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Patient Engagement in Research and Development Processes of Biotech Firms

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Although the issue of patient engagement has been debated for several years, research in the health sector continues to be mainly conducted on patients, seen as a source of data, and not with patients, considering their active contribution in the research process. The concept of patient engagement implies the need for integration between scientific competence regarding a given illness and knowledge based on the direct experience of the illness itself. In this sense, patients should be involved in the identification of health priorities/outcomes. The concept of patient engagement is interpreted in different ways. This fact can create confusion and impasse in practicing patient involvement in medical research. The aim of this article is to begin a deconstruction of the complexity of this concept. This work is based on data collected through a series of qualitative interviews with R&D directors of biotech companies and representatives of patient associations in Italy. Italian biotechnology companies interpret patient engagement as patient centricity, an organizational model that includes the patient's experiential knowledge in research and development processes. This means passing from an illness-centred model to a patient-centred one, and, consequently, interacting constantly with the regulatory agencies and their request for a result produced accordingly. Nevertheless, many factors contribute to the spread of skepticism regarding patient engagement in many pharmaceutical industries: uncertainty about patients' ability to contribute to research, additional costs, slowdown and interference with the research process, uncertainty about how to resolve conflicts, confusion about how to implement a patient-centred approach, uncertainty about the financial value that patient centricity provides. So, patient engagement is often limited to participation, clinical trials, or education about a new drug using health professionals as proxies. The interrelation between regulatory agencies, patients and industries is shaping the contemporary healthcare research and development landscape. Each of them in various forms is involved in a process of organization and change of perspective. Nevertheless, there are no common or shared protocols or best practices, and the initiatives of companies and patient organizations are generally sporadic and inconsistent, which limits their effectiveness. In the Italian context, as in all Western countries, patient participation is seen as a fundamental process, but its implementation is still a learning by doing performance.

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Introduction

Today, the involvement of users in the management of illness and health has become a challenge faced by health services and professionals, leading to a cultural change, especially in the doctor-patient relationship. In recent decades, in fact, there has been the development of care models oriented towards an ever greater enhancement of the role of the person, seen as an active and "expert" subject within the clinical-care process. The active participation of the patient in his or her own health care is recognized as a crucial component of high-quality services, particularly in the treatment of chronic diseases. This change has also been stimulated by the spread of information technology, which has led to a greater sharing of information and decision-making between patients and physicians. Indeed, the innovations linked to the use of smartphones and other mobile devices would make an epochal rethinking of the user's role in the care process not only technically possible, but also economically convenient (Graffigna et al. 2016, Prey et al. 2014).

While the participation of patients in treatment processes has thus received and is still receiving a lot of attention, their involvement in health research processes is still little discussed. Although there are currently some associations that deal with including patient participation in all areas of health policies[1], direct involvement in scientific research processes is still episodic and essentially limited to the clinical trial phases and post-approval activities (Anand et al. 2017). Even if researchers and clinicians agree on the promotion of patient engagement, there is currently no consensus on the most suitable strategies and tools for achieving this goal. The purpose of this work is to identify the different key players in research and development patient engagement and to understand their different roles and expectations, and how they interact each other's.

To better understand what role the patient can play in research and development processes in the health field it is necessary, first of all, to start with a definition of the concept of *patient engagement* that can guide practices of the stakeholders involved. The meanings related to the concept differ according to the different contexts in which it is used and the peculiarities of the different stakeholders. The operational modalities of patient involvement in scientific research processes depend on the strategies developed in this field by various actors, such as regulatory bodies, research centres, red biotech companies and philanthropic foundations (Callon and Rabeharisoa 2003), and on the interactions they establish with patient associations. Consequently, the practices adopted will derive from the interests, values and objectives of the actors involved, which must necessarily harmonize with each other. This makes it difficult to find a shared vision regarding when and how to structure the involvement of patients and care givers (Duffett 2017), and to identify the methods of recording and measuring the results that it can produce (Boutin et al. 2017, p. 35).

[1]These include the Agency for Healthcare Research and Quality (AHRQ), a US government agency, the Patient-Centered Outcomes Research Institute (PCORI), a United States-based non-profit organization, and the European Medicines Agency's (EMA) Patients' and Consumers' Working Party (PCWP), which is actively working on designing an inclusive public health policy whose priorities will result from the dialogue of all stakeholders with the idea of a bottom-up process.

Objectives and Methodology

The goal of this work is to identify the methods implemented by stakeholders to promote patient involvement, and how Italian companies involve patients in the development process of biotechnological products. This work is based on literature review and data collected through a qualitative field research based on in-depth interviews. We followed a grounded approach in order to highlight emergent categories from our interviewees (Miles & Huberman 1994). The research was carried out in the period 2017–2019 and involved two categories of subjects: the Italian Research and Development directors of the biotechnological industries (5 interviews) and the representatives of patient associations in Italy (21 interviews with a saturation criterion). The main difficulty was to involve pharmaceutical companies, which do not easily allow interviews, so we used personal networks and contacts with industry gatekeepers trying to include different categories of biotechnology companies (diagnostics, pharmaceuticals, medical devices). For the selection of patient associations we considered two dimensions: 1) the size of companies (number of loyalists), and 2) the type of disease to which they refer (e.g., cancer, epilepsy, etc.). Given the exploratory intent of the work – there is little literature in Italy regarding patient engagement in the development process of drugs and devices – we analysed the interviews in the light of the available literature, bringing out the meaning perceived by the various actors, highlighting some emerging categories with respect to patient engagement in this area.

To analyse the concept of patient involvement, this paper focuses on three subjects/stakeholders, who interact with each other: 1) patients (and their associations); 2) regulatory bodies; 3) biotechnology companies (Red Biotech). Following this idea, we would like to provide a description of the main issues concerning the three actors we have identified regarding the practices of patient engagement in medical research and development. Moreover, we seek to deconstruct the complexity linked to this concept.

Patients, Care Givers and Patient's Associations

The concept of patient engagement in health research can have different meanings. An analysis of the literature reveals that some authors define the term "patient" as someone (not necessarily the patient him- or herself) who possesses experiential knowledge (Boivin et al. 2014, Duffett 2017). According to Hoos et al. (2015), the expression "patient involvement", rather than "patient engagement" or "patient empowerment", better communicates the role that the patient should have throughout the research process. In his conception, it is necessary that patients provide advice and guidance in the development and management of the life-cycle of drugs. It is therefore necessary to give an unambiguous definition of what is meant by "patient" and "involvement", which is also able to clearly identify the main interested parties:

> First, the definition of patient needs to be wide in order to capture all relevant populations who can provide valuable insights through different lenses […]. It should

> also be recognized that, as well as having keen insight and a different perspective, caregivers may sometimes be trying to lead 2 lives—their own and that dedicated to the patient. Second, involvement should not stop with consultation but should proactively embed patients and patient needs at the heart of the development and life-cycle of medicines. Patients' views and opinions should be clearly sought and valued as an integral and essential part of the process, with the development of strategies and practical tools that facilitate genuine patient involvement (Hoos et al. 2015, pp. 2–3).

According to Hoos's idea, researchers should develop strategies and practical tools that enable them to assess patients' views and opinions. Engagement should not be limited to a simple initial consultation, but should be deeply embedded in the development and life-cycle of products, such as drugs or medical devices, through direct and constructive interactions with patients. With this in mind, research should make itself available to patients through a deep understanding of their medical conditions, the challenges they face in everyday life, their goals, their disease symptoms, the side effects of therapies and treatments, and the unmet needs concerning therapy and quality of life.

Duffet prefers to use the term "engagement", and defines it as the co-production process of the research: "the term 'patients' will refer to patients, family, and caregivers that have personal experience or have been affected by the health condition being addressed […] the term 'engagement' means when patients co-build research programs through meaningful and equal partnerships with clinicians, scientists and other research team members. This type of patient engagement should occur throughout the entire lifecycle of research" (Duffett 2017, p. 114). According to this conception, patients provide a type of knowledge and competence based on experience, which should be evaluated and then added to scientific knowledge (Rabeharisoa et al. 2014, Boivin et al. 2014, Duffett 2017). So, the knowledge of patients becomes complementary and important, because it is based on the experiences related to the management of the disease and the impact it has on quality of life.

It is necessary that health research centres define working methods and practices able to integrate patient knowledge in the various phases of the research and development process of a medical product. The methods and forms of involvement are currently quite heterogeneous, and there is no clear consensus on how and when the patient must enter directly into the research process. Duffet (2017) identifies different levels of involvement, ranging from a very superficial presence that sees the patient participate in meetings, but with a passive role, to the situation in which patients are the main researchers in clinical trials (Table 1).

In the event that the patient actively participates within the research groups, the problem of patient training arises. It is necessary to activate a process of co-construction of knowledge. The training should include some basic knowledge on health research methods to enable patients to participate and understand the discussions, but at the same time it should keep in mind that the role of patients must be different from that of researchers, because they must be the providers of unique knowledge that differs from the strictly scientific (Marlett et al. 2015).

In Italy, there are still few initiatives that foresee the involvement of the patient in the scientific research cycle. From the interviews carried out with patient associations, it emerges that a sensitivity towards this topic has not yet developed.

The associations are mainly concerned with attracting the attention of public opinion in order to raise funds for developing research concerning the diseases they represent. In particular, it emerges that the associations consider the indirect involvement of patients more appropriate, through the mediation of physicians, who possess sufficient scientific knowledge to participate in discussions with researchers and, at the same time, have a privileged relationship with patients, because they follow them in the course of their illness. For associations, patient engagement mainly concerns the doctor-patient interaction.

However, there are some sporadic initiatives in which the patient has the role of representative or consultant. In the first case, representatives of the associations participate in meetings. This participation serves to inform rather than to make patients an active part of the process. In the second case, the consultancy is carried out in the initial phases of the research, through the administration of questionnaires, to bring out new ideas or research insights, or in the phase of evaluation of the effect of already approved pharmaceutical products, whose objective is basically that of disclosing these results.

Table 1. *Levels of Engagement in Research (Duffett 2017, p. 115)*

Levels of engagement in research	Description	Example
Representative	Present but not an active participant	A patient or patient group that is invited to be present at a meeting but primarily as a passive role and without equal authority as others present.
Consultant	Providing input and views on a select aspect of research but still external to the research team	A patient participates in a focus group or completes a survey about an aspect of the research, but no other involvement with research team or decisions made.
Partnership	Equal partnership with research team, given opportunity to provide meaningful contributions and co-building of research	A patient is fully incorporated into the research team and contributes to the development of the research questions, clinical trial design, trial execution, and dissemination of results. The patient is acknowledged for contributions as a co-investigator.
Leadership	Actively controlling, directing, and managing the research	A patient is the lead investigator, responsible for developing the research either solely or as co-principle investigator with traditional researchers.
Advocate	Focus on patients' rights, lobbying for changes, often with a specific agenda	A patient or patient organization that lobbies the government for increased funding for research.

Innovation and Regulation

Innovation, especially in the health sector, creates questions, ethical dilemmas, and sometimes unwanted and even harmful unintended impacts. Historically, the response to such perspectives has been to govern innovation with its products and

impacts after they have already become part of society. If the impacts on society, health or the environment are deemed undesirable, one has the option of changing or introducing regulation to control them in order to protect society. Regulation turns out to be a powerful governance tool in this regard, and as a result, the pharmaceutical sector, like many areas of innovation, is quite tightly regulated (Owen 2012, p. 2).

End-user involvement in innovation through processes such as open innovation (Chesborough 2003, to name but one) is now well-established, and participatory agenda-setting and value-sensitive design have been established to varying degrees within research programmes across the EU (e.g. in the Netherlands[2] and the UK United Kingdom[3]). For example, the Alzheimer's Society in the UK has built up a research network of about 200 carers and dementia sufferers who collaborate in setting research priorities, prioritizing grant applications and participating in grant selection panels (Wilsdon et al. 2005).

The realization of economic and social value has long been considered a responsibility of scientific institutions (Guston 2004). More recently, this point has developed into the emergence of what have been termed social challenges (Lund Declaration 2009) towards which science and innovation are targeted. This general trend towards science and innovation driven by social challenges has a broader structure than just the generation of commercial value, and concerns the concept of responsibility.

Responsible innovation reflects the desire for a more institutionalized and consistently applied, cooperative, values-based approach, in which the principle of participatory agenda setting, through the involvement of citizens and stakeholders in the formulation of grand challenges, is institutionalized and formalized as part of a more generalized governance, on a pan-European scale (Owen 2012, p. 8).

The underlying principle aims to achieve a better alignment of research and innovation with societal needs.

> Responsible Research and Innovation (RRI) refers to the comprehensive approach of proceeding in research and innovation in ways that allow all stakeholders that are involved in the processes of research and innovation at an early stage (A) to obtain relevant knowledge on the consequences of the outcomes of their actions and on the range of options open to them and (B) to effectively evaluate both outcomes and options in terms of societal needs and moral values and (C) to use these considerations (under A and B) as functional requirements for design and development of new research, products and services. The RRI approach has to be a key part of the research and innovation process and should be established as a collective, inclusive and system-wide approach (European Commission 2013, p. 3).

[2]In the first decade of the 21st century, through an innovative design of an electronic patient registration system or a truly intelligent electric counter, researcher anticipated or prevented moral concerns by managing them at the design stage, reconciling efficiency, privacy, sustainability and security (van den Hoven 2013).

[3]Richard Jones (2008) reports on an experiment in which, through a process of public deliberation, the aims of research were discussed. The results were used to construct a call for research funding in the area of nanotechnology for medicine and healthcare. The public dialogues provided clear guidance on the relative priorities of six potential areas of application of nanotechnology for health care, informing and shaping the nature of the funding call itself, so that it could better respond to societal values.

From this perspective, several national health services nowadays consider it increasingly important to actively involve patients in the identification of healthcare priorities, pursuing as an ideal the position that reads: "nothing about patients, without patients" (Pushparajah 2018, p. 7).

In 2006, the European Medicines Agency (EMA) established the Patients' and Consumers' Working Party (PCWP), which has recently reaffirmed its commitment to improving patient engagement to ensure that the patients' views and needs are considered at every stage of the life-cycle of the development of medicines (EMA 2014). The EMA and the Heads of Medicines Agencies (HMA) strategies, for the period up to 2020, emphasize the need for patient-focused innovation, and state that "in order to stimulate development, there is a need to facilitate the translation of scientific advance into innovative medicinal products that meet regulatory standards, accelerate patients' access to innovative therapies with added valued for patients and are affordable to the EU Member States' health systems" (EMA and HMA 2015, p. 10). One of the three EMA focus areas, with the Committee for Medicinal Products for Human Use (CHMP), is the involvement of patients in the evaluation of the benefits and risks of medicines, and also provides guidance to EMA scientific committees on incorporating patients' views during these evaluations (EMA 2014).

Real patient experiences are increasingly being integrated into the regulatory output of the European Medicines Agency. Furthermore, current patient involvement in the EMA consists of patients participating as members, substitutes or observers in activities involving experts or activities requiring representatives of organisations. There is an increasing number of initiatives to educate patients to become partners with healthcare stakeholders, and to provide useful information that can help shape the life-cycle development of medicines, from early research to the sales activities that follow marketing authorisation[4]. This demonstrates EMA's interest in strengthening a closer collaboration with patients (Pushparajah 2018) in order to institutionalize exchange structures between researchers, clinicians and patients as advocated by Callon and Rabeharisoa (2003, p. 198).

[4]The Italian experience of EUPATI, a patient-led network coordinated by the European Patient Forum (EPF), is worth mentioning in this respect. The main objective is to provide scientifically reliable and comprehensive information to patients on pharmaceutical R&D, with the aim of increasing the ability of "expert patients" to be effective advocates and advisors in pharmaceutical development when sitting at the table with regulators, companies and other stakeholders.

A New Organizational Perspective

Pharmaceutical product development is an extremely complex practice through which Red Biotech companies are trying to develop a new organizational and business perspective based on patient centricity. This moves away from a disease-centric approach (Higgins et al. 2017) by seeking to provide opportunities to more closely meet patients' needs and improve their lives from a more meaningful perspective for them and their families (Yeoman et al. 2017).

In addition, working with patients fosters innovation and allows their goals to be met from the beginning of the process, with outcomes more closely aligned to their needs and desires. In this process, policy makers and funders seek to control costs and require comparative quality and effectiveness evidence, forcing healthcare providers to focus on patient impact, structuring patient-centricity as a product life-cycle sustainability issue for the company.

From the companies' point of view, there are two main meanings concerning patient involvement: the first concerns the handing over of biological samples for experimentation (cells, blood, etc.); the second concerns the sharing of the patient's needs and experience of disease. The second meaning is the one we have focused on, and there are areas that benefit less from this potential for involvement.

For example, in the field of diagnostics, patient engagement is a very marginal concept for reasons related to the specificity and purpose of the product. In business development, research lines,

> we do discovery tests for early diagnosis; we are working on the colon, on gene expression; we do independent research, but on what is mandated. We are early to develop some things: the easiest to use, the most effective, the most sensitive [...] we improve all the technology, but the guideline is set by AIFA and EMA. [...] We make gene analysis kits to see if there are mutations. The oncologist has the answer from the anatomopathologist, and says: 'You can make this drug'. Since the cycles cost €50,000 per year, you can't do it to every patient. For example, colon carcinoma, if it metastasises, has these drugs, then you have to see if there are mutations. If there are mutations, the drug is like water, we throw it away. So, if we don't do this discrimination, the cost to the health system becomes unsustainable (R&D director of diagnostics interview).

Other areas, however, benefit, or would benefit, from patient involvement in an extraordinary way, as in the area of medical devices. There are various types of devices: some provide therapy, others support the patients and their daily activities, and often have curative treatment functions. In this case, the feedback of the use of the device by the patient, and the possibility of being able to understand what the incremental improvements are with respect to the quality of daily life, is very important. Moreover, in general, one should not underestimate the motivational drive of direct contact between the researcher and the sufferer.

> I would find it very useful to talk to patients and their families: in the case where the patients were children, I learnt a lot. Not only did I learn what, outside of what is written in the articles what the real manifestations of that pathology are in someone's life, but I also got inspiration and motivation for my own work. [...] It's a highly motivating factor to have someone in front of you who says: I'm better off with these things here,

> I've improved this, regardless of the results on the tests that then go to the regulatory authorities (R&D director medical devices interview).

In the field of drug and gene therapy development, patient centricity has its most significant application impact. According to our interlocutors, it is in fact an organizational structure that is now indispensable both for the possibility of developing targeted drugs and for understanding the possibilities of developing and approving new lines of research. In particular, the discussion – now structural – with patients within the advisory boards of the EMA has been highlighted several times:

> […] have seen it several times, by their definition now, especially on rare diseases, they try to involve a patient representative even in discussions with sponsors, as we might be going to the EMA for advice. They talk about what are potential definitions of primary endpoints of a study, then there is a translator who in simple words says: 'Look at this study. The main objective is to improve coordination activities, motor activities,' and asks: 'Do you think this has a significant impact on your life? This kind of improvement?' [Seeing] pre- and post-therapy, the patient gives his opinion and says: 'This is a great improvement' when the agency would have classified that improvement as clinically non-significant (pharmaceutical R&D director interview).

Here we see a reorganization of scientific institutions (Callon and Rabeharisoa 2014) in which the advisory system prioritizes the patient's disease experience – i.e., the knowledge that companies and regulatory agencies lack, by practising responsible evaluation within the framework of social alignment. In this way, the advisory board not only has the function of advising a company on the type of clinical study that needs to be done to approve the drug for marketing, but also has a control function on the primary endpoints that could be developed and on which the product will be evaluated.

It also emerges how the R&D directors recognize the strategic role of patient knowledge sharing to achieve better results, but also point out several negative bureaucratic elements to the full achievement of this new patient-centred organization.

A further aspect to be considered is that of company size, so we will limit ourselves to saying that for small- and medium-sized enterprises, the costs of engagement are relevant both from an economic point of view and in terms of time and personnel resources to be employed. In particular for small enterprises – where the motivational aspect of the engagement on the researcher is potentially stronger – the inhibiting aspect linked to the fulfilments related to the respect of privacy, to the bureaucratic procedures in general, and in particular to those concerning the exploitation of the rights on the research results in the case of public-private partnerships, has been repeatedly stressed.

However, there is general support for the importance of a cultural change within organizations and companies to be in line with new regulatory requirements on patient involvement and to ensure that the pharmaceutical products and medical devices developed meet the timely needs of their patients.

Another aspect to be emphasized for patient centricity approaches is the economic sustainability of the research and development process. In a highly competitive environment, and with advances in medical knowledge, a "One Drug

Fits All" development, which worked until a few decades ago, is no longer sustainable. A drug today is more "active" than it was in the past, and it has become more difficult to identify a new one with a significant active difference in its efficacy. Companies, particularly small and medium-sized ones, are therefore shifting their activities towards personalized medicine and the development of drugs for rare genetic diseases involving smaller groups of patients with specific characteristics and unmet needs. This further highlights the advantages for companies with respect to patient involvement in drug life-cycle development, but also the complexity of the factors at play in reshaping the future scenarios of the sector.

Conclusion

The concept of patient engagement expresses the need to integrate scientific knowledge of the disease with knowledge based on experience. This means that patients should be involved both in the choice of research priorities and in the subsequent stages of implementing the process and producing the results.

However, it remains difficult to define such involvement explicitly, as there is a great variability due to the different meanings attributed to the concept and to the different needs of the involved stakeholders. Patients, regulatory agencies and companies are three players on the health landscape who have different epistemic cultures.

Individually, patients have no negotiation power (weak users) (Altieri 2009) and their associations in Italy are more focused on satisfying the direct need for which they were created (linked to specific pathologies and an idea of engagement mainly focused on direct need and on the doctor-patient relationship, rather than on the research process).

For some years, the regulatory agencies, and in particular EMA, have activated procedures that provide for the active participation of patients in their normative production. Patients participate in discussions with other stakeholders with equal authority. In this way, the experiences and needs of patients have entered the regulatory outcomes of EMA.

Companies interpret patient engagement as patient centricity, highlighting the fact that patient involvement can bring them benefits in various aspects. Although there are still many problems for the realization of this involvement, in some sectors, companies are moving towards an organizational model centred on the patient rather than on the disease, by activating an interaction with regulatory agencies. In our research, it emerges that the field/type of product the company deals with, the size of the company, and the personal motivation of researchers are relevant in the implementation of patient centricity.

The development of health research is shaped by the interrelationships between these three types of stakeholders, who are called upon to reorganize themselves according to a new perspective. This reorganization process should adhere to the principle of social alignment, in which the importance of the ethical dimension emerges in the field of scientific progress, which must include an impulse to align

the development of science, technology and innovation with the needs of society, through an inclusive and participatory dynamic.

In essence, a cultural change has taken place that has implications on the identity, objectives and practices of the actors involved, be they individuals or organizations. Regulatory agencies act as the engine of this cultural change by demanding patient-centred outcomes and regulating patient engagement. It should also be considered that the engagement institutionalization process has forced companies to review their organizational structure. Furthermore, this occurs at a historical moment in which the sustainability of large-scale trials with respect to the incremental efficacy of drugs is being questioned. This combination of factors is producing an effective shift, especially of small-to-medium-sized biotech companies, towards personalized medicine and orphan diseases, in which the number of referral patients is reduced.

Nevertheless, in the Italian context, and in the Western world in general, it is difficult to find common protocols or best practices that guide the application of patient engagement. Companies and patient organizations do not yet have a shared vision on either the very concept of "patient engagement" in health research, or the processes that must be activated at the organizational level. There is a general belief that patient engagement is an important aspect that cannot be overlooked, but its implementation is still a "learning by doing" performance, and this fact limits its effectiveness.

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