.[113] However, intention presupposes basic capacities of responsible agents, that is, agents that have the capacity of planning for the future and the capacity of giving reasons for actions according to adequate principles.[114]

The traditional research ethics' distinction between research and practice is based on two main aims, (P2) the promotion of 'well-being of patients' and (R2) the contribution or development of 'generalizable [scientific] knowledge'.[115] Hence, practice and research are defined as two different intentional activities. In turn, a different intention entails different principles for the ethical evaluation and different harm-benefit analysis of those activities.[116]

We should note that aiming at both patients' well-being and generalisable scientific knowledge is possible in certain circumstances. The priority of one of these aims does not imply the exclusion of the other. For instance, in the case of Matthew Farrow, the same intervention promoted the well-being of an individual patient and contributed to the generation of generalisable scientific knowledge.[117] However, hitting two birds with one stone is not always feasible or desirable. The development of generalisable scientific knowledge (research) requires systematisation and planning. In turn, systematisation and planning require time, special skills, and exclusive resources on top of whatever resources would be otherwise used for patients' care. Consequently, doing research may also carry an inherent potential for significant delay in promoting patients' well-being.[118] This explains why some authors argue

[112]Kieran Setiya, 'Intention' in Edward N Zalta (ed), *The Stanford Encyclopedia of Philosophy* (Metaphysics Research Lab, Stanford University 2015) https://plato.stanford.edu/archives/sum2015/entries/intention/ (accessed 11 November 2018).

[113]Thomas Scanlon, *What We Owe to Each Other* (Harvard University Press, 1998) 23.

[114]Ibid 21–22.

[115]For our conceptual analysis, we will interpret 'design' in the Belmont Report as the intention of an activity (Bernard A Schwetz, interview with Robert J Levine, 'Oral History of the Belmont Report and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research' (New Haven, 14 May 2004) www.hhs.gov/ohrp/education-and-outreach/luminaries-lecture-series/belmont-report-25th-anniversary-interview-rlevine/index.html [accessed 28 July 2020]). National Commission (n 14); Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 21.

[116]For completeness and economy of our conceptual analysis, it is useful to introduce self-interest as a third aim any act from a rational responsible agent may have (Taylor [n 2] 286). This allows us to formulate undue marketing or commercialization of new non-validated practice, a common concern in ethical frameworks, as inappropriate prioritization of self-interest over patient well-being and the commitment to contribute to generalizable scientific knowledge (e.g. ACOG Committee on Ethics [n 1] 1589; ISSCR [n 1] 25). However, to further simplify this analysis, here we will leave out problems of inappropriate self-interest. Charles Weijer, 'The Ethical Analysis of Risk' (2000) 28 *The Journal of Law, Medicine & Ethics* 344; Joe Brierley and Vic Larcher, 'Compassionate and Innovative Treatments in Children: A Proposal for an Ethical Framework' (2009) 94 *Archives of Disease in Childhood* 651.

[117]Eliane Gluckman and others, 'Hematopoietic Reconstitution in a Patient with Fanconi's Anemia by Means of Umbilical-Cord Blood from an HLA-Identical Sibling' (1989) 321 *New England Journal of Medicine* 1174.

[118]Taylor (n 2) 290.

that the duty to validate innovative practice should fall on research institutions rather than individual clinicians.[119]

Even if we characterise innovation as a learning activity, it may also entail a potential loss in patients' clinical benefit.[120] For our purpose of defining innovative practice, it is enough to show that in some cases different uses of interventions may entail prioritisation and trade-offs between the well-being of patients and the development of scientific knowledge. Our aim in this paper is not to assess the ethical justification of such trade-offs (if any) or their regulation.

In turn, having the intention or main aim to benefit patients does not imply doing so in a responsible way. Responsible innovation is using new non-validated practice following certain principles. For instance, defenders of innovation consider that moving new non-validated practice into sound research should be an essential ethical requirement of responsible innovation.[121] This ethical requirement can be seen as a form of bridging the gap between practice (main aim to benefit patients) and research (main aim to contribute to generalisable knowledge). For the defenders, innovative practice must remain the exceptional case to avoid undermining public trust, exploiting patients' hope and delaying sound research.[122] This latter obligation is described in the literature as the 'commitment to contribute to generalizable knowledge'[123] and is also present in the Belmont Report[124] and the Declaration of Helsinki.[125] However, as the literature shows, there are obstacles to operationalising this ethical requirement in real-world situations. For instance, lack of research infrastructures in new fields of medicine, lack of specific oversight structures for new non-validated practice, prohibition of national research funding in certain clinical areas (e.g. embryo research), etc.[126] Also, it remains unclear who should bear the duty of this ethical requirement.[127]

Also, for the defenders of innovative practice, instrumental rationality sets further limits on the responsible use of new non-validated practice. This can be captured by the concept of opportunity or 'right circumstances'.[128] Right circumstances comprise the right timing (not too early … not too late) and proper measures, usually judged from the perspective of an expert.[129] On

[119]Victor Laurion and Christopher Robertson, 'Why the Duty to Research Falls on Institutions Rather Than Individuals' (2019) 19 *The American Journal of Bioethics* 44.
[120]Faden and others (n 59) s21.
[121]Laurion and Robertson (n 119) 44.
[122]ISSCR (n 1).
[123]Sugarman (n 2) 945; ISSCR (n 1).
[124]National Commission (n 14).
[125]WMA (n 18) [37].
[126]Taylor (n 2) 286; ACOG Committee on Ethics (n 1) 1592–93; Rosemann, Bortz, and Vasen (n 90).
[127]Laurion and Robertson (n 119) 44.
[128]Taylor (n 2) 286.
[129]Hunter W Stephenson, *Forecasting Opportunity: Kairos, Production, and Writing* (University Press of America 2005) 1.

the one hand, individual patients with unmet health needs and serious conditions have a limited period of time or 'window of opportunity', if any, during which some intervention can be expected to promote their well-being. On the other hand, new knowledge and technology may entail potential uses that fit those unmet health needs, yet be still insufficiently validated for regular use. Opportunities for use of innovative practice lie in the fortunate intersection or right timing of both circumstances, 'or not at all'.[130] The creative response of doctors, but also of informed patients or relatives, rests not only in realising but also anticipating the existence of such opportunities. However, under the typical high levels of uncertainty, limited prospect of relief and the potential harms around these decisions, it is equally reasonable to accept human mortality and plan for a good end.[131]

Moreover, one important aspect of the attribute 'intention' is its connection to the discussion on the justification and regulation of innovation with the adequate harm-benefit analysis. For the defenders, interventions considered as innovations in a traditional research ethics' sense should be subject to a harm-benefit profile evaluation according to the standards of medical practice. Medical practice is an activity in the best interest of the patient, and not according to the best interest of research.[132] For instance, if the new non-validated intervention is the only reasonable intervention for unmet health needs of serious conditions, the defenders argue that high risks can be reasonably accepted, even outside of sound research. However, if an intervention is potentially inappropriate, although its use could otherwise contribute to the benefits of future patients or generalisable scientific knowledge, the defenders may argue that responsible doctors should discourage or refuse it. If our conceptual analysis is sound, this shows that novelty or insufficient validation of an intervention for regular healthcare use are not enough to determine whether something is a new non-validated practice. It is the main aim of an intervention – to benefit an individual patient or to develop scientific knowledge – which entails different thresholds of harm-benefit analysis and ethical evaluation, as shown in traditional research ethics and the authors that are based on its intellectual work.[133]

Finally, to show the importance of the attribute of intention in our definition of new non-validated practice, we close this section with three exemplary types of new non-validated practice. Current regulations allow for these medical practices because their intention is to benefit individual patients with no other reasonable options. Hence, these activities are exempt from clinical research regulations as such. These cases show that neither the levels of risk nor the lack of validation are necessary conditions

[130]Larcher, Turnham and Brierley (n 1) 36.
[131]Ibid.
[132]Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 21.
[133]Weijer (n 116) 344; Brierley and Larcher (n 116) 651; ISSCR (n 1).

for an intervention to be regarded as research – some arguing it ought to be different.[134]

First, it is the use of an intervention under expanded access (sometimes called 'compassionate use'), that is, an exceptional use of an intervention outside of sound research aimed to promote patients' well-being.[135] For example, expanded access during phase 3 clinical trial of imatinib allowed some ineligible patients to access the drug given their urgent medical needs and lack of alternatives. It might be the case that expanded access was riskier than well-designed research. Still, as currently practiced, expanded access can be considered as type of new non-validated practice, and not research.[136]

Second, some cases of post-trial access to investigational beneficial interventions, such as multiple antiretrovirals for HIV/AIDS in the late 1990s[137] or again imatinib in the early 2000s,[138] serve as examples of the use of new insufficiently validated interventions for the benefit of individual patients with no reasonable alternative. Post-trial access differs from expanded access in the sense that it is restricted only to former participants of a research study.[139] Post-trial access to new non-validated practice may be riskier for different groups of participants.[140] However, not every case of post-trial access would be a case of new non-validated practice. Post-trial access to new non-validated interventions should be called 'non-validated' only until an intervention becomes *new validated*, that is, when it reaches the level of safety and efficacy for regular healthcare use.[141] Likewise, most of the research regulations in countries where they are available consider that post-trial access to a beneficial intervention is an exceptional medical activity with the aim to benefit former participants, not research.[142]

[134]Emanuel (n 57) 1532.
[135]Levine, 'The Nature, Scope, and Justification of Clinical Research' (n 38) 217.
[136]Food and Drug Administration (FDA), 'Expanded Access' (2018) www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm (accessed 4 December 2018).
[137]Sean Emery and David A Cooper, 'Drug Companies Have a Duty to Continue Treatment' (1997) 314 *BMJ: British Medical Journal* 889.
[138]Gina Kolata, 'Slowly, Cancer Genes Tender Their Secrets' *The New York Times* (New York, 27 December 2005) www.nytimes.com/2005/12/27/health/slowly-cancer-genes-tender-their-secrets.html (accessed 13 August 2018).
[139]*MRCT Center Post-Trial Responsibilities Framework Continued Access to Investigational Medicines I. Guidance Document* (MRCT Center 2017) http://mrctcenter.org/wp-content/uploads/2017/12/2017-12-07-Post-Trial-Responsibilities-Guidance-Document-Version-1.2.pdf (accessed 28 July 2020); Yoram Unguru and others, 'Ethical Issues for Control-Arm Patients after Revelation of Benefits of Experimental Therapy: A Framework Modeled in Neuroblastoma' (2013) 31 *Journal of Clinical Oncology* 641; Ignacio Mastroleo, 'Post-Trial Obligations in the Declaration of Helsinki 2013: Classification, Reconstruction and Interpretation' (2016) 16 *Developing World Bioethics* 80 http://doi.wiley.com/10.1111/dewb.12099 (accessed 28 July 2020).
[140]Given that an intervention has been shown beneficial for the active arm of a study, it does not necessarily follow that the very same intervention as post-trial access would be beneficial to the patients of the control group with a more advanced stage of disease (see the neuroblastoma case in Unguru [n 139] 641).
[141]MRCT Center (n 139) 13, figure 1 'Post-Trial Responsibilities along investigational medicine approval pathway: from clinical trials to general access'.
[142]Ibid 74–75.

Third, novel 'off-label' uses, that is, first or recent unapproved uses of an approved product by a regulatory authority, are also cases of innovation as new non-validated practice, until these uses show a sufficient level of validation for regular healthcare. An example is the successful use of ustekinumab, a biological product approved for psoriasis, in a 19-year-old patient with an immunodeficiency (leukocyte adhesion deficiency type 1 or LAD1) who previously showed a high risk of losing all his teeth and an intractable nonhealing wound in his lower back.[143] Research regulatory authorities recognise the intention of the activity as different from research. Regulatory authorities use formulations such as 'when the intent is the practice of medicine' or 'in the best patient interest' to justify such uses in contexts where there are no reasonable alternative options.[144]

The above stated examples illustrate that the intention to benefit an individual participant is a necessary attribute of the definition of innovation in traditional research ethics and our refined definition. To give those examples, we have presented the defenders' view that at least some cases of expanded access, post-trial access and novel 'off-label' uses are ethically permissible and responsible if they comply with certain ethical principles and institutional policies. However, both detractors and defenders of innovation may find our proposal useful. It shows our definition of innovation as new non-validated practice can unify, under one single concept, activities that might have been considered unconnected. Hence, we believe that our refined definition of innovation is important to further discuss the justification and regulation of these and other activities that can potentially be identified as new non-validated practice.

5. Conclusion

In this paper, we proposed an enhanced definition of innovation as new non-validated practice. We argued that this is a better term for referring to the first or recent use of interventions that introduce a significant change, with an insufficient level of evidence of safety or efficacy for regular healthcare, and with the main aim to benefit individual patients. The objective of the paper has been to develop this definition as well as to gain rational acceptance for our proposal. We acknowledge that to forge consensus on new language use in medicine may take time. In the meantime, authors, research authorities, and other stakeholders should explain precisely what they mean when using

[143]Niki M Moutsopoulos and others 'Interleukin-12 and Interleukin-23 Blockade in Leukocyte Adhesion Deficiency Type 1' (2017) 376 *New England Journal of Medicine* 1141; Jeremy Sugarman, 'Ethics Rounds: Offering Patients Innovative Therapy: When Is It a Good Idea?' (n 73).

[144]FDA, '"Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices' (2018) www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm (accessed 13 August 2018).

the term innovation and the like.[145] Our urge to propose a better definition of innovative practice for medicine is motivated by our awareness of the real-world consequences that it has on patients, science, and public health. Just as the members of the National Commission did, we care about the appropriate use of language because it is necessary for the evaluation of responsible action, the prevention of confusion and the maintenance and promotion of public health.[146]

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[145]Lilford (n 5).

[146]Confucius, *Analects: With Selections from Traditional Commentaries* (Edward Slingerland tr, Hackett Publishing Company, Inc. 2003) analect 13.3; Levine, 'Clarifying the Concepts of Research Ethics' (n 25) 25.