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The grey zones of technological innovation: negative unintended consequences as a counterbalance to novelty

Maureen McKelvey [a] and Rögnvaldur J. Saemundsson [a,b,c]

[a]Institute of Innovation and Entrepreneurship, Department of Economy and Society, School of Business, Economics and Law, University of Gothenburg, Gothenburg, Sweden; [b]Innovation Management Department, Halmstad University, Halmstad, Sweden; [c]Department of Industrial Engineering, University of Iceland, Reykjavik, Iceland

ABSTRACT

The purpose of this article is to better understand the challenges of avoiding the dark side of technological innovation. Specifically, we analyse 10 public investigations started as a reaction to a major crisis in regenerative medicine at the Karolinska Institute, Sweden, associated with the clinician-scientist Paolo Macchiarini. We interpret the reaction as an attempt to restore the balance between the stimulation and regulation of technological innovation processes by clarifying ambiguities in the regulation at the interface between research and practice. We conceptualise these ambiguities as grey zones – situations when it is unclear if the benefits of experimentation outweigh its risks – and propose that grey zones are continually created and resolved as actors in innovation governance systems counterbalance the generation of novelty and the risk of negative unintended consequences.

KEYWORDS

Innovation governance; negative unintended consequences; grey zones; medical innovation; innovation policy

1. Introduction

Technological innovation has both positive and negative impacts upon society (Stirling 2017). While the negative impacts are in this special issue referred to as the dark side of innovation one might (with implicit reference to the movie Star Wars) refer to the positive impacts as its light side. The new knowledge generated as outcomes of scientific, technological and innovation processes can lead to great benefits for society – such as increasing living standards through improved food safety or new medical procedures – but the process itself, which is inherently a process involving trial-and-error, may expose people, or the environment, to undue risks or even harm (Moreno 2001). The purpose of this article is to better understand the challenges of avoiding the dark side of technological innovation. We explore how actors in the innovation governance system counterbalance the stimulation of novelty for future benefits for society with the regulation of novelty, in order to avoid the risk of unintended consequences.

Let us first consider why this issue matters, when we consider the relationship between public policy and innovation governance. The rationale for public policy makers to spend money to stimulate science, technology and innovation is the expectation of future

CONTACT Rögnvaldur J. Saemundsson rjs@hi.is University of Iceland, Hjardarhagi 4-6, 107 Reykjavik, Iceland

positive effects, such as improving living standards or solving societal challenges (Mazzucato 2018). In this positive view, society benefits from science and technology in the long-run through the introduction of new products like the iPhone, new services like microloans, new clinical practice to cure malaria, and new organisational forms to bring ideas to market through entrepreneurship. Specifically, the type of public policy that we are interested in here relates to science, technology and innovation, often known as innovation policy (Borrás and Edquist 2019). Following previous research, innovation policy is here defined as public policy intended to stimulate the creation and use of new scientific and technical knowledge, due to its potential future benefits for society, by promoting collaboration among multiple actors involved in developing science, technology and innovation, such as universities, research institutes, industrial firms, and user communities (Edler and Fagerberg 2017). Contributions also analyse how collaboration occurs, when the development of science, technology and innovation relies upon diverse types of actors, which each have their own aims and incentives for participation (McKelvey, Zaring, and Szücs 2019). The broader concept of innovation governance is used to denote how these different types of actors, together with public regulatory authorities, shape how innovations are produced, introduced, and diffused by collectively regulating issues of societal concern (Borrás and Edler 2014). As the stimulation of science, technology, and innovation are issues of societal concern, especially for medical innovation (McKelvey, Saemundsson, and Zaring 2018), we explicitly include it as a part of innovation governance.

We have chosen to study a major crisis within medicine, more specifically in regenerative medicine in Sweden. The crisis, associated with the clinician-scientist Paolo Macchiarini, played out at the prestigious Karolinska Institute – the home to the Nobel Prize in Medicine – and sparked a public outcry due to the belief that the involved clinician-scientists had overstepped ethical boundaries in their search for novel treatments. We consider the crisis as a focusing device that we use to analyse the dynamics of innovation governance more generally. Crises within science, technology and innovation tend to lead to public concerns about the negative effects and associated risks of innovation, which in turn promote additional demands for more inclusive, responsible and transparent innovation processes (Stilgoe, Owen, and MacNaghten 2013). Hence, the empirical study enables us to analyse the deliberations and reactions of actors in an innovation governance system that find themselves needing to respond to negative unintended consequences of a strong stimulation for research excellence and major industrial impact. We propose an extension of the concept of grey zones – which we define as situations when it is unclear if the benefits of experimentation outweigh its risks. We also propose that grey zones are continually created and resolved as innovation governance systems counterbalance the generation of novelty and the risk of negative unintended consequences.

2. Conceptual framework

This section discusses and defines relevant concepts and relationships for the conceptual framework guiding our study, which is based on three components, namely: a conceptualisation of innovation governance; an evolutionary perspective on the

generation and use of new scientific and technical knowledge; and the empirical setting of medical innovation. At the end, we visualise our framework.

Our first component is a definition of innovation governance. From a broad interdisciplinary perspective, Borrás and Edler (2014) define innovation governance as how actors involved in the development of science, technology and innovation collectively regulate issues of societal concern by shaping how innovations are produced, introduced, and diffused in society. Thus, one starting point here is that the innovation governance system has two purposes, namely to stimulate and to regulate innovation processes.

Innovation researchers have long held that innovation is an uncertain and complex process because it relies upon mutual interactions and knowledge flows across private actors like firms, societal actors like universities, non-profit organisations and professional societies, as well as public actors like government agencies (Fagerberg, Mowery, and Nelson 2005). From this stream of literature, we extract the broad notion that actors involved in innovation governance attempt to both stimulate and regulate the generation and use of scientific and technical knowledge useful for innovation. We also note that innovation governance is complex, in the sense that a wide variety of actors are involved, each with their different aims and different ideas of which issues are of societal concern. Furthermore, the uncertainty about the outcomes of innovation processes – especially if they are related to emerging science and technology – require some forms of tentative governance that is revised as new knowledge becomes available, e.g. about negative unintended consequences (Kuhlmann, Stegmaier, and Konrad 2019).

Therefore, in this paper, we define innovation governance as a dynamic, systemic, multi-level process involving diverse sets of actors – which may be directly engaged in, or external to, the innovation process – and which are concerned with the stimulation and regulation of innovation. This builds upon McKelvey, Zaring, and Szücs (2019), which articulates the collective action and public resource pools as well as monitoring problems in the development of science and technology involving multiple actors. Analysing the institutions and monitoring aspects of the innovation governance system is important, because both the public sector and the private sector are investing money into research and development for science and technology. The public sector wants new knowledge which can be diffused widely and improve society, whereas the private sector is primarily concerned with developing and using such knowledge to generate profits through innovations. This perspective has been applied to medical research and innovation specifically. McKelvey, Saemundsson, and Zaring (2018) define in more detail what constitutes collective action at the intersection between medical research and clinical practice. They argue collective action for medical research is particularly difficult to regulate because it usually takes place in collaboration between universities, university hospitals, and industrial firms. Moreover, they propose a distinction between self-regulation by the actors involved in medical research and clinical practice as compared to external regulation by government agencies and similar.

Therefore, we follow a definition from McKelvey, Zaring, and Szücs (2019) and also used for medical innovation in McKelvey, Saemundsson, and Zaring (2018). Here, we conceptualise that collective action and public resource pools are created jointly by public and private actors. Furthermore, these diverse actors develop norms, incentives and institutions, to support the interaction required for the collective action to be successful

and which also helps monitoring and regulating undesirable behaviour not conforming to the common interests of the actors involved.

Summarising our first component, we define innovation governance as attempts by diverse set of actors to stimulate and regulate the generation and use of new knowledge involved in science, technology and innovation processes. Thus, we see innovation governance as involving two separate goals, namely on the one hand stimulating science, technology and innovation as collective action due to the expected future benefits and, on the other hand, the regulation of the collective action process to avoid undesirable behaviour. Furthermore, we acknowledge the tentative and dynamic nature of innovation governance, especially in the context of emerging science and technology.

Our second component is an evolutionary theoretical perspective applied to the generation and use of new scientific and technical knowledge. At the most general level, an evolutionary perspective for social sciences is concerned with how the characteristics of entities evolve as the entities adapt to their environment, and usually involves a framework specifying the generation of variety, selection processes and the retention of elements selected (Campbell 1987; Nelson and Winter 1982). In relation to our topic of scientific and technical knowledge useful for innovation, we draw upon a stream of literature that has connected the evolutionary process of variety generation and selective retention to the process of problem solving (Consoli et al. 2016; Kline and Rosenberg 1986; Thomke, von Hippel, and Franke 1998; Vincenti 1990). Central to this perspective is the idea that innovations based on new scientific and technical knowledge derive from an inherently uncertain process of problem-solving, i.e. a series of repeated trials of potential solutions to a given problem. Such repeated trials lead to results which are used, in combination with insights about where possible solutions are to be found, in order to revise or refine the solutions, and the process continues until an acceptable result is reached. Thus, even if the process is uncertain the generation of variety is not blind as conceptualised in Darwinian evolution but rather Lamarckian as it is guided by insights by people as to where possible solutions are to be found (Hodgson 2015; McKelvey 1996).

But where do the insights come from that guide the actors involved in these repeated trials for possible solutions and generate variety? A first aspect to consider is the relationship to theory and practice. Following Fleming and Sorenson (2004) we propose that there are two major classes of insights that guide the search for possible solutions. First, there are *theory-driven* insights based on generalisable scientific knowledge, which provides the equivalence of a map that predicts the feasibility and efficacy of particular set of solutions. With the help of the map, the actors can engage in search for possible solutions, which can be directed towards the most promising parts of the map. Second, there are *experience-driven* insights based on previous experience. This includes experience from solving similar problems where the search proceeds in incremental steps and the feasibility and efficacy of the direction taken are difficult to predict in advance. A second aspect in the literature is that theory and practice may involve different epistemological communities. In this view, there is a distance between research as science, and practice as technology. The former focuses on the creation and validation of generalisable knowledge and the latter focuses more upon solving specific practical problems (Nightingale 1998, 2004). Thus, the implications are that bridging research and practice requires the combined insights from theory-driven search (informed by science) and experience-driven search (informed by practice).

In order to combine theory-driven and experience-driven problem-solving processes in our conceptual framework, we rely on one specific contribution which conceptualises problem-solving as engineering design (Vincenti 1990). Engineering design may be informed by science (theory-driven), but is also heavily dependent on practice (experience-driven). Furthermore, Vincenti (1990) argues that in engineering design, different means are used for testing and selecting the variety that is generated. On one hand, direct trials in real-world settings are used, e.g. flying in a full-sized prototype airplane. On the other hand, indirect trials are used where the complexity of real-world settings is reduced, e.g. by using a simplified, or a virtual, version of the test object (miniature airplane in a wind tunnel) or by decomposing the original problem into more controllable sub-problems (testing full-size wings in a wind tunnel). Simplified or virtual solutions provide an incomplete and indirect way of interacting with reality but reduce the number of possible solutions that need to be tried under real-world settings, which are less controlled and where failure tends to have more dire consequences (Campbell 1987; Thomke, von Hippel, and Franke 1998; Vincenti 1990).

Thus, for this second component, we propose that the generation and use of new scientific and technical knowledge – which is the subject of innovation governance – is conceptualised as an evolutionary problem-solving process operating at the intersection between research and practice. We mean that at this intersection – where there is true uncertainty about future outcomes – the generation of variety is guided by a combination of theory-driven and experience-driven insights with the selection of variety through both direct or indirect trials. Our interpretation is that because direct trials tend to be less controlled, and take place in existing systems of practice, they usually pose larger risks of negative unintended consequences as compared to indirect trials.

Our third component relates the two components above to the empirical setting of medical innovation. Here, we can follow extant literature on medical innovation, which provides an evolutionary perspective on the generation and use of scientific and technical knowledge. Specifically, this literature stresses how and why medical research and clinical practices operate as separate, but co-evolving, epistemic communities that, taken together, shape the growth of knowledge of medical technologies and their use in clinical practice (Consoli and Mina 2009; Gelijns and Rosenberg 1994; Metcalfe, James, and Mina 2005; Morlacchi and Nelson 2011; Rosenberg 2009). Thus, equivalent to the distance between science and technology in the general innovation studies literature, the medical innovation literature has identified the epistemological distance between medical research and clinical practice. Moreover, the above distinction we made between direct and indirect trials is especially salient for medical innovation because direct trials, such as clinical trials, involve humans while indirect trials do not.

Specifically, this medical innovation literature has what we consider three main approaches to studying how the epistemological distance between medical research and clinical practice may be bridged. One stream of literature stresses that bridging occurs at the organisation level, specifically hospitals. This literature emphasises the centrality of hospitals in medical innovation – generally with a positive effect on innovation – where innovations include a wide range of new medical devices, pharmaceuticals, and clinical procedures (Hopkins 2006; Lander and Atkinson-Grosjean 2011; Thune and Mina 2016). Another stream of literature stresses that bridging occurs at the individual level of the scientist-clinician. This literature focuses upon the role of clinician-scientists, that are

jointly employed by hospitals and universities, and argue that these individuals help solves a perceived paradox of modern biomedicine, namely the limited impact that the molecular revolution has had on clinical practice (Lenfant 2003; Vignola-Gagné, Biegelbauer, and Lehner 2014). Finally, a third category of literature stresses the importance of clinical research as a set of activities. This literature is concerned that the prominence of theory-driven research in molecular biology and molecular genetics has led to a reduced emphasis on clinical research, which is more experience-driven and better connected to medical practice (Ahrens 1992; Gittelman 2016; Hirsch 1997). We combine the three approaches.

Thus, for this third component, we stress the importance of clinical research. We conceptualise that medical research and clinical practices operate as separate, but co-evolving, epistemic communities involved in the generation and use of new scientific and technical knowledge for medical innovation. These communities are bridged by clinician-scientists conducting clinical research in hospitals. Our rationale follows. The important role that hospitals play within science, technology and innovation processes is directly related to their organisational role as the venue for clinical research involving patients (direct trials). Such clinical research is performed by clinician-scientists, who may complement their research on patients in hospitals with laboratory research outside the hospital that involves computer simulations, animal models and cell systems instead of patients (indirect trials). Thus, we specify that individual clinician-scientists, through their joint appointment at a university and a hospital, are part of a collective action including both organisations. Through clinical research activities, the individual and organisational level meet in an attempt to generate and use new knowledge by bridging the epistemological communities of medical research and clinical practice in the context of the hospital and involving patients.

Taken together, we combine these three components into our conceptual framework, visualised in Figure 1.

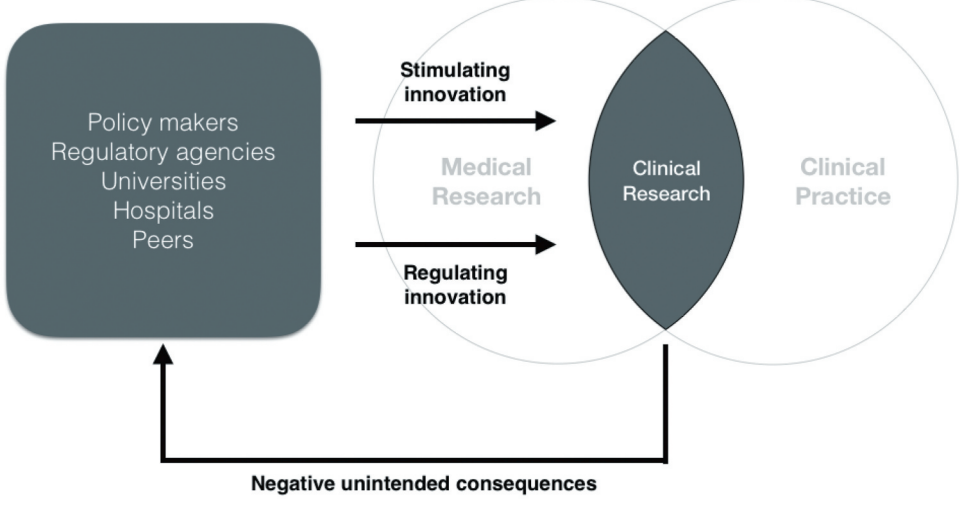

Figure 1. Conceptual framework guiding the study of the reaction to a recent crisis in regenerative medicine.

As shown in Figure 1, this paper is concerned with innovation governance for clinical research. We have defined clinical research narrowly, as the generation and use of new knowledge by clinician-scientists in the context of the hospital and involving patients. We conceptualise clinical research as related to both medical research and clinical practice, as shown by the overlap of the two circles. Therefore, the process of clinical research is seen as an evolutionary problem-solving process, where the generation of variety can be guided by theory-driven or experience-driven insights, but where selection is done through direct trials. This is regulated by the wider innovation governance system, which consists of policy makers, regulatory agencies, universities, hospitals and medical research peers. Innovation governance can include both the stimulation and regulation of clinical research activities, as represented by the two arrows in the middle. Furthermore, we propose that negative unintended consequences are not fully dealt with by existing regulation, which means that the system needs to react to them when they occur as represented by the arrow at bottom of the Figure.

3. Methodology

Our research design is a longitudinal single case study of a crisis related to innovation governance. We chose a single case study design because the selected case is both extreme and complex (Flyvbjerg 2006; Yin 1994). The case study chosen is extreme with regards to the magnitude of the reaction by the innovation governance system and provides a unique opportunity (as compared to other country and time-points) to analyse what each relevant actor specifies they consider as normal and deviant behaviour, what is contested, as well as what regulatory changes they propose. Furthermore, the case involves a complex system of governance and provides unusually rich information, which we analyse in relation to our objectives.

At the time of writing, there are two existing publications in our field which provide detailed, but different, information about other aspects of the Macchiarini crisis. Berggren and Karabag (2019) focus upon scientific misconduct – also known as fraud and dishonesty – using theories from organisational theory about institutional complexity. They develop a perspective of three types of competing logics (market-oriented, medical, and academic) of institutional fields, and do not address innovation governance, other than mentioning fragmented control. McKelvey, Saemundsson, and Zaring (2018) describe the historical development of the Macchiarini crisis, and explicitly analyse the complex interactions between different organisations using the theoretical lens of innovation governance. They do so in order identify challenges for public policy, balancing between scientific excellence, translational research, and opportunities for scientific misconduct. In contrast to this paper, McKelvey, Saemundsson, and Zaring (2018) do not address our focus on the interface between scientific research and clinical practice nor they do not consider reactions to the crisis. Two additional papers do discuss limited issues related to the intersection (Arnason 2019; Sethi 2019). Therefore, the novelty in the current article is that we provide a more detailed understanding of this intersection between medical research and clinical practice, which is extremely important for medical innovation but poorly conceptualised in relation to innovation governance.

In this article, the official investigations form the basis of our analysis. Ten public investigations were carried out, leading to 10 lengthy reports that represent the

perspective of each actor in the innovation governance system. Under the Swedish public information law, all official investigations and material at authorities must be made available upon request, and many are posted on websites. While a few things are in English, the documents are primarily in Swedish, a language that both authors master and so translations below are done by the authors. We explicitly chose not to conduct interviews, partly due to the contested nature of the case, and partly due to the extensive nature of the written documentation.

We have gathered data during four years through an iterative process, with two separate steps of data gathering, also in relation to theoretical development.

The first step of the data collection began in January 2016, when both authors watched the TV documentary, which sparked a wider public interest in the scandal emerging around the clinician-scientist Pablo Macchiarini and the Karolinska Institute (KI). The authors immediately agreed to develop a joint IT-based retrieval system to systematically gather all documentation from 2010 to end of 2016 from: the university (Karolinska Institute, KI); the university hospital (Karolinska University Hospital, KuH), main research financiers (Swedish Research Council, Swedish Heart and Lung Fund); Retraction Watch; scientific journal articles mentioned in relation to accusations of scientific misconduct; influential national newspapers and magazines; as well as downloaded copies of websites from this group (due to the possibility they would be shut down). Based on this material, the authors jointly wrote up a thorough empirical description of the case, with approximately 100 pages of detailed description of the main events ordered chronologically. Based upon this chronological case, McKelvey, Saemundsson, and Zaring (2018) was published, constituting a detailed descriptive case on much more limited material than the current paper, as well as a different goal. Later, up until January 2019, we continued to gather press releases, articles in professional magazines and the popular press, and blog entries, which provided information about the 10 official investigations.

The second step of data collection for this paper specifically was to gather all official investigations (10) and related statements, which we have categorised as reactions to the crisis. As specified in the Appendix, the material from the investigations, reports and statements, consists of more than 1,000 pages of text. This documentation represents detailed information, and an unusually rich opportunity to map the perspectives. Each of these documents has slightly different foci, but all address the interface of scientific research and clinical practice. One author read all documentation, hand-coded, and categorised their statements as to 1) what activities they considered to constitute clinical research, i.e. generation and use of new scientific and technical knowledge at the intersection between medical research and clinical practice, 2) their investigation as to what went wrong, e.g. the negative unintended consequences, and, 3) their proposed regulatory improvements to avoid similar crises in the future. Both authors discussed the results and appropriate categories of analysis.

Through this critical reading of the sources, we reconstructed the sequence of events – and the involvement of each of the actors. We thereafter derived three phases relative to theory, which we call the stimulation of innovation, the generation of negative unintended consequences, and reaction by innovation governance actors, which we used to structure the presentation of the case study. Moreover, as an outcome, we categorise the activities constituting clinical research into three conceptual categories as search for new

knowledge, search for new solutions, and support for new solutions. Finally, one author wrote up the initial analysis, and then new weekly versions were then jointly discussed by both authors, through weekly meetings over 18 months, and both authors engaged in revisions of the manuscript.

There are many limitations to our research design of a single case study, chosen as extreme for theoretical reasons. We do not claim that the case is representative nor valid across countries, nor even within Sweden over time. However, we have chosen it as an extreme case for theoretical sampling, as it provides new insights into the dynamics of innovation governance at the interface between medical research and clinical practice.

Although not the focus here, we acknowledge that there is a wider interest in the topic of fraud and inappropriate scientific conduct across fields of research (Hall and Martin 2019). The literature describes many similar crises related to scientific misconduct within regenerative medicine specifically (Cyranoski 2012; Kim and Park 2013; Bik, Cadadevall, and Fang 2016; Adam. 2019). Moreover, we acknowledge the expanding stream of research which addresses scientific misconduct – such as fraud, falsification, dishonesty, retraction, inappropriate image duplication and other dubious academic practices.

4. Results

We present and analyse our case study in two parts below. First, using categories we found in our case study, we briefly describe the crisis and summarise it as three phases: stimulation, unintended consequences, and reaction. Second, we specifically analyse the reaction of the innovation governance actors to the negative unintended consequences of the crisis, by focusing on the regulation of the interface between medical research and clinical practice.

4.1. The three phases of the crisis

Figure 2 gives an overview of the sequence of events (2008–2016) leading up to the crisis and the actions of the actors of involved with the governance of medical innovation, the

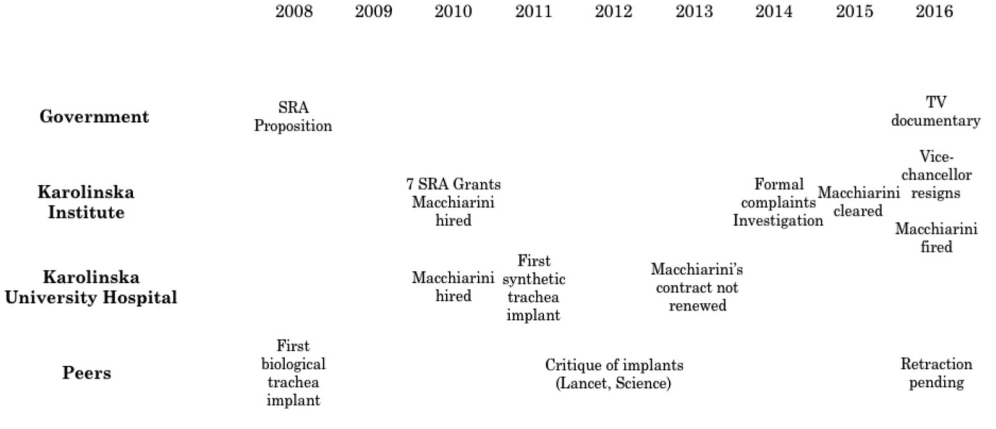

Figure 2. Overview of the sequence of events leading to the Macchiarini crisis and actions of actors involved in the governance of medical innovation.

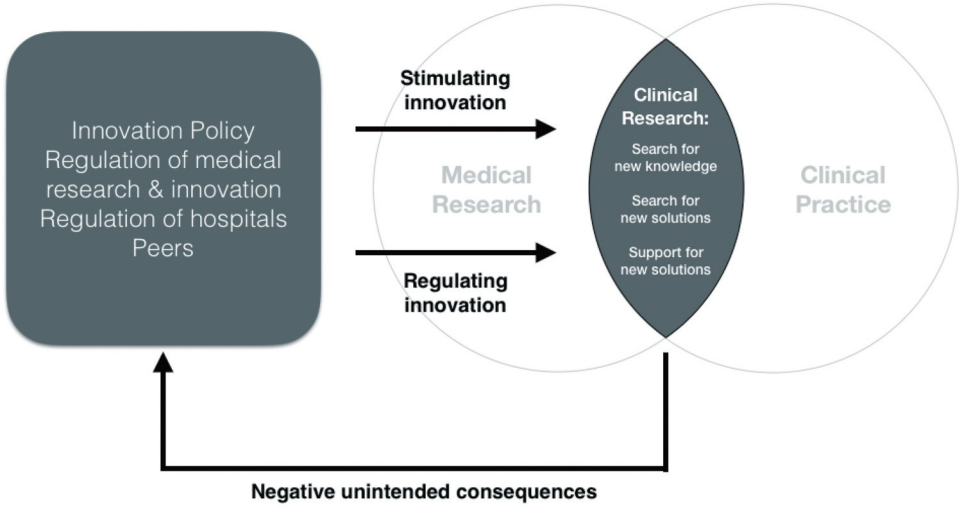

Figure 3. Specification of clinical research activities.

Government, the Karolinska Institute (KI), the Karolinska University Hospital (KUH), and research peers.

The origin of the crisis can be found in a very large public policy initiative to promote excellent science. When presenting their annual research bill in 2008, the Swedish government initiated a new funding for selected Strategic Research Areas (SRA). The objective of this initiative was to increase international competitiveness of Swedish industries as well as to produce the highest international excellence in science (Swedish Executive Government 2008). For the total SRA policy initiative, the government invested a total of 590 million EUR between 2010 and 2014 (Swedish Research Council 2015).

In 2010–2014 the Karolinska Institute (KI) received money from the SRA initiative – one of seven SRA grants obtained by KI – for a 'strategic research program in Stem Cell Research and Regenerative Medicine' that 'supports research that advances our understanding of stem cell biology and approaches to bring regenerative medicine to the clinic, for future treatment of diseases for which there currently are no therapies' (StratRegen 2016). We estimate that during the period 2010–2014, the KI research programme received a total of around 15,5 million EUR. Furthermore, KI used the SRA program as a platform to obtain a number of additional large grants in regenerative medicine from various other sources – mostly public ones but also foundations – in order to establish and support a number of research centres in the area. In total, we estimate that KI obtained and spent between 33 and 50 million EUR on regenerative medicine between 2010 and 2014.

As a way to realise the KI ambition to achieve the highest international excellence in regenerative medicine, KI recruited the clinician-scientist Paolo Macchiarini in 2010 and also established the Advanced Centre of Translational Regenerative Medicine (ACTERM) research centre for him to lead. One reason for recruiting him was that Macchiarini and his colleagues had carried out a human trachea transplant operation in 2008 using stem cells and a biological implant. Their operation was novel, and widely

acclaimed as revolutionary for the field of regenerative medicine (Vogel 2013). KI hired him with the expectation that he would improve his method for airway transplants and 'adapt the procedure to other intrathoracic organs of increasingly complex architecture' (Karolinska Institute 2016). Through the influence of KI on the Karolinska University Hospital (KUH), Macchiarini was also jointly employed by the hospital. KUH emphasised that his primary role was to conduct translational research bridging medical research and clinical practice.

In 2011, Macchiarini and colleagues at KUH performed the first of its kind stem cell-based trachea implant using a synthetic scaffold made of polymers. One more operation followed later the same year and another a year later. In later public investigations, it was determined that the group had not followed the formal procedures for ethical approval of research studies for any of these operations. Nor did they follow the formal procedures for the approval of the use of pharmaceuticals for advanced therapy, which was required because the trachea scaffold was seeded with stem cells. The reason given for not obtaining the appropriate formal procedures was as follows. Through informal contact with regulatory agencies and internal conferences at KUH, the clinical managers made the judgement that the decision to operate could be based on the patient's critical condition and on the lack of alternatives, and therefore did not require formal regulatory approval (Asplund 2016). However, the operation was used for medical research. Despite not obtaining permission for a research study, the authors later wrote up the operation of the first patient as the subject of a research publication (Jungebluth et al. 2011). Moreover, KI reported the results to the government, and specified that it considered these operations to be highly successful and also an outcome of the KI regenerative research program (Swedish Research Council 2012). Later investigations showed that the involved physicians did not follow professional guidelines, such as the Helsinki declaration on ethical principles for medical research involving human subjects. This declaration states that even if unproven interventions may be used in the hope of 'saving life, re-establishing health or alleviating suffering' they should not be repeated, or if done subsequently, where possible, be made the object of research (WMA 2008). Therefore, according to these guidelines, at least the two latter operations should have been a part of an approved research project.

In parallel, scientific misconduct was quickly alleged. The operations for the trachea implants were initially hailed and reported in journal articles as very successful. However, some research peers argued that it was impossible that the implants were working as well as reported in the 2011 paper. Several things happened in relation to these allegations. Macchiarini's contract with KUH was not renewed in 2013, despite pressures from KI to continue the joint appointment (Asplund 2016). Moreover, in 2014 four physicians jointly employed by KI and KUH filed a formal complaint about scientific misconduct at KI, suggesting that scientific papers authored by Macchiarini had incorrectly described the benefits of the implants. In 2014 a Belgian professor also filed a formal complaint to KI accusing Macchiarini for scientific misconduct. Following an internal and external investigation of the allegations – as required by university regulation – KI freed Macchiarini of scientific misconduct in 2015 (Hamsten and Samuelsson 2015a, 2015b). At this point, the internal university decision to clear his name was taken, despite the fact that the external examiner (Gerdin 2015) had been very critical in his report.

In early 2016 the Swedish public television (SVT) aired a three-hour documentary called 'The Experiments' (Experimenten), filmed by Bo Lindquist (2016). The documentary followed Macchiarini over several years as he implanted synthetic tracheas at KUH and in Russia, and presents information that suggested that the operations lacked proper scientific support and regulatory approval. Furthermore, it showed leaders of the prestigious KI defending the clinician-scientist's conduct despite mounting evidence of its inappropriateness. A public outcry followed in Swedish media. After initially supporting him, and following various resignations from prestigious posts, KI finally decided to relieve Macchiarini of his duties and close down the ACTREM centre. These interlinked events initiated a series of 10 public investigations (see Appendix for a complete list) to restore confidence in the governance of medical research and innovation in clinical practice.

Based on our analysis we summarise the crisis as three phases of stimulation, negative unintended consequences, and reaction, as seen in Table 1.

Table 1 shows the details for each actor in the innovation governance system. The first phase is characterised by the stimulus from the major funding of regenerative medicine in Sweden, which is initiated and led by the government, and high expectation of the clinical value of regenerative medicine in general and Macchiarini's research in particular. The second phase is characterised by the emergence of the negative unintended consequences of the stimulus. These appear as the execution of an unsuccessful high-risk clinical procedure that was made possible by scientific misconduct and the bypassing of regulatory procedures and ethical guidelines, and further amplified by inappropriate handling of allegations of misconduct. Finally, the third phase is characterised by the reactions of the actors involved in the governance of medical innovation, once the TV documentary had resulted in a public outcry. In the next section, we analyse these reactions in more detail with a focus on the regulation of the interface between medical research and clinical practice.

4.2. Reacting to negative unintended consequences

To regain public confidence in the governance of medical innovation, official investigations were initiated that focused on what had happened, why it had happened, and how it could be avoided in the future. Our focus is on the intersection between medical research and clinical practice, i.e. clinical research, which we have defined as the generation and

Table 1. The Macchiarini crisis summarised as three phases of stimulation, unintended negative consequences, and reactions and how each phase relates to the actors in the innovation governance.

Actor	Stimulation	Unintended negative consequences	Reaction
Government	SRA funding.	Bypassing of regulations.	Investigation (2,8,9,10).
Karolinska Institute (KI)	Research centre.	Inappropriate recruitment process Influence on KUH. Scientific misconduct. Handling of allegations.	Investigation (1,4,6,7)
Karolinska University Hospital (KUH)	KI influence.	New high-risk clinical practice.	Investigation (3)
Peers	First biological trachea implant.	Bypassing of ethical guidelines.	Investigation (5)

use of new knowledge by clinical-scientists in the context of the hospital and involving patients. Thus, we focus on how – in the investigations – the activities constituting clinical research were defined, how they were supposed to be regulated according to existing regulation, and what changes were suggested to avoid similar crises in the future.

Most of the investigation reports refer to the same sources when defining what activities constitute clinical research. On one hand, they refer to the Health and Medical Services Act (Hälso- and sjukvårdslagen) and the Patient Safety Act (Patientsäkerhetslagen) for defining clinical practice and its relationship to science. On the other hand, they refer to the Ethical Review Act (Etikprövningslagen) when defining research. Furthermore, they relate these concepts to other concepts used by the medical profession. Some of these concepts are concerned with activities performed by clinicians and scientists, but others are concerned with exceptions, i.e. situations under which standard regulations do not apply (Table 2).

According to Swedish law and regulation, clinical practice is defined as medical measures – based on science and confirmed experience ('vetenskap och beprövad erfarenhet') – that are used to prevent, diagnose and treat diseases and injuries (Asplund 2016; Gerdin 2015; Heckscher, Carlberg, and Gahmberg 2016; Lindvall and Engström 2016; SMER 2016; SOU 2017). The concept of confirmed experience is not defined in the law nor is it an internationally established concept. Thus, many of the reports discuss the boundaries of confirmed experience in order to identify the boundaries between clinical practice and medical research.

Lindvall and Engström (2016), who wrote a report on behalf of The Swedish Society of Medicine and the Royal Academy of Sciences, use the concept of non-confirmed treatment ('obeprövade behandlingsmetoder') and medical innovation for measures that physicians historically have used to treat seriously ill patients, which, despite being often based on science, cannot be seen as confirmed by experience. These measures may be early in their development or may have been used for other patient groups or indications. The rationale for using these measures in clinical practice has been the seriousness of the illness and the lack of alternative treatment options. Similarly, SMER (2016) defines innovative therapy as a clinical procedure that is being used without its benefits and risks being evaluated in clinical trials and whose efficacy has not been confirmed by experience. Innovative therapy, or non-confirmed treatment, are mentioned in most of the reports, usually with a reference to the Helsinki declaration and guidelines by the International Society for Stem Cell Research for the existence and justification of such procedures.

Table 2. Concepts used by the medical profession and Swedish law and regulations, as reported by investigation reports in the wake of the Macchiarini crisis, to define activities at the intersection between medical research and clinical practice.

Not defined by Swedish law and regulation	Vital indication. Compassionate use.	Non-confirmed treatment. Medical innovation. Innovative therapy. Clinical research. Translational research.
Defined by Swedish law and regulation	Hospital exception. Compassionate use program.	Clinical practice. Clinical trials. Research.
	Exceptions	Activities

The exceptions are usually reviewed in the investigation reports as possible justification for the use of non-confirmed treatment or innovative therapy. The hospital exception and the compassionate use program are specifically concerned with the possibility to produce and use pharmaceuticals that are still in development and both require approval from the Medical Products Agency. Vital indication and compassionate use are ethical principles justifying the use of unusual measures in urgent situations (vital indication) or when no other known alternatives exist (compassionate use). However, according to Asplund (2016), these principles cannot be used in order to bypass regulation.

The concept of clinical trials is defined in Swedish law and regulation as concerned with a clinical investigation of the effects of the use of a pharmaceutical or a medical device on humans or animals (SOU 2017). Lindvall and Engström (2016) define clinical trials specifically in the context of pharmaceuticals as the study of the efficacy and safety of a pharmaceutical. For pharmaceuticals clinical trials are always required and, in some cases, they are required for medical devices. Knowledge about the benefits and risks of the pharmaceutical, or the device, is increased during the process, which is required before they are used in clinical practice (Asplund 2016).

According to Swedish law and regulation, medical research is defined as two types of activities. First, as systematic experimental or theoretical activities that have the aim of generating new knowledge. Second, as science-based development activities. Lindvall and Engström (2016) further define clinical research as research that involves patients, animals, or cell systems with the aim to generate scientific results useful for the development of new diagnostic methods or therapies that can solve a health problem, or identify factors that can improve health. Asplund (2016) does not provide an explicit definition of clinical research, but argues that when clinical research involves patients it becomes a mix of clinical practice and research. Both Lindvall and Engström (2016) and Asplund (2016) stress that the aim of clinical research involving patients is to generate new knowledge that can be applied to groups of patients as opposed to individual patients. Finally, Heckscher, Carlberg, and Gahmberg (2016) refer to translational research as research that aims to improve knowledge flows between research and practice in order to increase patient benefits.

After analysing how activities related to clinical research are defined in different investigate reports we make the following observations. First, there is consensus that clinical practice based on confirmed experience is not considered a part of clinical research. Also, there is consensus that research involving human subjects at the hospital is clinical research. Second, the goals of what research should lead to are expressed in various ways. In some cases, the generation of new knowledge is expressed as a goal in itself, whereas in other cases the goal is expressed as to increase patient benefits or to develop new or improved treatments. Moreover, in some cases the goal is expressed as to provide scientific support for the efficacy of a certain treatment, e.g. use of a particular pharmaceutical. Third, we interpret that there is ambiguity around the regulation of activities that are variously referred to as the use of non-confirmed treatment, medical innovation or innovative therapies. In Table 2, they are in the top, right-hand quadrant. These are activities that professionals believe have played an important role for progress in medicine, and should be within the boundaries of clinical research, but are not explicitly acknowledged by Swedish law and regulation.

Turning to the regulatory changes suggested by the authors of the investigation reports to restore confidence and avoid similar crises in the future, we focus on those

directly related to clinical research in hospitals.[1] Our interpretation is that the majority of the suggested changes are related to the use of innovative therapies in extreme cases with the aim to specify more clearly than before under which conditions innovative therapies may be used and what decision-making procedures are required. While the decision to consider the use of an innovative therapy as a treatment option is supposed to originate from physicians, and be supported by patients' informed consent, the use of the therapy must also be supported by scientific knowledge and other medical professionals. Furthermore, the scientific rationale, along with evaluation of benefits and risks, needs to be documented and approved, first by clinical management and then by an external regulatory entity that specialises in reviewing applications for the use of innovative therapies. An exception is allowed if the health of the patient is likely to quickly deteriorate, in which case an application for review should be sent afterwards. Once an innovative therapy has been used for the first time, its further use is contingent upon the creation of a research study, subject to regulatory requirements of such a study.

The focus of the regulatory changes reported above on the use of innovative therapies reflects what the investigators identified as a major issue related to clinical research in hospitals, namely the justification for direct trials on human subjects. For each of the three patients, Macchiarini and his colleagues justified their decision to perform the surgery based on the ethics of clinical practice rather than the ethics of research. The investigators did not agree and their conclusion was based on the fact that Swedish law and regulation did not allow for the use of non-confirmed treatments as a part of clinical practice even in extreme cases, thus requiring ethical approval according to regulation concerning research on human subjects. The investigators did not propose any major change to the regulation of research on human subjects, because they – implicitly rather than explicitly – seemed to assume that the unintended negative consequences could have been avoided if the regulation was correctly applied. The regulatory process would have discovered the weak scientific basis for the operations and not approved the operations until the scientific evidence was strong enough.[2] However, most of the investigators, e.g. Lindvall and Engström (2016), SMER (2016) and SOU (2017), acknowledge that the use of non-confirmed treatments in extreme cases is a legitimate activity at the interface between medical research and clinical practice and should be accounted for in Swedish law and regulation. However, it should be subjected to external regulatory approval and not be applied more than once unless as a part of a research study.

5. Revisiting the conceptual framework

Having presented the case study of the crisis as three phases of stimulation, unintended consequences, and reaction and also analysed the reaction, we now return to the conceptual framework presented in Section 2.

[1]Other suggestions for regulatory changes that are not directly related to clinical research activities in hospitals concern routines for recruitment of clinician-scientists, processes for handling allegations of scientific misconduct, documentation of research activities, delegation of authority, and clarity in responsibility of joint activities by universities and hospitals.

[2]This assumption can be questioned in hindsight as the authors of scientific publications of results from animal studies preceeding the operations have been found guilty of scientific misconduct by providing misleading presentation, interpretation and description of the results and failing to present raw data on which these results were based (see e.g. CERB (2016)).

In the framework, we defined clinical research as the generation and use of new knowledge by clinician-scientists in the context of the hospital and involving patients. Furthermore, we conceptualised clinical research as an evolutionary problem-solving process, where the generation of variety is guided by theory-driven or experience-driven search, but where selection is done through direct trials, i.e. real-world settings involving patients. We defined innovation governance to include both the stimulation and regulation of clinical research activities. Furthermore, we expected that negative unintended consequences were not fully dealt with by existing regulation due to the tentative nature of innovation governance in the context of emerging science and technology.

Presenting the crisis as three phases has been useful for understanding the tentative nature of innovation governance and the challenges associated with the balancing of stimulation and regulation. Regenerative medicine is 'a field of medicine devoted to treatments in which stem cells are induced to differentiate into the specific cell type required to repair damaged or destroyed cell populations or tissues' (NIH 2015:23). One of the applications of regenerative medicine is the replacement of failed organs by artificial organs – as done by Macchiarini and his colleagues at the Karolinska University Hospital. In the last century a large body of scientific and technical knowledge was built about human organ transplants and such transplants are today performed as routine practice in many hospitals around the world. Regenerative medicine is an alternative to human transplants, but is yet to become a routine clinical practice. Instead, regenerative medicine is a fast-moving international field of research and innovation fuelled by large-scale funding (Coccia 2014; Salter and Faulkner 2011; Salter and Salter 2010). Thus, regenerative is a field where governments around the world – including the Swedish government – are stimulating research and innovation, while at the same time there are ambiguities in terms of how research and innovation should be regulated. We suggest that these ambiguities, in turn, generate negative unintended consequences and a reaction by the innovation governance system to restore confidence and avoid similar situations in the future. In this case study, the reaction is to specify more explicitly how clinical research is to be regulated and the role of external regulators. Their responses can be interpreted in two ways. It can be interpreted as stricter regulation because it extends the role of external regulators, but it can also be interpreted as a way to legitimise activities that are considered important means for technological innovation.

We find that the ambiguities in the regulation of clinical research are not evenly distributed among the activities that constitute clinical research. To elucidate these differences, we propose that clinical research is divided into three types of activities (Figure 3):

(1) S*earch for new knowledge* aims to increase our basic understanding of life and diseases without necessarily searching for new treatment options. This activity is primarily theory-driven, i.e. informed by science, and the innovation governance actors agreed it should be regulated as research activity.
(2) S*earch for new solutions* aims to increase patients' benefits or develop new or improved treatments. This activity is primarily experience-driven, i.e. informed by practice, but many of the innovation governance actors argued that the regulation

of these activities is not clear, e.g. how decisions are made about the use of innovative therapies in extreme cases.

(3) S*upport for new solutions* aims to test and compare the efficacy of particular pharmaceuticals, medical devices, or treatment procedures. This activity is primarily theory-driven and the innovation governance actors agreed that this activity is either regulated as research or by specific regulation concerning clinical trials.

Our proposed division of clinical research into search for new knowledge, search for new solutions, and support for new solutions, highlights the difference between experience-driven and theory-driven search activities. While there is a high degree of consensus about the regulation of search for new knowledge and support for new solutions, which are primarily theory-driven activities, we found less consensus about the regulation of the search for new solutions, which is primarily experience-driven. Most innovation governance actors agree that the regulation does not clearly specify if, and under what conditions search for new solutions may be applied, even if clinician-scientists seem to agree about the importance of such activities for (past) progress in medicine (Ahrens 1992; Asplund 2016; Hirsch 1997). This ambiguity seems to have normalised action within the medical profession, either intentionally or unintentionally, that appeared to outsiders as deviant (Hedgecoe 2013). This likely creates the unintended consequences that generated the public outcry. In response, the regulation of clinical research was adjusted, in this case study, by more clearly specifying under what conditions search for new solutions may be used and how the decisions to use them are reviewed by actors in the innovation governance system.

6. Conclusions and future research

The purpose of this article is to better understand the challenges involved in avoiding the dark side of technological innovation processes. Using a longitudinal case study of medical innovation, we have explored how actors in the innovation governance system counterbalance the stimulation of novelty for future benefits for society with the regulation of novelty, in order to avoid the risk of unintended consequences. We analysed how actors in the respective innovation governance system reacted to negative unintended consequences; a reaction that we interpret as an attempt to restore the balance between the stimulation and regulation of technological innovation processes by clarifying ambiguities in the regulation at interface between research and practice.

Our first set of conclusions is concerned with the impacts of the ambiguities in the regulation of the interface between research and practice. We propose to conceptualise these ambiguities as *grey zones*. We define grey zones as situations when it is unclear if the benefits of experimentation – direct trials – outweigh its risks. We argue that grey zones are connected to the activities at the interface between research and practice, and specifically those we conceptualise as search for new solutions. Search for new solutions is characterised by experimentation in real-world settings which may include humans as well as socio-technical systems whose continuous operation is important for human well-being. The mere possibility of serious harm creates ambiguity about the level of risk analysis, and the scope of the expected benefits, that are needed in advance to justify the search. This ambiguity is further amplified by the different perspectives of research and practice when it

comes to the beneficiaries and risk takers in the context of a new practice. For practice, the focus is on the benefits and risks of single constituents, while for research the benefits tend to be more general for the same level of risk. For example, from the perspective of clinical practice, the unique situation of each patient – due to anatomical variations, condition of the disease, or available methods and resources for treatment – needs to be considered when selecting treatment options. If the benefits outweigh the risks for the individual patient, then deviations from standard practice, such as doses of approved pharmaceuticals, use of approved pharmaceutical for different indications than originally intended, and new uses of approved medical devices, are accepted (Schwartz 2014). From the perspective of medical research – where the objective is to search for generalised knowledge – the benefits are much larger for the same level of risk as the beneficiaries also include all future patients that would benefit from the new practice.

Moreover, we propose that grey zones are continually created and resolved over time, as innovation governance systems counterbalance innovation and the risk of negative unintended consequences. We argue that the main reason for the continual existence of grey zones is the inherent uncertainty of technological innovation, as generated through an inherently uncertain process of problem solving (Consoli et al. 2016; Kline and Rosenberg 1986; Thomke, von Hippel, and Franke 1998; Vincenti 1990). When a particular class of problems emerges (e.g. cancer) different classes of solutions are developed to solve them (e.g. surgery, radiation therapy, and chemical therapy). Search at the interface between research and practice generates new scientific and technological knowledge related to the nature of the problem and the efficacy of the different sets of solutions. This includes knowledge about the benefits and risks of applying a particular class of solutions to a particular class of problems, which will reduce grey zones. However, new classes of problems will always emerge as well as new classes of solutions that can be applied to both new and existing classes of problems. For these new classes of solutions there may be great expectations about their potential benefits, but – at least to begin with – limited knowledge about how these benefits are realised. Furthermore, there will also be incomplete knowledge about the risks that need to be taken to develop the knowledge and artefacts for consistent and reliable use of the solutions in practice and the risks of repeated use. Thus, inherent uncertainty about future problems and solutions means that, even if some grey zones are resolved, new ones will emerge along with emerging science and technology.

Our second set of conclusions is for medical innovation specifically. There have been longstanding debates in medicine about the relative effectiveness of different means for generating and selecting new clinical practices. Already in the early 20th century, when the Rockefeller Institute of Medical Research and the associated Rockefeller Hospital were established, physicians debated whether ideas generated by scientists at the laboratories of the Institute should be tested by physicians at the hospital or if physicians working at the hospital should generate ideas through observing and measuring patients at the bedside followed by investigations in the laboratories before being confirmed by application in the hospital (Hirsch 1997). Recently, observers including Gittelman (2016), have associated the progress in 20th century medicine to the experience-driven, approach and the current slowdown of progress to the dominance of a theory-driven approach to innovation. We believe that our conceptual model and interpretations from our case study provide an opportunity to bring a more nuanced perspective to this debate.

In contrast to the arguments about a shift in beliefs about the relative effectiveness of the two approaches put forth by Gittelman (2016), we propose that the current prominence of theory-driven approach to medical research and innovation may be better explained by the role of the innovation governance system in shaping the means available for generating and applying new knowledge at the intersection between medical research and clinical practice. Even if experience-driven activities were more effective in generating and selecting among ideas of new clinical practices, their effectiveness is counterbalanced by their potential for negative unintended consequences. When unintended consequences emerge, they will lead to reactions by actors in the innovation governance system, which may subsequently make experience-based activities less available as means for generating and applying new knowledge due to more stringent external regulation. An interesting opportunity for further research is to test this proposition by empirically studying changes in innovation governance of medical innovation in selected fields as multiple phases of stimulation, negative unintended consequence, and reaction.

Our final set of conclusions relate to the more general debate about the intersection and relationships between scientific research and technological innovation, and, hence, the relationship between theory-driven search and experience-driven search. Nightingale (2004) argues that it is difficult, and often impossible, to accurately predict complex phenomena from first principles, even if they may be predicted through experience of empirical regularities. Thus, it is difficult, and often impossible, to develop new practice without experience-driven search and direct trials, even if the new practice is inspired and guided by scientific research. At the same time, the increasing power of predictive science (Arora and Gambardella 1994; Fleming and Sorenson 2004) suggests that the importance of theory-driven indirect trials for technological innovation is increasing reducing the need for experience-driven direct trials. We propose that the continual ambiguity around searches for new solutions at the interface between research and practice – primarily an experience-driven activity using direct trials – provides pressure for using indirect trials, such as computer simulation, because there will be less risk for negative unintended consequences. These pressures will be stronger in times of crisis and in those real-world settings where the risks of unintended consequences are higher.

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ORCID

Maureen McKelvey http://orcid.org/0000-0002-1457-7922
Rögnvaldur J. Saemundsson http://orcid.org/0000-0002-8563-9078

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Appendix – Overview of investigations

No	Date of initiation	Investigations	Initiated by	Date of report	No of pages
1	Nov 2014	External investigation of formal complaints of scientific misconduct	KI Vice chancellor	May 2015	41
2	Feb 2015	Clinical innovation	Swedish National Council on Medical Ethics (SMER)	Nov 2016	82
3	Feb 2016	Circumstances of operations performed 2011–2013	KUH director	Aug 2016	145
4	Feb 2016	External investigation of how KI has handled the Macchiarini case	KI board	Sep 2016	202
5	Feb 2016	Propose recommendations for clinicians and researchers working at the crossroads between clinical research and healthcare	The Royal Swedish Academy of Sciences and Swedish Society of Medicine	Jun 2016	10
6	Feb-Mar 2016	Scientific misconduct (re-opened)	KI vice chancellor	Multiple statements 2017–2018	-
7	Apr 2016	Additional scientific fraud investigation.	KI vice chancellor	Multiple statements 2017–2018	-
8	Jun 2016	Criminal investigation (public prosecutor)	Health and Social Care Inspectorate (IVO) and The Medical Products Agency (LMV) (independently)	Oct 2017	5
9	Jun 2016	Review of regulation concerning research ethics and the interface between clinical research and clinical practice	Executive government (SOU)	Dec 2017	482
10	Mar 2017	Monitoring KI in Feb 2016 – pending investigation.	Swedish Higher Education Authority (UKÄ)	Nov 2017	32