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DIFFUSION AS A VALIDATION PROCESS: LEARNING FROM PATIENT INNOVATORS

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Abstract

Randomized, controlled clinical trials, although important for ensuring safety and efficacy, are criticized for being an inadequate validation process for certain medical innovation modalities and conditions. The main limitations and causes for critique are high costs, long duration, low patient recruitment, design rigidity and ethical issues.

At the same time, there is growing evidence that patients and their family members innovate in treatments, therapies, and medical devices. These patient innovators are increasingly recognized as an important source of innovation. Although there is a fairly complex structure developed to formally validate healthcare products, little is known about the paths patient innovators take to validate their solutions before involving health regulators.

In this context, we attempt to answer the following research questions: What are the patterns of the validation processes undertaken by patient innovators for their innovations? How can current practices of patient innovation validation be improved from its comparison with observational studies and clinical trials?

To address these questions, we study cases of patient innovators who attempted to share their innovations with other patients. More specifically, we structure the observed processes of patient innovation diffusion as a process model for an iterative observational trial process in which incremental validation of the innovation is performed by diffusing it to other patients. We contrast this process with a general streamlined process of randomized clinical trials.

We argue learning from the patient innovators practices is important for discussing viable frameworks and structures for improving the safety and efficacy of these processes. We discuss related implications to innovation research, management and policy.

Keywords: user innovation; patient innovation; diffusion; validation of health-care innovations; observational trials

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1. Introduction

Louis Plante is a patient with cystic fibrosis, a disease that causes “the body to produce unusually thick, sticky mucus” that “clogs the lungs and leads to life-threatening lung infections” (CF Foundation, 2013). One day, he was forced to leave a concert due to extreme coughing. After realising that this episode was likely caused by the fact that he was standing next to one of the concert speakers, he thought that maybe he could develop a device that, with the use of ultrasounds, would allow him to increase his release of mucus by coughing, thus decreasing the risks of lung infection. Louis proceeded to invent the “Frequencer”, an “electro-acoustical transducer” that dramatically increased his quality of life, not only because it was much more comfortable than the standard treatment at the time, which involved periodical physical percussion of the thorax in an inclined position to increase expectoration, but also because the amount of mucus he was releasing was significantly larger. After realising that the Frequencer was working for him informally, and getting better with each modification, Louis proceeded to discuss with his doctor ways to prove the effectiveness of his invention. Together, they designed a small trial and performed it on him. Afterwards, they tried the device on two other patients with pulmonary conditions, and it didn’t work for them. The device was further altered as a consequence. Then a series of more successful trials were developed in a hospital setting, after a white paper on the scientific bases for the invention was written. Eventually, Louis founded his own company, but he was still looking for further proof of the effectiveness of his device: he made his Frequencer able to receive data from an electronic scale with via USB and to send results of the expectorated mucus weight back to him electronically.

A patient from Florida, USA, suffering from skin cancer, experimented with applying a mixture of chilli peppers and alcohol on his skin and realised that this had an impact on his lesions. He based his experiments on having done literature research on the use the active ingredient of hot peppers in the treatment of other ailments. He tried to approach doctors, hospitals and universities with the intention of perform trials on other patients, but nobody followed through. Nevertheless, he has been responding to requests for help from people around him with other symptoms of skin cancer. Because of variable levels of efficacy on

other people, he experimented with higher concentrations of his medicine. Unfortunately, because he was unable to perform any structured trial or study, the effect of his invention is not, to this date, conclusive.

These are two examples of patient innovators who after partially or completely solving their health problems were interested in helping others. In order to do so, they looked for advice in different places, consulted with many people, changed their inventions due to feedback they collected and then had other people test them on themselves. However, they attempted different validation paths, rendering their inventions diverse success results.

The phenomenon of patient innovation has been recently documented: patients and caregivers have been shown to innovate in treatments, therapies and medical devices (Habicht, Oliveira, & Shcherbatiuk, 2012; Shcherbatiuk & Oliveira, 2012). Patients as a source of medical innovation may be of especial importance in this time of rising health care costs and stalled innovation in medicine.

Health expenditure is a very important part of the economies of developed countries. In 2012, it represented 9,3% of total GDP in OECD[1] countries. Without taking into account the recent stagnation due to the economic crisis, health expenditure has grown steadily from 2001 to 2009, between 4 and 5%[2] each year. This increase, of which some is on research and development, has however been accompanied by a stagnation of breakthroughs in medical innovation, measured by the number of new drugs discovered per year (Landers, 2004).

The inefficiencies of the current health system, with mostly profit-driven research and development of novel pharmaceuticals and other therapies are also evident in rare diseases. With an estimated number of diseases between 6,000 and 8,000[3], some with only a handful of patients, the current pace of medical innovation will never be able to successfully solve or manage all these conditions. The lack of alternatives available in the market creates higher needs to patients, which serve as incentives to innovation, as shown by Habicht et. al (2012).

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[1] http://www.oecd-berlin.de/charts/health/

[2] idem

[3] http://www.eurordis.org/about-rare-diseases

In this work, we study cases of patient innovators who attempted to share their innovations with other patients, identifying the main steps in the process, difficulties they face, and the innovators' responses. In order to do this, we try to address the following research question in this work:

- What are the patterns of the validation processes undertaken by patient innovators for their innovations?
- How can current practices of patient innovation validation be improved from its comparison with observational studies and clinical trials?

Learning from the patient innovators practices is important for discussing viable frameworks and structures for improving the safety and efficacy of these processes. We discuss related implications to both innovation research and policy.

In section 2 of this work, we review the existing literature on patient innovation, integrating it in the relevant context of user innovation. We also provide an overview on the current standards of practice in validation of medical innovations in the United States and Europe, providing basis for contrast with observed practices of patient innovators. Section 3 describes the methodology of the research. Section 4 includes the results of the surveyed sample and a proposal of a theoretical model. We structure the observed processes of patient innovation diffusion as a process model for an iterative observational trial process in which incremental validation of the innovation is performed by diffusing it to other patients. This process model is characterized by feedback loops on every step, enabling the continued improvement of both the innovation and the study design. Section 5 provides interpretation and contextualisation of such results within the literature and interviews, comparison of the proposed model against the existing formal model of validation, and implications of the study for research and policy decision making.

2. Literature Review

2.1. Patient Innovation

Patients have not typically been considered relevant sources of innovation in the health sector due to their perceived unwillingness to innovate and low technical and scientific

knowledge. However, recent research has shown that users create radical innovations (e.g. Røtnes and Staalesen 2009), and patients and caregivers have been shown to create innovations in the medical field, in the form of treatments, therapies and medical devices (Habicht et al., 2012; Shcherbatiuk & Oliveira, 2012).

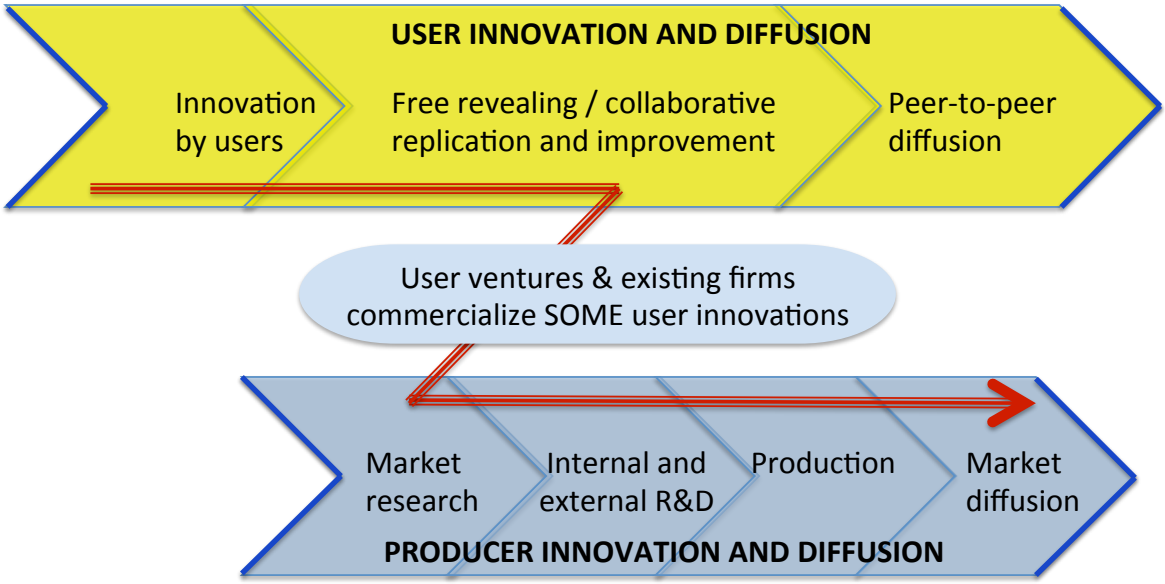
Patients, caregivers and family members who innovate are considered patient innovators (PI) when they are the first ones to create a medical innovation with the primary purpose of using it, as opposed to being producer innovators, who develop innovations with the main objective of obtaining profit from them (Shcherbatiuk & Oliveira, 2012; von Hippel, 2005).

The study of patient innovation is part of the larger academic field of user innovation, which studies the importance of user in the creation of novel products and services.

2.1.1. User Innovation

Only in recent decades did the academic community start acknowledging the importance of the phenomenon of user innovation. Producer innovation occurs when it is developed by individuals or firms who expect to benefit from selling a product or service, whereas user innovation happens when it is developed by individuals or firms who expect to benefit from the use of a product or service (von Hippel, 2005). Raasch and von Hippel (2012) show that the two paradigms, user innovation paradigm and producer innovation paradigms, have important interactions, namely the "competition and complementarity between the innovations diffused via the two channels".

Figure 1 - User and producer innovation paradigms (Raasch & von Hippel, 2012)



Big manufacturers and producers tend to develop strategies of market segmentation, and to produce products or services that match what they perceive are the needs of these segments. However, when the heterogeneity of the user's needs is high, the segmentation tends to be insufficient, and this strategy of "one size fits all" renders many users dissatisfied with the solutions that are available in the market. In an analysis of Apache security software, it was found that a high heterogeneity of the needs in the market accompanied a high willingness to pay to get software improvements, and that innovating users were more satisfied than others (Franke & von Hippel, 2003). Similarly, most medical technologies and pharmaceuticals are developed with the purpose of reaching the many rather than the few, sometimes leaving the immediate needs of some patients unattended.

Some patients and caregivers, having an acute, often very specific and hardly-transferable perception of their needs, are well positioned to develop themselves solutions to their problems. The unique knowledge of user needs, both idiosyncratic and of a larger user group, is acquired by users through their own use (von Hippel, 1986) which, in the case of patients, is translated as their everyday lives with their conditions. Information "stickiness", meaning the difficulty, cost or impossibility of transferring information, decreases the capacity of users (patients) to advise producers of their needs, often shifting the locus of innovation to the user (von Hippel, 1994).

Research shows that user innovation is more prevalent among "lead users", a subset of the population of users who face needs before the market (are trend leaders) and who benefit significantly from the development of a solution for those needs (von Hippel, 1986). The importance of lead user has been shown empirically by a number of studies of the "lead user method", using methods of identifying the two characteristics stated above and their correlation with a higher propensity for user innovation (Franke, Von Hippel, & Schreier, 2006; Herstatt & von Hippel, 1992; Urban & von Hippel, 1988).

2.1.1.1. Importance of User Innovation

Although the economic importance of user innovation in medicine has not yet been soundly established, it has been proven to be an important phenomenon in a variety of fields, including industrial products such as scientific instruments (Riggs & von Hippel, 1992), computer-aided design (CAD) software (Urban & von Hippel, 1988), library information

systems (Morrison, Roberts, & von Hippel, 2000), construction materials (Herstatt & von Hippel, 1992), security software (Franke & von Hippel, 2003); consumer products such as sports equipment (Baldwin, Hienerth, & von Hippel, 2006; Franke & Shah, 2003; Franke et al., 2006; Lüthje, Herstatt, & von Hippel, 2005; Shah, 2000) , automobiles (Kline & Pinch, 1996) and juvenile products (Shah & Tripsas, 2007); and services such as banking (Oliveira & von Hippel, 2011). Habicht et al. (2012) found that in the field of medical devices for cystic fibrosis, 50% were developed by patients.

Recent studies have shown that there is a significant percentage of people over 18 years old who engage in user-innovations. In the US it was determined to be 6,1%, in the UK 5,2% and 3,7% in Japan (von Hippel, Ogawa, & de Jong, 2011), supporting the argument that the phenomenon is relevant and still under-studied.

2.1.1.2. Diffusion of User Innovations

When patient innovators share their solutions with others, they may end up saving other patients' lives (Habicht et al., 2012). In order to being able to save many lives, patients and other user innovators who successfully created a novel solution are faced with a challenge: they can become user entrepreneurs, they may sell or license their idea, they can freely reveal their idea in a community, or do nothing to diffuse their innovation and perhaps a valuable contribution to the world gets lost.

Diffusion of innovations by users may thus generally be separated between market diffusion, in which they either become user entrepreneurs or sell or license their innovation for commercialisation by an existing company, and peer-to-peer diffusion, to individuals or an established community. The first is defined as the transfer of an innovation involving a transaction or some form of exchange, whereas the later involves negligible cost in the transfer of innovation-related information to potential adopters (Raasch & von Hippel, 2012). We also consider diffusion to non-potential adopters as a valid form of peer-to-peer diffusion, given that diffusing the knowledge of existence of a certain innovation through non-adopters may be a means for reaching other potential adopters. Patient innovators can therefore not only diffuse to other patients or doctors, who may be potential adopters, but also to their friends and family, their lawyers and their online hobby communities, who may act as further diffusers of their medical innovation. Furthermore, the two forms of diffusion may be

performed in sequence, whereby a user could share their innovation to their community and later become a user entrepreneur.

The user innovation paradigm suggests that the main drivers for user innovation are the expected benefit from developing (Raasch & Hippel, 2012) and from using the solution created (von Hippel, 2005). Unlike producers, who profit from diffusion, users may benefit very little from the use of others. Therefore, diffusion is considered an externality to the process of user innovation. This means that all effort in diffusing will only be exercised while its benefits are expected to be superior to the costs of diffusing the innovation (Raasch & von Hippel, 2012). One way users have been found to increase the associated benefits is by creation of a community brand as by-product of its member interactions, as in an empirical case of the Apache software community (Füller, Schroll, & von Hippel, 2013).

We explore further the phenomenon of user entrepreneurship, which was the path undertaken by most of the sample of patient innovators present in this work. Entrepreneurship is the existence, discovery, evaluation and exploitation of opportunities to create future goods or services (Shane & Venkataraman, 2000). It is often defined by the creation of new organisations, although this is not a necessary condition for entrepreneurial activity to occur: the service or good created may be sold to others or rise in the midst of an existing organisation (Shane & Venkataraman, 2000).

The main conceptual difference between entrepreneurs in general and user-entrepreneurs is that the latter not only commercialize the new product or service but are also users of it. There are two types of user-entrepreneurs: professional-user entrepreneurs, who use their innovations in a professional setting; and end-user entrepreneurs, who employ their innovations in their day-to-day lives (Shah & Tripsas, 2007).

User-entrepreneurs may start selling their product or service and thus become manufacturers or providers either by formal evaluation of market potential or through previous indications for demand by public exposure of the innovation. The latter case is named the “accidental entrepreneur”, whereby development, experimentation, adaptation and some adoption are performed before formal evaluation (Shah & Tripsas, 2007)

Users can choose to either sell their ideas to other users or companies and now, with decreasing bureaucracy, can outsource steps of the value chain (production, customer

service, shipment) becoming “causal entrepreneurs” or even create entirely new companies (von Hippel et al., 2011).

The phenomenon of user entrepreneurship has been found to be relevant in a variety of industries, including radical sports equipment – windsurfing, skateboarding and snowboarding (Shah, 2000), mountain bicycle (Luthje, Herstatt, & von Hippel, 2002) and kayak rodeo (Baldwin et al., 2006) – the stereo components industry (Langlois & Robertson, 1992) and juvenile products (Shah & Tripsas, 2007). In the field of medical services and devices industry, evidence has also been collected of relevant existence of user-entrepreneurs (Lettl, Herstatt, & Gemuenden, 2006; Shcherbatiuk & Oliveira, 2012).

Also relevant in the study of user entrepreneurship is the model of how user innovations become commercial products developed by Baldwin et al. (2006). In this model users start by recognising a “design space” – a set of new innovation possibilities – before creating their innovation, then join communities due to the higher efficiency of collective innovation and later emerge as user-manufacturers. They theorise that innovators benefit from freely revealing their designs with other user-innovators, and that at a certain point user-purchasers emerge, who are more interested in buying than in developing the new designs for themselves. The phenomenon of free revealing in communities has been shown to take place in communities of sports enthusiasts, often in informal settings (Baldwin et al., 2006; Franke & Shah, 2003). The main advantages of freely revealing are the ability of other users to test, suggest improvements and diffuse innovations, thereby progressively signalling the features and designs that may become commercially attractive. Nevertheless, there is also evidence that most consumers do not actively share knowledge of their innovation, due to lack of incentives (von Hippel et al., 2011).

Similarly, users who have decided to become entrepreneurs often share with others before formally venturing into commercialisation, receiving suggestions for improvements and diffusion through word of mouth, thus benefitting from the contributions and feedback of communities (Shah & Tripsas, 2007). Users in communities may even serve as beta-testers, providing iterative feedback to improve the solution (Franke & Shah, 2003).

The user entrepreneurship model proposed by Shah and Tripsas (2007) shows how users, after innovating, receive feedback from two sources: from the interest others may take

on observing them publicly use their innovation and from the members of their community due to freely revealing. After this, they may or may not recognise the opportunity for commercialising their innovation.

Feedback loops are also very important in medicine. Drugs follow an innovation process where larger changes occur at the pre-clinical stages, whereas medical devices have higher incremental change throughout the trial process, ranging from the device to the design of the trial or post-operation indications (Christensen et al., 2007). Gelijns and Rosenberg (1994) refer to the “pill” and endoscopes as landmarks of how feedback loops from patients and clinicians play a major role in incremental innovations, adding new uses for drugs as examples of such innovation in a clinical practice setting. These feedback loops show that medical innovation is not only caused by technological breakthroughs but also by iterative modifications, and this information could help shape the design of clinical trials (Christensen et al., 2007).

Motivations for diffusion, sources, and types of feedback and the impact of feedback in the innovations themselves may still be largely understudied in the field of user innovation. To the best of our knowledge, it has not yet been explored in the context of patients and caregivers who innovate and diffuse their knowledge to others.

To be able to contrast standard medical innovation with informal innovations that patients and caregivers are creating when faced with their diseases, we need a general outlook at medical innovation and the forms of scientific validation of innovations that constitute the current standard in medicine, their main characteristics and limitations.

2.2. Current Practices of Validation of Medical Innovation in Europe and the USA

Innovation in medicine includes the scientific, technological, and clinical developments that originate new medical products, processes, or procedures, which may be diagnostic, therapeutic, preventive, or administrative (Rettig, 1994). We may separate some of them into several modalities: drugs, medical devices, procedures, and clinical practices (Christensen et al., 2007).

The requirements of health regulators and the modalities of the innovations influence the research designs used to assess risk and effectiveness of innovations (Christensen et al., 2007), as well as the legal requirements for approval of innovations. In the USA, surgical procedures and clinical practices, the latter defined as the definition of the standard procedures, pharmaceuticals, and devices used to treat a particular disease, follow a less formal process than medical devices or drugs (Christensen et al., 2007). Legal oversight is limited or non-existent, and clinical testing may be required only by insurance companies, responsible for paying for such practices (Friedman, Furberg, & DeMets, 2010).

Due to the intrinsic differences in the level of risk and novelty of pharmaceuticals and medical devices, these two types of innovation require different processes of evaluation and validation. In the USA, the Food and Drug Administration (FDA) requires that most new drugs (under the name of investigational new drugs, or INDs) undertake a multi-phase process (FDA, 2013a). On the other hand, medical devices' regulatory requirements concern mostly engineering and technical characteristics, with clinical data being more important the riskier the device, both in the USA and in Europe (Friedman et al., 2010; Kramer, Xu, & Kesselheim, 2012).

The number of yearly approvals of drugs and medical devices is very different, which may hint at both the differences in difficulty to create novel products and contrasting approval speeds between the two innovation modalities: in 2012, FDA's Centre for Drug Evaluation and Research approved 39 new drugs and 63 supplements for already approved drugs, including new uses for drugs (CDER, 2012, 2013). In contrast, 3130 new devices were approved, with additional 894 modifications to previously approved devices accepted by the FDA.

2.2.1. Types of Medical Studies

There are two main types of studies to test innovations in medicine: experimental and observational. The first type requires the study subjects to undergo some type of therapy, whereas observational studies (OS) are those in which the scientist only observes interactions that exist between subjects of the study and other variables, not controlled by the investigator. While observational studies can be either prospective or historical (the

observations can be recorded after the test was initiated, or can be obtained from past records or events), experimental trials are only prospective (Friedman et al., 2010).

Experimental trials typically take the form of clinical trials, either randomized or non-randomized. On the other hand, the most common types of observational studies are cohort and case-control studies.

2.2.1.1. Experimental studies

Clinical trials are typically considered the gold standard of medical trials (Campbell & Fitzpatrick, 2000; Concato, Shah, & Horwitz, 2000; Scott & Baker, 2007). Because they are experimental and not observational, clinical trials involve intervention of one or multiple diagnostic, preventive, or therapeutic drugs, biologics, devices, regimens, or procedures. (Friedman et al., 2010).

The trials most favoured in current medicine are the controlled, double blinded, randomized trials. The control may take the form of placebo, active treatment, dose comparison or may be historically derived, but the selection of the trial subjects should be randomized when the control is concurrent with the active arm of the trial (Mitsumoto, Dorsey, Beck, Kieburtz, & Griggs, 2009)

2.2.1.1.1. General Criticism and Limitations

Randomized, controlled clinical trials, although important for ensuring safety and efficacy, are frequently criticized for being an inadequate validation process for certain innovation modalities and conditions. The main causes for critique and limitations are their high costs, long duration, low patient recruitment, design rigidity, short-term analysis of adverse effects and ethical issues.

The estimated capitalized costs of the development process of a new drug in the USA have been estimated to range from $100 million to $1 billion, with a prominent study which includes the costs of the failed pharmaceuticals providing an average at approximately $802 million, of which time costs account for approximately 50% (DiMasi, Hansen, & Grabowski, 2003; Field & Boat, 2011; PhRMA (Pharmaceutical Research and Manufacturers of America), 2007). This generates a high barrier of entry for trials, usually only possible for pharmaceutical companies and other research institutions.

The duration is an issue reflected not only in terms of cost for sponsors but also as opportunity cost for patients in desperate need for new, more effective treatments. The average time for a Phase III cancer clinical trial has been calculated to take a median of 2,5 years, ranging from approximately 435 to 1,604 days (Dilts, Cheng, Crites, Sandler, & Doroshow, 2010), while the entire clinical process (Phases I, II and III) was estimated to take about 7,5 years from the beginning of clinical testing to marketing. The entire "bench to bedside" process takes between 10 and 15 years (DiMasi et al., 2003).

Cancer Therapy Evaluation Program (CTEP) sponsored trials between 2000 and 2007 showed that about 40% failed to achieve minimum patient recruitment levels (Stewart, Whitney, & Kurzrock, 2010). While some will do with a lower number of patients, other estimates claim that 13% of trials do not even start due to poor patient accrual (Prescott, Counsell, Ross, & Devon, 1999). The main reasons pointed out for difficulties in recruitment are related to narrow patient eligibility criteria, unwillingness of patients to participate in trials and difficulties in reaching to patients (Lovato, Hill, Hertert, Hunninghake, & Probstfield, 1997).

A relevant limitation of clinical trials concerns the lack of flexibility in its design, given that it can only verify or deny a hypothesis (Cooper, 2012), whereas data-set based observational studies may have more flexibility on the analysis and the research questions. This flexibility allows for the analysis of data to generate itself new research questions without the need to undergo further interventions with patients. The same applies for analyses of long-term effects on patients (Christensen et al., 2007).

The Declaration of Helsinki of the World Medical Association, although bearing no legal force, is internationally recognised as the cornerstone of ethics in human research (Binns & Driscoll, 2000). It postulates that experimenting on human subjects should occur after proper laboratory and animal testing, that the potential benefits of experimenting have to be higher than the predicted risks, that the interests of the individual are more important than the interests of society, that any investigation should be approved by an ethics committee (or IRB), that individuals have to be fully aware of the risks and consent to participate and that impact on the patients' health should be minimised (Binns & Driscoll, 2000; World Medical Association, 2008). Given so, ethical issues may rise over each of the building blocks of the

randomized controlled trials. There are clear ethical issues with randomizing patients when there is no current alternative standard of care (offering some a possibility of cure and the control group no possibility of cure) and with performing sham (placebo) surgeries to patients (Buchwald, 1997). Furthermore, studying risk factors cannot be performed via clinical trial because it is unethical to expose subjects to factors that may cause them any harm or disease (Stroup et al., 2000). Ethical issues are very often raised as an argument against the use of randomized clinical trials and testing through observational studies (Benson & Hartz, 2000; Naylor & Guyatt, 1996).

2.2.1.2. Observational Studies

Observational studies are an epidemiological instrument, defined as the process of empirical association between alterations in a certain variable, usually either an exposure or an intervention, and changes in another variable of interest (Stroup et al., 2000). They can be used to determine causality, riskiness and effectiveness in situations where, due to ethical issues or others, randomization is not possible or advisable (Benson & Hartz, 2000; Christensen et al., 2007; Naylor & Guyatt, 1996). The most common forms of observational studies are case-control studies and cohort studies. Contrarily to controlled, randomized clinical trials, observational trials have no randomization of subjects at the initial stage, rather using statistical techniques to avert bias (Christensen et al., 2007).

Case-control studies are retrospective analyses in which the groups of participants are defined on the basis of presence of absence of a certain outcome or condition of interest, such as a disease. Cohort studies, on the other hand, can be retrospective (historical cohorts) or prospective, and the participants are selected on the basis of presence or absence of a certain variable, either an exposure or an intervention (e.g. smoking); there is no randomization in the allocation of the control (Christensen et al., 2007; Friedman et al., 2010; Ioannidis & Haidich, 2001).

2.2.1.2.3. General Criticism and Limitations

The main flaw attributed to observational studies concerns the validity of their conclusions. Because there is no randomization, there is a high risk of bias: its cohorts or case-controls are defined usually based on an exposure or a disease, which may have

unidentified confounding variables that may lead to spurious or biased connections, such as (but not limited to) age, socio-economical status and education (Benson & Hartz, 2000; Mausner & Kramer, 1984). Consequently, the hierarchy of research designs in medicine favors clinical trials over observational studies, mainly based on a series of comparative studies from the 1970s and 1980s that show that biases in observational studies render more positive results than corresponding trials (Benson & Hartz, 2000).

The obvious limitations that observational studies have are related to the fact that they are not experimental, and therefore conclusions can only be ascertained over phenomena outside the control of the researcher. This implies that new techniques and therapies, unless experimented on by patients for reasons or means other than those consequential of the investigator's initiative, are not in the realm of observational studies.

2.2.1.3. Experimental Studies versus Observational Studies

The debate has been reopened recently with some articles that show that observational studies' conclusions are correct most of the time with no systematical inflation of results when compared to clinical trials on the same subject, possibly due to better data sets and newer statistical methods (Benson & Hartz, 2000; Concato et al., 2000). Other authors show high correlation between the results of the two types of studies, although with some variability in the magnitude of the efficacy of the treatments tested (Ioannidis & Haidich, 2001). Arguments for the control of bias have also been argued for outside the medical literature (Shadish, Clark, & Steiner, 2008)

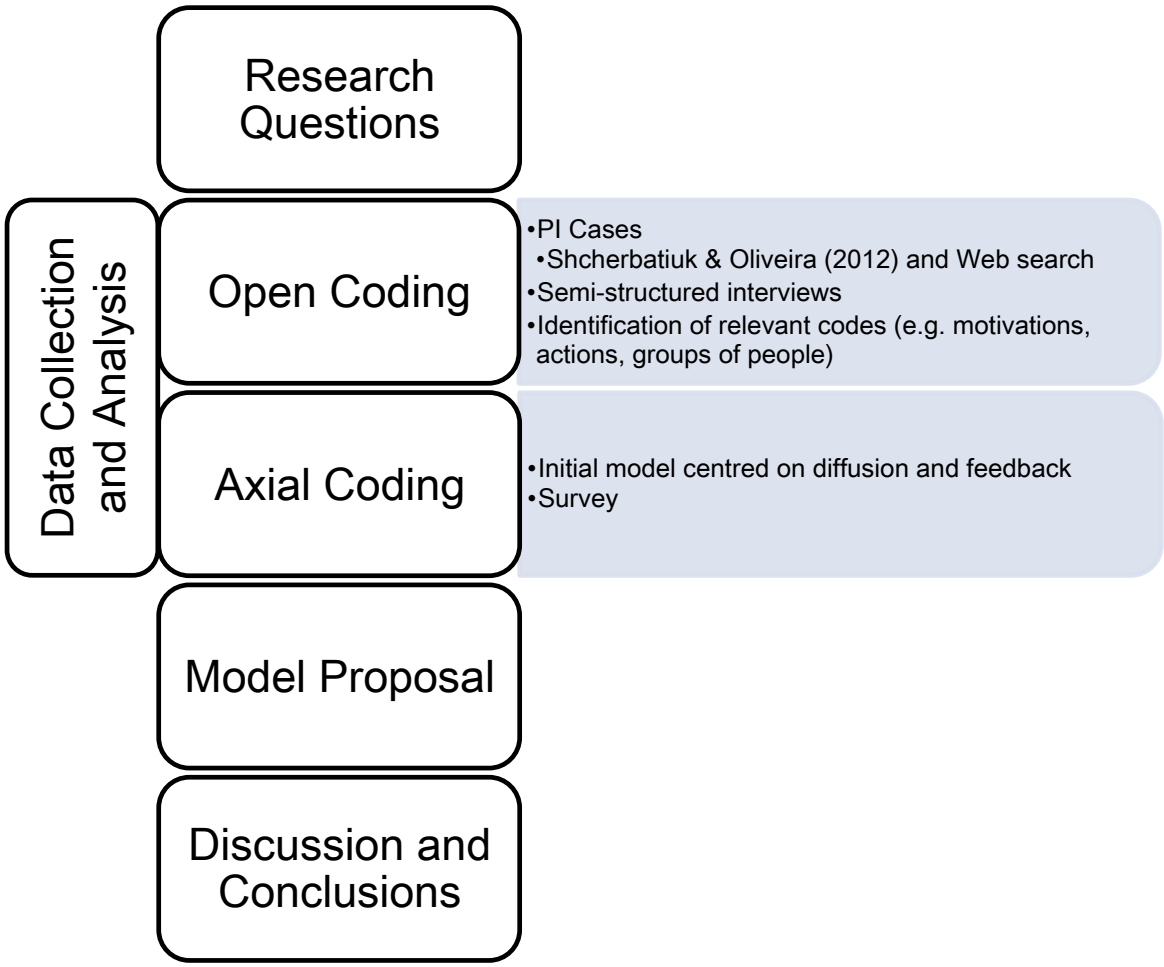
Several authors argue that observational studies and clinical trials should not be held one against the other, but should rather be addressed as complementary, and the focus should be on understanding their strengths and weaknesses and their uses (Concato et al., 2000; Friedman et al., 2010).

3. Methods

Figure 2 outlines the methodology used in this work. The analytical method chosen to develop this study is grounded theory (Glaser & Strauss, 1967). This method of analysis is defined by empirically developing theory empirically with the use of induction, not deduction

(Egan, 2002). It is particularly useful when there is not yet a developed theory that appropriately describes the phenomenon in study (Glaser & Strauss, 1967). In fact, although there is some literature on diffusion to the market and to established communities (e.g. Baldwin et al., 2006; Franke & Shah, 2003), peer-to-peer diffusion of innovations and its relation to validation practices is, to our knowledge, largely unexplored by user innovation theory in general, and patient innovation literature in particular. The gap in the literature that motivated this investigation is consequence of the literature review developed in the context of this master thesis. This approach was taken with great care, given that in grounded theory analysis, pre-conceived theoretical frameworks may bias the process of inferring theory from data (Glaser & Strauss, 1967). To address this issue, at each step we introduced activities to challenge inference from the data.

Figure 2 - Methodology



We begin our grounded theory process with data collection. To identify cases of patient innovators we searched through academic literature and online resources found in Google

searching, including online newspapers and the MIT Inventor of the Week archive with 100 medicine and health innovators[4]. The most valuable resource was the literature on patient innovators (Shcherbatiuk & Oliveira, 2012). In online searching, we used keywords that include combinations and variations of “patient”, “inventor”, “innovator”, “entrepreneur”, “built his/her own”, “medical device”, “necessity is the mother of invention” and “cured him/herself”.

Of the many innovators identified from both sources, we only considered patient innovators that created innovations primarily for their own use, or of someone close to them, as defined in the user innovation theory (Shcherbatiuk & Oliveira, 2012; von Hippel, 2005). Our sample was further reduced by our choice to only consider primary sources of information, the patient innovators. As a consequence, the sample consists only of individuals still living – which unfortunately is often not the case. In addition, we could not find contact information for all the innovators.

The final sample consists of a total of 57 patients, caregivers or family members who were innovators, of which 22 (39%) were found in Shcherbatiuk and Oliveira’s database (2012). Croswell (1998) proposes that the following steps in grounded theory building are open coding, in which data is categorised; axial coding, in which the central phenomenon is identified, as well as its relations to other categories; and finally the proposal of a theory.

The process of open coding was initiated when we started collecting data. We conducted three semi-structured phone calls with patient innovators who were readily available, to learn about their experiences in innovating and diffusing, from inception to present state.

To perform open coding, we sought to divide the data collected in sets of categories that put together multiple observations. Table 1 outlines some of the category sets identified. For example, one of the interviewed patients shared their innovations with doctors with the main purpose of asking for medical feedback, whereas another did so with the main intention of getting them to test the solutions on other patients. From this information we generated the category “motivation” that is further divided in subcategories, two of which represent the described cases.

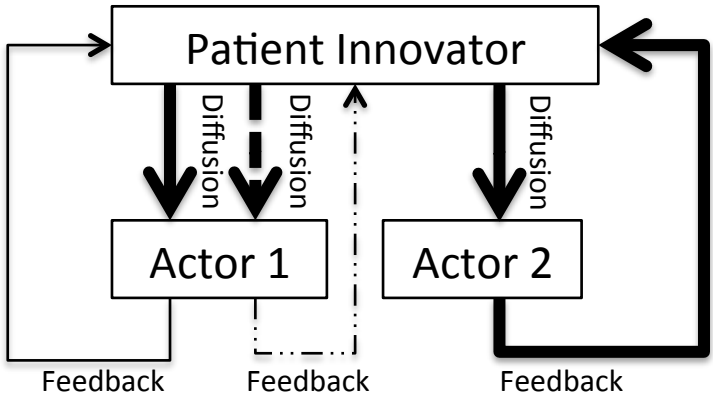
[4] http://web.mit.edu/invent/iow/i-archive-mh.html

Table 1 - Outcome of coding – central phenomena and related categories

Central phenomena	Categories (generated during open coding)
Diffusion	Motivations
	Actors/Recipients
	Means of reaching Actors
Feedback	Active request
	Impact on the innovation
	Testing
	Testing procedures

Within the process of axial categorisation we find that central to the phenomena observed are "diffusion" and "feedback". The grouping of categories generated in open coding and central phenomena is represented in table 1. Diffusion appears to form an iterative process of feedback that has some impact on the innovation itself, and that not only different actors have different feedback outputs, but also that different types of diffusion may lead to different types of feedback. Instances of verbal feedback ought to have a significantly different impact on the medical innovation than feedback from other patients who experimented the innovation on themselves, for example. This process is graphically represented in Figure 3. Learning further from patient innovators, we should be able to understand what those differences are.

Figure 3 - Axial Coding



Between axial coding and building of the theory, more data was required with a higher degree of structure. Taking advantage of the contact list of patient innovators previously created, an online survey was developed.

3.1. Online Survey

As the categories and phenomena related to our research questions were emerging we developed a survey to further explore our findings in a more structured way, using our sample of 57 patient innovators identified. The survey embodied open and closed questions (see Appendix 2). It was sent to the 57 patient innovators identified and answered by 12, only 10 of which completed all the answers.

The draft version of this survey was pre-tested on a group of academic colleagues and improved based on their feedback. All questions in the survey were referring to the periods before health regulators were involved. This information was communicated to the survey respondents in a clear, simple, and visible manner. Involving health regulators in this research is interpreted as a point from where innovations enter standardized process of validating medical innovations. Our focus of analysis was the exploration of the informal ways with which patient innovators attempted to validate and diffuse their innovations.

The survey is divided in three parts. The first part aims to capture information on the innovations developed (description) and its effect on the innovators' lives, as well as to establish the motivations for its development. This latter point serves the purpose of understanding if respondents are user innovators in concurrence with the theory, namely if they expected high personal benefits from creating their innovation (von Hippel, 2005). Where possible we apply measures already used in the extant academic research. The levels of satisfaction with the standard of care and with the patient innovation is measured on 7-point Likert scales (as in Oliveira et al.) We adapted scales used by Lüthje et al. (2002) to measure the newness of the solution, the personal benefit of creating it and the market demand perception.

The second part of the survey aims to explore further roles of different subcategories of people identified as relevant in the open categorisation phase. We divided the population of targets of diffusion between family members and friends, doctors, others (e.g. academics or engineers), nurses and caretakers, lawyers, other patients and manufactures and business

people. Related to each of these groups, the patient innovators were asked whether they discussed, shared or showed their innovation with each. They were asked to code their motivations for diffusion (including receiving feedback or advice, testing, altruism ("help other patients"), profit, funding, business partnership and recognition). Then, they were inquired whether they asked and/or received feedback. As a proxy for understanding if validation occurred as a consequence of diffusion, they were asked whether the feedback received had led to modifications of the innovation.

The third part of this survey is developed with the main purpose of understanding if and how structured were any attempts to validate informally their innovations, in the form of studies or trials. Additionally, we tried to identify the sources of resistance that patients-innovators were faced with throughout the whole process.

Where appropriate we offered open-ended questions to allow for maximum collection of information.

4. Results

4.1 Survey Results

Patient innovators reported, on average, a significant difference of quality of life before and after having developed their innovation (from 2 before to 6 after, in a scale of 1 to 7). This result is significant but may, nonetheless, be distorted by self-reporting bias by under- and over-evaluation of, respectively, perceptions pertaining to the moments before and after the innovation. Patients identified as the main reasons for creating their solutions personal use (or of a family member), learning or developing new skills and helping others. They have identified likely commercial adoption of and personal benefit from their innovation (at the time of development) at approximately 5 in a scale of 1 to 5. 83% of respondents experimented their innovations on themselves, and all of them reported that self-testing directly led to modifications on their innovations.

Table 2 shows how and with whom the patient innovators shared information about their innovation, and the outcomes of these activities. The results suggest that patient innovators most actively contact family members and friends, doctors and other patients. Of these,

doctors were identified as the ones providing less feedback or advice (60%). One patient illustrates this in an open answer of the survey: “they [my doctors] seemed not to have much time to spend on me or the idea.”

Patient Innovators in our sample have all indicated that at least one patient and at least one “other (e.g. academic or engineer)” had impacted the innovation. This impact on the innovation is in fact a source of validation, be it general praise or criticism or more constructive interactions, such as suggesting changes to the original innovation or its use. The results suggest that validation is iterative and occurs as a consequence of the patient innovators having diffused their innovations.

Table 2 – Diffusion and Feedback

	PI shared with them?	Received Feedback?	Actively asked for feedback/ advice	Feedback caused modifications
Family members and friends	100%	91%	91%	70%
Doctors	92%	60%	90%	67%
Patients	92%	89%	78%	100%
Manufacturers and business people	75%	100%	100%	71%
Others (e.g. engineers, academics)	67%	100%	100%	100%
Lawyers	58%	100%	100%	29%
Caregivers and nurses	50%	80%	100%	75%

When the means patient innovators used to reach other people are considered, the results suggest that personal connections play a significant role. Most of the groups with which patient innovators communicate are either already known (naturally, family members and friends, and doctors) or contacted by referral from others. Internet (both searches and website/blogs) plays an important role in connecting patients but also finding individuals with specific type of knowledge (technicians and academics). These results are shown in Table 3.

Table 3 – Means of diffusion

	PI already knew them	By referral from others	Internet search	Media	Blog or website
Doctors	83%	17%	0%	0%	8%
Family members and friends	100%	25%	0%	0%	8%
Patients	33%	42%	33%	0%	25%
Manufacturers and business people	25%	50%	8%	8%	8%
Caregivers and nurses	25%	25%	17%	8%	8%
Lawyers	17%	25%	17%	8%	0%
Patent office	17%	42%	8%	0%	0%
Others (e.g. engineers, academics)	33%	17%	25%	0%	17%

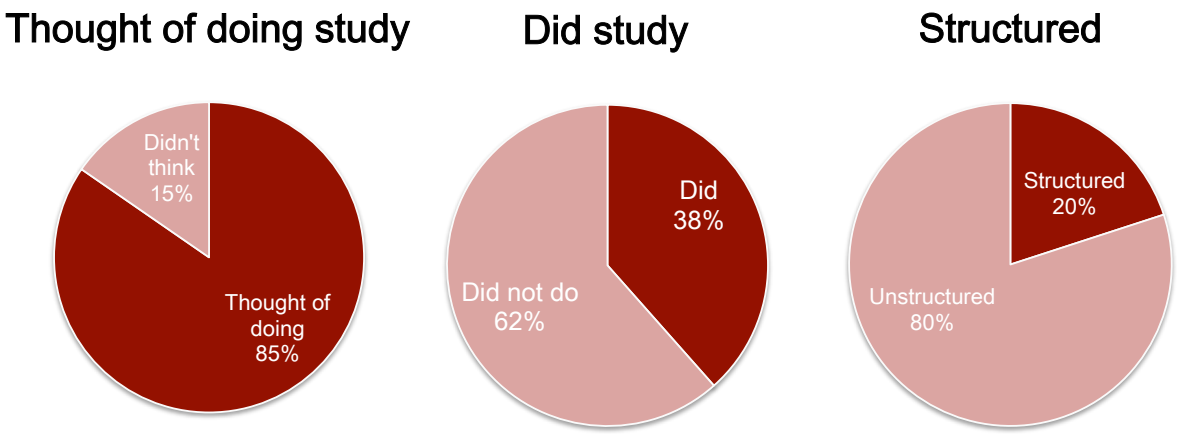
The main motivations for diffusion to other groups of people were the pursuit of validation, both from feedback and testing, the latter especially relevant regarding patients (to test on them) and doctors, nurses and caregivers (to test on other patients). Generosity or altruism also plays a great role, with recognition being credited by patient innovators as the less important factor to motivate their sharing. These results may be distinctive to this specific group of user-innovators. In contrast, in open source communities, for example, enjoyment-based intrinsic motivations are identified the strongest drivers for innovation and diffusion (Lakhani & Wolf, 2003). Table 4 sums up the findings.

Table 4 – Motivations for diffusion (all measures are on the following scale: 1 – Not important; 2 – Somewhat important; 3 – Very important)

	Doctors	Family and friends	Other patients	Manufact. and business people	Caregivers and nurses	Lawyers	Others
To ask for feedback / advice	2,6	2,6	2,6	2,9	2,6	3,0	2,8
To help other patients	2,9	2,0	2,8	2,7	3,0	1,5	2,2
To sell to them	1,7	1,4	2,0	2,4	2,0	1,7	1,2
To get funding	1,8	1,6	1,6	2,3	1,5	1,3	1,6
Recognition	2,0	1,2	1,5	1,9	1,8	1,0	1,6
Business partnership	1,8	1,5	1,1	2,6	1,5	1,3	2,2
To test the solution on them	1,7	1,5	2,6	1,7	2,3	1,5	1,8
To test the solution on other people	2,8	1,8	2,3	1,9	3,0	1,0	1,4

The results suggest that despite most of the patient innovators having thought of doing some trial or study (85%), only 38% undertook some sort of testing scheme, of which only 20% appear to be structured (Figure 4). Some examples: “Asking questions, encouraging them to have sleep tests using the device”, “Opinion of patients” and “gave to many patients to experiment over the years”. Patient innovators interviewed pinpointed money, regulations and time as the main deterrents for the development of a trial or study. Other resistance sources are outlined in Appendix 1.

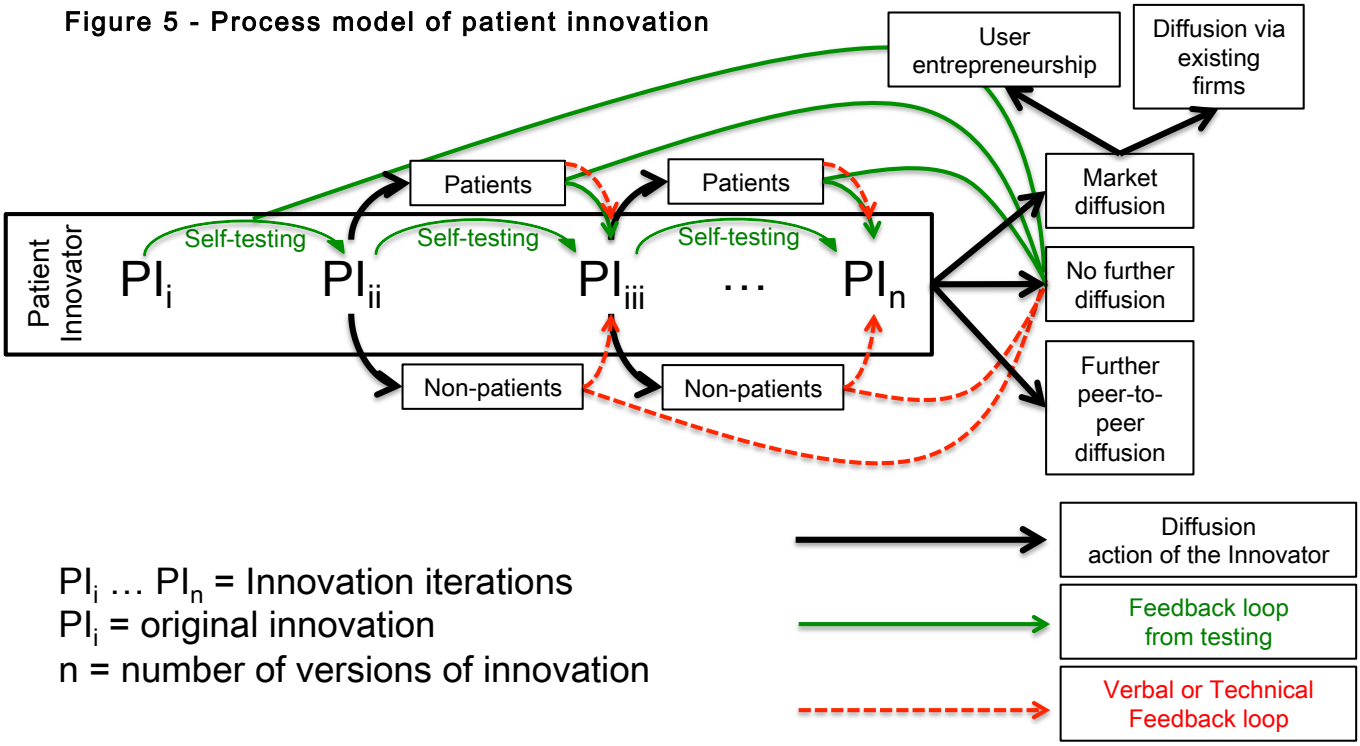
Figure 4 - Informal studies



4.2. Process Model Proposal

We structure the observed processes of patient innovation diffusion and propose a process model for an iterative process in which incremental validation of the innovation is performed after, and because of, diffusion to other people (Figure 5). This process model is characterized by feedback loops that lead to new iterations of the innovations, enabling its continued improvement.

Figure 5 - Process model of patient innovation



Three types of feedback loops were observed. The first is the consequence of self-testing: the patient innovator, or the person at their care, usually experiments the solution on him or herself. Of our 83% of survey respondents who have self-tested, 100% have indicated this to be a direct cause of modifications over the original innovation. The second type of feedback loop is what we call verbal or technical feedback, which includes medical, technical, legal or emotional counsel or advice. Relevant actors providing this type of feedback include doctors, family and friends, technicians, researchers, nurses and caregivers. The third type of feedback loop is also the consequence of experimentation, but of other patients. It includes data and verbal accounts, both structured and unstructured, of outputs, means of experimenting, side effects and other comments associated with the experimentation

process. Although patients can also be involved in verbal or technical feedback, they are, other than the inventor, the primary source for the third type of feedback, testing the innovation.

One important aspect of this model is that, other than self-testing, it is diffusion to others that causes the acquiring of information necessary to the creation on newer iterations of the innovation.

Although the diagram presented is not exhaustive, it attempts to show the main likely options the patient innovators are faced with. At any point in the process, the patient innovators may choose to abandon the innovation altogether, as a consequence of either their self-testing results, the verbal or technical feedback or the testing feedback they have received. They may also choose to stop diffusing it for different reasons, perhaps associated with other resistance sources. Other options at any moment are market diffusion, either by setting up a firm (user entrepreneurship) or selling or licensing their innovation through an existing firm, and also continuing the process of peer-to-peer diffusion, through free revealing in their community.

5. Conclusions and Discussion

Patient innovators have been found to share mainly with their personal contacts - with family members and friends, doctors and other patients, with doctors being the group of individuals providing the less amount of feedback. We speculate that this may be related to resistance to patient-originated innovation. This is corroborated by another result of our survey that identifies unwillingness to take risks from doctors as a significant resistance source faced by patient innovators (Appendix 1). Patient innovators mainly diffuse to communities of people they already know or ask their communities for referrals to reach other people with the purpose of diffusing to them. This is in line with previous literature, which refers to user-innovators sharing with their communities (Baldwin et al., 2006; Franke & Shah, 2003). However, the Internet seems to play an important role especially in the recruitment of other patients, and establishing links with individuals with complementary knowledge to what the innovators want to achieve (academics and engineers). This may be important information in informing policy makers or the general public of the need to find

tools for recruitment of patients and venues for establishment of networks for the sharing of experiences between patients of the same diseases and individuals with skills and knowledge that may help patients embody their ideas for innovation.

Diffusion was shown to have impact in the innovations themselves, via the two described feedback loops. The entire sample identified other patients and other people (technicians, engineers, academics) as groups of people whose feedback impacted led to modifications in the innovations. One patient who developed an insulin pump hints the reasons why, when asked why they had not shared with doctors: “Because my solution is oriented to patients’ everyday use and, as a diabetic patient, I think that the patients are the ones that have the knowledge in the topic of everyday use of the device. I consulted the technical aspects with engineers, because I know my doctor doesn't really know about insulin maintenance.”

Based on these results, we propose that the act of diffusion not only precedes but causes a process of incremental validation, through feedback loops that cumulatively lead to modifications in the innovations, consistently with the process model detailed above. This premise is strengthened by the fact that the main motivations we found for the diffusion actions were to obtain feedback or advice and for patient testing purposes.

However, the validation phenomena observed are rather unstructured. Incremental validation, as defined in this work and based on the interviews, can be attained by two different methods: one is by getting feedback or advice from different people, the other from having other people test the innovation on themselves (see Figure 4). The latter, however, can itself be done in many different ways, with different degrees of structure, accuracy and, consequentially, scientific credibility. We define a structured study as one bearing at least two of the fundamental marks of clinical trials, outlined before: controlled, randomised, and blind testing. Similarly, observational studies should only deemed structured in case of statistic treatment of results to remove or reduce bias.

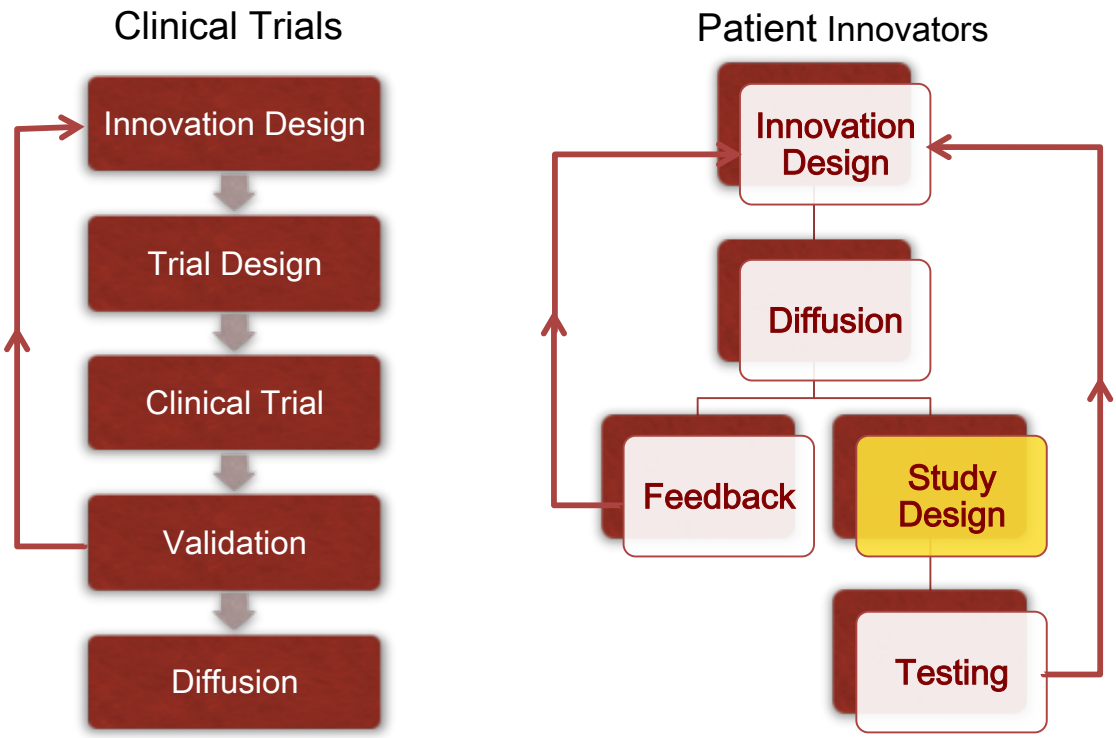
What we have found is that despite most of the respondents having declared interest in developing some form of trial or study, only approximately 38% actually self-reported having developed some sort of testing, and of these we considered only 20% as structured attempts. Some patient innovators developed surveys to scan the market before developing the products, others made phone calls asking those who used how they felt, but none used

statistical techniques to avert bias and very few used any form of controls. None of the trials in our sample involved blinding.

5.1 Contrasting the model with current practices in medicine

We contrast the model proposed with a general streamlined process of randomized clinical trials, outlining some differences and similarities. The objectives of contrasting them are 1) to consider if the structure and execution of clinical trials and observational studies may be of help to improve these patient-led informal studies and 2) to consider whether the practices of informal validation by patient innovators can help in addressing some of the limitations and criticisms of clinical trials.

Figure 6 - Comparison between clinical trials and patient innovators processes



Adapted from FDA (2013)

One point of divergence between the two models concerns the sequence of diffusion and validation. Whereas in typical clinical trials for drugs and medical devices innovations have to be proven safe and, in some cases, proven effective before they can be marketed and used by patients outside the control of practitioners, in the case of patient innovators what we see occurring is that use, experimentation and general diffusion of the innovations occurs mostly

before there is reliable data on safety and efficacy other than that obtained through self-validation.

Some of the main characteristics of clinical trials and observational studies were not found in the majority of patient innovators cases analysed. When compared to the building blocks of clinical trials, the testing procedures in which patient innovators engage are limited in number and in structure and lack controls, blinding, and randomization. When compared to observational studies, the main difference is that patient innovators are not using statistical techniques to avert or reduce selection bias.

Comparing clinical trials with observed practices of informal validation is particularly interesting from the perspective of the limitations and objections to clinical trials, namely high costs, long duration, low patient recruitment, design rigidity, and ethical issues.

Although we did not directly collect data related to the costs associated with the validation attempts, the fact that people diffused and requested feedback mainly to and from people already known or that someone referred them to shows that at least the costs of recruitment of potential testers and collection of technical, medical or legal advice are low.

Long duration is generally not a pressing issue for patients in informal validation processes. The reason for this is that other patients are experimenting, thus having access to the innovation during the process of validation. Given that adaptations can occur at any point during iterative validation, the hypotheses, testing procedures and innovations under testing are flexible. This means that, for example, if an innovation is slightly improved or modified, the patient innovator can simply ask their fellow patients to experiment with it without having to redesign testing procedures or having to find a new population of testers. In contrast, the hypotheses and procedures in clinical trials are generally rigid and stay fixed in a trial process. If any change is needed the trial process is restarted.

The main ethical issues of clinical testing in patients are mainly related to the impossibility of research organisations to knowingly expose patients to situations where they know the risks outweigh the expected benefits. In these informal settings, however, patients themselves self-select to experiment with solutions, given their high need and dissatisfaction with the standard of care. Patient recruitment is thus lower than in clinical trials, also due to the easier access to already known communities. Nevertheless, unlike most clinical trials,

because of the incremental manner in which validation is performed, the decision of initiating or not the study should be less dependent on the amount of testers available.

In what concerns patient recruitment, we cannot speculate to the differences of ease of recruitment of the two processes. Whereas in clinical trials there may be ethical, bureaucratic, and geographical barriers to patient accrual, in informal studies initiated by patient innovators credibility and safety barriers may hinder ability to recruit patient. However, unlike most clinical trials, because of the incremental manner in which validation is performed, the decision of initiating or not the study should be less dependent on the amount of testers available at the onset of the study.

Because there is no randomisation used in most of the validation practices observed, and due to the self-selection of most patient that experiment with the innovations in this sample, these observed processes of patient innovators have higher resemblance to observational studies than to clinical trials. However, the lack of structure or, more exactly, the absence of attempts to control for selection bias with any statistic techniques, leads us to classifying most of these processes as informal observational trials. These informal observational trials have generally no formal study design, which if existent could render the validation attempts more sound and valid, better convincing the scientific community of its merits, and perhaps informing future clinical trials.

5.2. Policy and Managerial Implications

The phenomenon of informal validation of patient innovators is happening, and it is seems it is here to stay. The key questions are what can we as a society do to make it better, and what can we learn from it?

Our results and model show that the observed processes of diffusion initiated by patient innovators play a major role in the informal validation of their innovations. The two feedback types observed, verbal feedback from the communities where the patients are embedded in, and data collected by other patients experimenting with the innovation, suggest possible areas around which to focus when considering ways to improve this process and increase individual and societal benefit. The help may consist of providing venues for information exchange to happen, increasing the reach to patients and other people to increase verbal and experimentation feedback, and improving the quality of the feedback.

Our data, research (e.g. Kuene et al. 2012), and common knowledge suggest internet and, in particular, online communities and blogs as potential venues for information exchange, collaboration in innovation development, and accumulation of valuable knowledge about experiences related to diseases and solutions to fight them. Yet the problem is to gather a critical mass of patients that would extend the reach of patients interested to share their innovation and possibly get feedback. We review below some of the attempts to provide such a venue – online platforms for patients and medical professionals.

When the quality of the feedback is considered, it is instrumental to ensure that there is some structure in the process and that the information gathered can be used for informing other clinical trials or the scientific community. This structure can exist in the form of reducing bias through the use of statistical tools or by performing random, blind controls whenever possible. In lay terms, it is important to increase scientific language and methods as the preferred choice for communication among patients who innovate, provide feedback, and experiment.

A good way to ensure the quality of the feedback is by providing of tools and practical guidance for patient innovators. This needs to be carefully balanced so that the process is not introducing too much of a burden to innovators and decreases the chances of the tools being used.

The lack of tools for control and advising for patient innovators looking to test and improve their creations and for patients in desperate situations, hoping to experiment with the latest ideas and innovations, may pose higher threats to public health than if the process is guided and assisted. However, providing guidance and assistance opens a number of issues, from legal responsibility in case of mistreatment to a threat of bureaucratizing the process to an extent that inhibits further development of innovations.

While to this point we referred mainly to the policy makers role, most of the considerations also represent opportunities from a managerial perspective. This relates to development of venues and tools, but also education and guidance services, for both entrepreneurs and healthcare-related companies.

A number of online venues for research entities, medical professionals, and patients have surfaced in recent years. Although the list that we introduce in the following paragraphs has

no intention of being a thorough enumeration of current validating technologies, it may serve as indication of the rising movement of the importance of information technologies, specifically the Internet, in the processes of validation of medical innovations.

The FDA is perhaps one of the first to have acknowledged the power of the web in crowdsourcing patients and clinicians data, having created a platform for the reporting of adverse effects of medical devices, MedWatch (FDA, 2013b). Also with the intention of reducing barriers to participation in medical validation, Pfizer has announced a virtual clinical trial, in which all data collected is self-reported by patients (Roehr, 2011).

It is not only policy makers and pharmaceutical companies who are using the crowd. Users are starting projects that use big data and other tools that take advantage of information provided by other patients to further advance medical knowledge. One of these tools is Patientslikeme[5], a for-profit "health data-sharing platform" that aggregates high amounts of health data to perform observational studies. A study performed in this platform disproved a previous scientific paper regarding the effects of lithium carbonate in amyotrophic lateral sclerosis (ALS), by systematically collecting and analysing self-experimentation information provided by patients (Wicks, Vaughan, Massagli, & Heywood, 2011). However, it does not appear to be generally suited for the testing of user innovations. Genomera[6], another online project, is "crowd-sourcing health discovery by helping anyone create group health studies" (Genomera, 2013). Users are able to create their own communities which can help them come up with a suitable testing design for their hypothesis or question and others will serve as the testers, applying this design and sharing symptoms and outcomes. Randomise Me[7] is a website dedicated at providing any person tools to create their own randomised, controlled trial, either individual or collective, with a tutorial to explain the building blocks of trials. Some examples of trials made include "Does eating cheese give you nightmares?" and "Does listening to the song that has been stuck in your head help you forget about it", which, albeit humorously, show how similar questions could

[5] http://www.patientslikeme.com

[6] http://genomera.com

[7] http://www.randomiseme.org

be posed for testing therapies and solutions patient innovators have came up with, helping validate both their self-testing and the results of the testing of others. Another interesting company, named Quantified Self[8], “is an international collaboration of users and makers of self-tracking tools”, organising a community of people with the purpose of helping others “get meaning out of their personal data” (Quantified Self, 2012). These and many other online “health 2.0” platforms have a common role of innovation intermediaries (Kuenne, Temidayo, & Moeslein, 2013).

Some issues should be raised with some of these tools, however. Self-reporting bias is a problem that should be accounted for, possibly with the use of controls. Variability in the testing patients’ ability to apply and test the innovations may also pose problems, and this is especially important with medical devices, given that drugs generally require less technical skills and have thus greater uniformity in its use (Christensen et al., 2007).

This work also provides keywords and criteria to help others find cases of patient innovators for further studies of the phenomenon.

5.2.1. Implications for the Patient Innovation project

This study has important managerial and policy implications for the current practices of validation and diffusion of heath-care innovations, and more specifically for those developed by patients of chronic diseases, as pointed out in 5.2..

Furthermore, this study is integrated in a larger and international research project entitled "Patient Innovation", which is responsible for the creation of a non-profit international, multilingual and free platform[9], designed to allow patients and caregivers to show and share their answers and practical solutions developed to fight their diseases. By sharing, patients may help themselves and others, stimulating value creation from the network effect – the contributions of others for the same solutions or alternatives helps create a unique database of solutions developed by patients with different diseases. This database is searchable by diseases, solutions and symptoms, and is self-managed by patients.

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[8] http://quantifiedself.com

[9] http://www.patient innovation.com

The learning acquired in this paper may allow for a better understanding of what patient innovators are doing, mainly in what concerns their diffusion and validation practices, as well as identification of resistance sources. We feel that the perceived need for validation tools for patient innovators should prove important to the development and eventual success of the Patient Innovation platform. To be more specific, the main take ways presented here, and its implications, will be further developed to be presented to the Advisory Board of the Patient Innovation, which include five renowned scholars and scientists, including two Nobel Laureates[10].

5.3. Limitations

The sample used in this analysis is mainly comprised of cases that can be considered successful, in which there were some diffusion attempts that led to us finding them online. Therefore, the results give no perspective on the incidence of diffusion among patient innovators in general, which may provide interesting results on understanding the most successful diffusion and validation practices.

There are other sample issues that may be overcome with a different study. First, all the results were found online, thus excluding other offline sources, such as hospitals and doctors' offices. Secondly, although we attempted to communicate with 57 patients, the survey includes only responses from 12 patient innovators, of which only 10 were complete. There are, undoubtedly, many other patient innovators out there. Finally, our sample was mainly of Canadians and Americans; other populations might have generated different results.

Patient innovators may also incur in some misrepresentation in the answers they provide. In one of our interviews, one patient informed us that he had shared with no other patients,

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[10] The members of the Advisory Board of the PAtient Innovation project include:

- Prof. Aaron Ciechanover, Professor, Technion-Israel Institute of Technology (Nobel Laureate in Chemistry 2004)
- Prof. Eric von Hippel, Professor, MIT Sloan School of Management
- Prof. Katherine Strandburg, Professor, New York University School of Law
- Sir Richard Roberts, Chief Scientist, New England Biolabs (Nobel Laureate in Physiology or Medicine 1993)
- Prof. Robert Langer, MIT

only to recant himself in a later email explaining that he was afraid that by sharing with others, which he did profusely, he was in some way breaking the law. This is an indication that patient innovators may have understated the number of attempts they made of having other patients experiment their innovations.

5.4. Future Research

The grounded theory method allows for discovering hypothesis as the data is analysed, expectedly with fewer preconceptions than in most other empirical scientific methods. We have outlined some trends in the processes of diffusion and validation of patient innovators, in a sample of mostly successful cases, of which diffusion was effective.

Further research is required to understand what happens in different, larger samples of patient innovators. Furthermore, this study of patient-to-person diffusion should be studied in a broader population of patients that does not only include successful patient innovators, to understand on the one hand which diffusion behaviours and, on the other, if validation initiatives led to higher success rates of the innovations.

Peer-to-peer diffusion practices observed in this project may not be exclusive to the medical field, and further studies on the diffusion of innovations, both products and services. A larger understanding of the pitfalls and successes of the behaviours and agents innovators contact in their attempts to diffuse and get market and technical feedback may help future innovators pursue the best strategies to ensure the success of their innovation.

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Appendix 1 – Resistance measures

	None	Low	Medium	High
Lack of technical skills / knowledge	20%	0%	60%	20%
High standards for scientific proof and regulatory approval (e.g. clinical trials)	40%	10%	0%	50%
Strong intellectual property (e.g. patents) and other legal constraints	20%	20%	30%	30%
Ethical concerns	56%	33%	11%	0%
Unwillingness from doctors/researchers to take risks	10%	40%	20%	30%
Lack of financial resources	10%	10%	0%	80%
The invention has only little commercial value/market potential	20%	50%	20%	10%
Lack of time	20%	10%	40%	30%
Other	50%	0%	0%	50%

Appendix 2 – Survey Script

All the questions in this survey are related to your solution and the steps undertaken by you in showing it to other people. We are interested in your actions before engaging any health authority (e.g. FDA, Health Canada, EMEA, Institutional Review Board, Ethics Committee). Our interest is to understand whether and how patient innovators get feedback from others in the initial stages of development of their solution.

1. Please describe the problem that motivated your solution.e.g. the condition from which you (or a family member) suffered.

2. Please identify your level of satisfaction with the solutions available for your problem (or your family member's) before your innovative idea.
(1 - Very Dissatisfied; 7 - Very Satisfied)

3. Please describe your innovative idea as specifically as possible so that we can understand it fully.

4. Please identify your level of satisfaction with the solution you created.
(1 - Very Dissatisfied; 7 - Very Satisfied)

5. For each line, please choose to which of the statements you identified your solution more with when you decided to develop it.

- 1 - It is a small improvement / modification of an existing solution; 5 - It is a totally new solution
- 1 - I would (or my family member) personally benefit very little from the solution; 5 - I would (or my family member) personally benefit very much from the solution
- 1 - Few people would adopt this solution if commercially produced; 5 - Many people would adopt this solution if commercially produced

6. How important were the following reasons for the creation of your innovation?
(1 – Not important; 2 – Somewhat important; 3 – Very important)

- For personal use/for the use of a family member
- For pleasure/entertainment
- To learn/develop new skills
- To sell/make money
- To help others
- Other (Which?)

7. In which year did you start developing and/or applying your solution?

8. Did you try your solution on yourself (or your family member)?
(Yes; No)

9. Did you change/tweak it as a direct consequence of having tried it on yourself (or your family member)?
(Yes; No)

10. Approximately how many times did you modify your solution?

11. With approximately how many people did you share your solution? Before engaging with health regulators (e.g. FDA, Health Canada, EMEA)

12. With whom did you discuss, share or show your innovation? Before engaging with health regulators (e.g. FDA, Health Canada, EMEA)

- Doctors
- Family members and friends
- Other patients
- Manufacturers and business people
- Caregivers and nurses

- Lawyers
- Patent offices
- Others (e.g. engineers, academics)

13. How did you find/reach them?
(For each of the selected groups of people)
- I already knew them
- By referral from others
- Internet search
- Media (e.g. TV, newspapers)
- Blog or website
- Social network
- Other (Which?)

The following questions are related to doctors.

14.1 Why didn't you show, share or discuss your solution with them?
(Shown only if doctors were not selected)

14.2 With how many did you discuss, share or show your solution?

14.3 How important were the following reasons for showing, discussing or sharing your device with them?
(1 – Not important; 2 – Somewhat important; 3 – Very important)
- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition
- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

14.4 Did they give you feedback, advice or suggestions?
(Yes; No)

14.5 Did you ask for feedback, advice or suggestions?
(Yes; No)

14.6 Did this feedback lead to modifications in your solution?
(Yes; No)

14.6.1 Why not?

The following questions are related to family members and friends.

15.1 Why didn't you show, share or discuss your solution with them?
(Shown only if doctors were not selected)

15.2 With how many did you discuss, share or show your solution?

15.3 How important were the following reasons for showing, discussing or sharing your device with them?
(1 – Not important; 2 – Somewhat important; 3 – Very important)

- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition
- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

15.4 Did they give you feedback, advice or suggestions?
(Yes; No)

15.5 Did you ask for feedback, advice or suggestions?
(Yes; No)

15.6 Did this feedback lead to modifications in your solution?
(Yes; No)

15.6.1 Why not?

The following questions are related to other patients.

16.1 Why didn't you show, share or discuss your solution with them?
(Shown only if doctors were not selected)

16.2 With how many did you discuss, share or show your solution?

16.3 How important were the following reasons for showing, discussing or sharing your device with them?
(1 – Not important; 2 – Somewhat important; 3 – Very important)

- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition
- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

16.4 Did you try to measure in any way the effects of the use of your solution?
(Yes (How?); No)

16.5 Did they give you feedback, advice or suggestions?
(Yes; No)

16.6 Did you ask for feedback, advice or suggestions?
(Yes; No)

16.7 Did this feedback lead to modifications in your solution?
(Yes; No)

16.7.1 Why not?

The following questions are related to manufacturers and business people.

17.1 Why didn't you show, share or discuss your solution with them?
(Shown only if doctors were not selected)

17.2 With how many did you discuss, share or show your solution?

17.3 How important were the following reasons for showing, discussing or sharing your device with them?

(1 – Not important; 2 – Somewhat important; 3 – Very important)

- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition
- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

17.4 Did they give you feedback, advice or suggestions?

(Yes; No)

17.5 Did you ask for feedback, advice or suggestions?

(Yes; No)

17.6 Did this feedback lead to modifications in your solution?

(Yes; No)

17.6.1 Why not?

The following questions are related to caregivers and nurses.

18.1 Why didn't you show, share or discuss your solution with them?

(Shown only if doctors were not selected)

18.2 With how many did you discuss, share or show your solution?

18.3 How important were the following reasons for showing, discussing or sharing your device with them?

(1 – Not important; 2 – Somewhat important; 3 – Very important)

- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition

- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

18.4 Did they give you feedback, advice or suggestions?
(Yes; No)

18.5 Did you ask for feedback, advice or suggestions?
(Yes; No)

18.6 Did this feedback lead to modifications in your solution?
(Yes; No)

18.7 Why not?

The following questions are related to lawyers.

19.1 Why didn't you show, share or discuss your solution with them?
(Shown only if doctors were not selected)

19.2 With how many did you discuss, share or show your solution?

19.3 How important were the following reasons for showing, discussing or sharing your device with them?
(1 – Not important; 2 – Somewhat important; 3 – Very important)

- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition
- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

19.4 Did they give you feedback, advice or suggestions?
(Yes; No)

19.5 Did you ask for feedback, advice or suggestions?
(Yes; No)

19.6 Did this feedback lead to modifications in your solution?
(Yes; No)

19.6.1 Why not?

The following questions are related to other people (e.g. engineers, academics).

20.1 Why didn't you show, share or discuss your solution with them?
(Shown only if doctors were not selected)

20.2 With how many did you discuss, share or show your solution?

20.3 Please name their professions.

20.4 How important were the following reasons for showing, discussing or sharing your device with them?
(1 – Not important; 2 – Somewhat important; 3 – Very important)

- To ask for feedback / advice
- To help other patients
- To sell to them
- To get funding
- Recognition
- Business partnership
- To test the solution on them
- To test the solution on other people
- Other (Which?)

20.5 Did they give you feedback, advice or suggestions?
(Yes; No)

20.6 Did you ask for feedback, advice or suggestions?

20.7 Did this feedback lead to modifications in your solution?
(Yes; No)

20.7.1 Why not?

21. Please provide a general sequence of the people to whom you showed your solution by dragging the alternatives. 1 is first, 2 is second, etc.

- Doctors
- Other patients
- Caregivers and nurses
- Patent office
- Family members
- Manufacturers
- Lawyers
- Others (e.g. engineers, academics)

22. Did you get unrequested feedback from people reached through any of these means?
(Yes; No)

- Media (e.g. TV, newspapers)
- Blog or Website
- Social network
- Other

22.1 Did this feedback lead to modifications in your solution?
(Yes; No)

23. Before engaging health regulators, did you think of doing some sort of study or trial?
(Yes; No)

24. Did you actually do any study or trial? (before engaging health regulators)
(Yes; No)

24.1 Please describe it. If it included randomization and blinding, please include it in your description.

24.2 Why not? You may select more than one.

- Patient recruitment
- Financial reasons
- Time
- Problems with the solution
- Regulatory/legal concerns
- Ethical concerns
- Other

25. Did you engage any health regulatory board?

- No
- FDA
- EMEA
- Health Canada
- Ethics Committee or Institutional Review Board
- Other(s) (Which?)

26. In which year did you first engage a health regulatory board? (e.g. FDA, Health Canada, EMEA)

27. Did you experience any of the barriers listed below? Please indicate to which degree.
(1 – None; 2 – Low; 3 – Medium; 4 – High)

- Lack of technical skills / knowledge
- High standards for scientific proof and regulatory approval (e.g. clinical trials)
- Strong intellectual property (e.g. patents) and other legal constraints
- Ethical concerns
- Unwillingness from doctors/researchers to take risks
- Lack of financial resources
- The invention has only little commercial value/market potential
- Lack of time
- Other (Which?)

28. Did you file a patent for your solution?
(Yes; No)

29. What is your age?

30. In which country do you reside?

31. What is your gender?
(Male; Female)

Appendix 3 – Sample data

Relation with need	Name of Innovation	Description	Type	Online sources
Patient	ReWalk	Robotic Exoskeleton for legs	MD	http://rewalk.com
Daughter	N/A	Device that helps an assistance dog in pulling its owner's wheelchair and a dog leash that requires little motor control to use	MD	http://web.mit.edu/invent/iow/casper.html
Patient	Diabetes Book	Daily control of blood sugar	TH	http://www.diabetes-book.com
Nurse	IV House	“Polyethylene site protector, shaped like a computer mouse, that is soft, smooth-edged, transparent, and attachable with a single piece of tape. The "IV House" is safer, quicker and less expensive than other methods of IV site protection.”	MD	http://web.mit.edu/invent/iow/rozier.html http://www.ivhouse.com
Patient	SiteSaver	“A device that attaches the IV needle and tubing to the patient’s hand securely and comfortably"	MD	http://edisonnationmedical.com/success-stories http://blog.edisonnation.com/2012/09/bob-heitkamp/ http://matnd.com/
Family member	Cloud4Cancer	Artificial "brain" to detect breast cancer	MD	http://www.nbcnews.com/technology/17-year-old-girl-builds-artificial-brain-detect-breast-cancer-908308
Patient	SolRxTM 1000 Series Home Phototherapy	Medical UVB home phototherapy equipment for psoriasis treatment	MD	http://www.solarcsystems.com/us_aboutus.html
Mother	i-Port	Injection port and inserter	MD	http://www.parade.com/health/diabetes-blog/archive/the-amazing-i-port.html http://www.i-port.com http://baptisthealth.net/en/patient-visitor/Documents/diabetes_news/82823198DiabetesNews_July_sept2007.pdf
Patient	Med-Track 360	Organiser software for cancer patients	MD	http://detroit.cbslocal.com/2011/10/17/new-software-organizes-cancer-care-for-patients/

Patient	Heal in comfort	"ultra soft, moisture management shirt that is designed for comfort, as well as holding the post operative equipment"	MD	http://www.healincomfort.com/healincomfort-is-featured-in-cnn-ireport/
Patient	TrueFIT	Mask for sleep apnea	MD	http://www.abc.net.au/tv/newinventors/txt/s3246976.htm
Patient	Thera Cane Massager	Cane Massager	MD	http://www.theracane.com
Nurse	AutoMedic	Pressure Relief Bed	MD	http://www.jurus.com www.business-opportunities.biz/2009/12/11/intentor-eliminates-bedsores-with-new-hospital-bed/ www.freepatentsonline.com/5233712.html
Patient	Passy Muir	Tracheostomy & Ventilator Swallowing and Speaking Valve	MD	http://www.passy-muir.com
Granddaughter	ClearRx	"An intuitive pill bottle and information system that includes a redesigned bottle, easy-to-read label, removable information card, color-coded rings and redesigned warning icons."	MD	http://web.mit.edu/invent/iow/adlerd.html
Daughter	CADEX 12	Diabetes Medical Watch	MD	http://www.cadexwatch.com
Patient	VBPM Kinetic Recliner™.	Recliner with with pendulum movement to facilitate blood circulation	MD	http://vbpmkr.com
Patient	Prokarin	Medicine for relieving MS symptoms	PH	http://www.elainedelack.com/elaine-delack.html http://www.msprokarinstory.com
Nurse	Pedi-Neb	Nebulizer administration tubing	MD	http://www2.nursingspectrum.com/articles/print.html?AID=4200
Patients	Auvi-Q™	Epinephrine auto-injector with the height and width of a credit card	MD	http://www.intellijject.com/solutions/the-product/
Patient	Log for Life	On-line diabetes log	MD	http://ethanmullis.carbonmade.com/about
Father	The Total Knee	A prosthetic knee suitable and safe for a child to run around on	MD	http://www.ossur.com/?PageID=12664
Patient	Cancerfin	Mixture with hot peppers extract for curing skin cancer	PH	http://www.newcancerfin.com
Patient	PerfIC Cath	Urinary Catheter	MD	http://www.adaptamedical.com
Mother	ePer 100	Cystic Fibrosis chest therapy electrical percussor	MD	http://www.eper.ca

Nurse	N/A	Programmable Turning Bed	MD	http://www.abc.net.au/tv/newinventors/txt/s1625367.htm ; http://smartech.com.au/contact.htm
Patient	RespireAide	Sleep Apnea device	MD	http://www.respireaide.com
Patient	Positional Therapy Pillows	Pillow to support the ideal position for patients with acid reflux	MD	http://www.positionaltherapypillows.com/About_Us.php
Patient	Mobilegs	"A more patient-friendly crutch"	MD	http://www.mobilegs.com/index.cfm?fuseaction=home.aboutus
Patient	Hanky pancreas	Fashion for diabetes	MD	hankypancreas.com
Patient	CTi brace	"A Knee brace that protects the knee in much the same way that a ski boot protects the ankle, proved highly effective."	MD	http://www.ossur.com/?PageID=12664 http://www.thumpertalk.com/topic/314006-cti-vs-asterisk/
Nurse	Vollman Prone Positioner	Bed that facilitates the turning and positioning of critically ill patients in prone position	MD	http://www.vollman.com http://www2.nursingspectrum.com/articles/print.html?AID=4200
Patient	CastCooler	Cast Cooler	MD	http://www.castcooler.com ; http://web.mit.edu/invent/iow/morlan.html
Patient	Shower Shirt	Water-proof garment for mastectomy patients	MD	http://www.theshowershirt.com
Patient	Frequencer	Electro-acoustical transducer for release of mucus through coughing	MD	http://www.dymedso.com/site_usa/patient/en/patient_louis.htm
Patient	BLOB	Insulin delivery device to minimise the injection gesture	MD	http://www.diabetesmine.com/2011/06/grand-prize-winner-blob-minimizing-insulin-injections.html
Friend	DryBath	"The world's first bath-substituting lotion." "A water-less bathing lotion (...) differing from the anti-bacterial hand washes by eliminating the heavy alcohol smell."	CO	http://www.youtube.com/watch?v=hNoTVnzGQg8 http://headboy.org http://www.healthfiend.com/weeklytop/2012-medical-health-innovations-and-breakthroughs/
Patient	Quietus Liners	Mask liner	MD	http://www.quietusliners.com
Friend	The Stark Hand	Natural Dexterous Hand	MD	http://www.popsci.com/node/54124 http://www.swisswuff.ch/tech/?p=427

				http://www.southcountytimes.com/Articles-i-2011-06-24-175737.114137-STARK-HAND.html
Mother	MyPokit	Wearable pocket for feeding tubes and other infusion lines	MD	http://www.mypokit.com
Son	MycroLab	Medical diagnostic system able to perform multiple tests on a sample as small as a drop of blood in a fraction of the time and at a fraction of the cost of processing by a conventional laboratory	MD	http://www.theaustralian.com.au/news/mothers-necessity-nurtured-invention/story-e6frg6n6-1225751566177 http://www.mycrolab.com/ http://www.abc.net.au/tv/newinventors/txt/s2669552.htm
Brother-in-law	Buzz POD	simple but very effective device for preventing you, the sleeper, remaining on your back whilst asleep.	MD	http://www.buzzpod.com.au/contactus.php
Father	OmniPod	Insulin pump	MD	https://www.myomnipod.com
Father, Nurse	PocketFlow Spacer	Asthma inhaler	MD	http://www.vivosmartmedical.com/contact
Patient	Neck Brace	Multifunctional neck brace that unloads stress from the neck and allows for head rotation	MD	http://www.hopkinsmedicine.org/dome/0606/feature1.cfm
Patient	Ortho-Glide	"saucer-shape disc with replaceable adhesive pads to help patients exercise during recovery"	MD	http://www.mdti.co.uk/Ortho-Glide/ http://www.ideaconnection.com/invention-success/Ortho-Glide-00026.html
Patient	Crohnology	Website for Chron's patients	MD	https://crohnology.com
Patient	Shane's Neck Brace	Low profile, flexible neck supporter	MD	http://shanesneckbrace.com/
Nurse	Bili Bonnet	Soft and flexible eye mask for premature infants with jaundice who have to undergo ultraviolet therapy.	MD	http://web.mit.edu/invent/iow/rogone.html http://www.small-beginnings.com
Mother	Neurolumen	Low-level laser, multimodal technology to control pain levels	MD	http://www.neurolumen.com/about.php
Doctor	Biffy Bidet	Bidet for cleaning people with little mobility or dexterity	MD	https://www.biffy.com/
Patient	Telescoping Herbst device	Othodontic device to correct overbite	MD	http://www.partmaker.com/news/cstudy_article.asp?releaseId=162#.Uc8WJBauDy8
Patient	The Wahls Protocol	Diet and protocol to control multiple sclerosis symptoms	TH	http://www.terrywahls.com

Patient	N/A	Prosthetic arm with a socket to integrate a smartphone.	MD	http://news.cnet.com/2300-17938_105-10009933.html
Nurse	One-Step Gravity Feeding Med-Flow Adapter	Mechanism for providing medication without interrupting feeding	MD	http://www2.nursingspectrum.com/articles/print.html?AID=4200 http://www2.mskcc.org/patient_education/_assets/downloads-english/566.pdf
Son	SilentAlert Resident Attendant System	"Remote monitoring system that can be used by caregivers to keep track of the daily activities of elderly people who are either still living at home or are in assisted living or nursing homes"	MD	http://www.bizjournals.com/pittsburgh/print-edition/2012/06/01/newcare-solutions-ways-monitor-elderly.html http://silentfallalert.com http://www.bluetreealliedangels.com/news_topic.aspx?id=71&date=6/1/2012

The coding for the types of innovation is the following: MD – Medical Device; TH – Therapy; CO – Cosmetic; PH – Pharmaceutical .