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Patient in Control in Clinical Trials – European Initiatives for Improving Patient Empowerment in Clinical Trials Through Technical Implementation of Legal Norms*

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Abstract—**Patient empowerment is acclaimed as one of the major trends in the health care area bringing forward new conceptions how to involve patients in clinical research in a more (inter)active way. Patients and clinicians could benefit from more flexible consent-management and improved communication processes. This is where technology comes as an asset - the novel technological approaches promise to give more control to the patient, lessen the burdens on the researchers and all that in compliance with the legal and ethical requirements (e.g. data protection). The views of the European projects EURECA and p-medicine serve as examples for European approaches to patient empowerment.** ***Keywords:*** **patient empowerment, clinical trial, informed consent, data protection, technical applications.**

I. Introduction

"Patient empowerment" and its implementation by technical solutions has currently got major attention in the public debate. The central idea is that patients shall be encouraged to take a more active role in their own health care management [1]. It is a concept with rising popularity and seen as a solution to condition national health care systems for the future. The changing age pattern and the connected rising number of people with chronic diseases as well as the expected decrease in numbers of healthcare professionals calls for innovative modifications in the area of health care [2]. Besides the expected savings and a more effective utilization of the health care resources, patient empowerment is believed to be one of the key ways to achieve the goal of personalized medicine [3]. E-health technology shall be one of the driving factors to empower the patient [1] .The ideas and concepts for practical deployment of this concept are manifold, but a primary focus has been on how daily health care routine could be facilitated.

Not only in care but also in medical research there is a strong movement towards giving patients a more active role. Patients' consent into research is for ethical and legal reasons of fundamental importance. Helping patients to manage their consent is therefore a goal to meet in a process of patient empowerment and can be supported by electronic means. The European Union Seventh Framework Programme (FP7) has contributed worthwhile directions and concepts to use e-health tools in the clinical trial area, also with regard to the active involvement of the patient; nonetheless further development in this area is needed. Two projects currently funded by the FP7 – EURECA [4] and p-medicine [3] - put strong emphasis on empowering patients through the development of respective tools, which shall involve patients more actively in the health care decision process and in clinical research.

II. Patient Empowerment – Changing Old Habits

A. The Patients' changing role in the Health Care Setting

The long-prevalent paternalistic approach in the health care area with clearly defined roles between patients and doctors is shifting towards 'patient-centred care', 'patient engagement' and 'patient empowerment' [5]. These changes are strongly influenced by technology and the internet enabling patients to have access to an immense pool of (health) information. Further driving factors are the trends of healthcare consumerism, the growth of alternative medicine, the principles of self-help and mutual aid, the need of cost-reduction and a gain of efficiency in healthcare and the increasing importance of patient organizations and activism [6].

Patients' attitudes regarding this change of the paternalistic model vary and depend on many factors, such as the level of knowledge, access to sources of information, or the health condition of the patients. An essential precondition for a more active patient participation is the possibility of receiving good-quality health information and the capability of interacting productively with others in the health care team [5], [6].

B. Special Features of Patient Empowerment in Clinical Trials

In the context of clinical trials patient empowerment on the one side can contribute to the strengthening of the

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patient's position; on the other side it can conduce a lot to the quality of a research study. One of the key elements in clinical trials as well as in care to protect patients' rights and autonomy is the requirement of informed consent, but we will see that patient empowerment goes beyond this. Nevertheless, it is true that principally the patient who consents to take part in a clinical trial has to conform with the conditions stipulated by the researchers. Researchers always have to observe professional rules and therefore there will be limits for the patient to realize his or her particular wishes and perceptions. The patient remains, however, free to cancel his participation in the research study at any time.

III. Current Hurdles with Regard to Consent in a Clinical Trial

The argument that patient authorization for all medical experiments (including clinical trials) is needed is generally accepted. The atrocities of the Second World War were especially significant in convincing society at large of the need to regulate authorization procedures. Through the twentieth century the duty to obtain patient consent was embodied in legislation and ethical guidance at international and national level, starting with the Nuremberg Code [8].

However, as much as consent is acknowledged as a precondition of clinical trials, agreement on the practical realization of this principle is lacking. Focal points of the discussion include the controversy with regard to defining consent, the information duties of the doctor, patients' understanding of provided information, inclusion of vulnerable subjects and their capacity to consent, the possibility of re-using clinical data for other research (secondary use) and the necessity of consent in such a setting, etc. Some of the issues with regard to realization of consent will be discussed below.

A. Information duties towards the trial participant

Information is a prerequisite of valid consent, irrespective of its objective (whether it is treatment, trial participation, or data processing). The information duties towards the patient are complex: in the first place it has to be considered on which topics the information should be provided. Here different regulations offer different guidelines. For example Art. 2(j) of the Clinical Trials Directive [9],– a legal act which has to be implemented into the national law systems of all the Member States of the European Union - specifies that consent has to be preceded by information on the nature, significance, implication and risks of the clinical trial. On the other hand the Declaration of Helsinki [10] determines in Art. 24 that participants in research projects should be provided with information on "the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal."

Despite differences we can still recognize certain similarities between the different legal documents. What poses a bigger difficulty is the uncertainty of the situation when it comes to the required depth and detail of information that shall be provided to the patient [11].

One of the terms used for describing the amount of information is "appropriate" [12]. However, what is appropriate information and how should it be assessed are focus areas of the ethical and scholarly debate with regard to information duties towards the patient.

There are two opposing stances with regard to what may amount to appropriate information. On the one hand it is argued that patients should receive all information appropriate for a reasonable person, as only with comprehensive information can they really make a meaningful choice. By contrast, those who are against such an approach claim that the need for such extensive information is a myth and patients are rather burdened by the information they cannot comprehend. Furthermore, lengthy informed consent forms are used rather to protect physicians and investigators against possible legal proceedings than provide patients with an insight on the course of the trial. Finally, supporters of this stance argue that too much insight raises patients' level of anxiety, while not really improving the quality of choice that they are making [13].

Irrespective of this debate, efforts are being taken to improve patients' understanding in consent procedures (both in the area of clinical trials and treatment) [14], [15]. The main message out of literature review is that patients' comprehension depends on their health literacy, but interventions aiming at improving that comprehension can be effective (especially with respect to general understanding or the risks involved) [15].

B. Secondary use of data

Translational research is gaining momentum – the new technological and bioinformatics advances open up novel possibilities for health-care and research. The medical data collected in previous years during patients' treatment or earlier clinical trials can be re-evaluated and updated today. An analogous situation exists in the closely connected area of research with biological samples. There is evidence that the secondary use of data has already resulted in a number of medical discoveries [16].

The scientific community, as well as society at large, has a vital interest in the fruitful use of such datasets [17]. Nevertheless, using the information for purposes that are not covered by prior informed consent of the patient poses difficulties and requires consideration in the ethical and legal domain. From the viewpoint of ethics patient autonomy has to be weighed against societal interests (1). In the legal debate especially data protection and privacy laws require attention; moreover, the lack of clarity in consent requirements needs to be taken into account (2). Those two aspects will be considered below.

1) Ethical considerations

Many clinical studies seek to obtain a broad consent for yet unknown future research, or at least permit an application to the ethics committee for permission for the secondary use of collected data. From the ethical point of view such proceedings are contentious for three major reasons:

Firstly, the quality of such consent is often questioned – as the information to make consent "informed" is at the point of consenting not yet available [18], [19].

Secondly, convincing patients to consent for future unknown endeavours which they eventually may disagree on may actually lead to reduced trust in research in general, as well as to lower rate of recruitment, or biased research results, as better informed individuals might refuse to participate.

Thirdly, in the future research projects, participating patients might benefit from the new discoveries; however, an attendant circumstance of such studies might be a prior destruction of any reference tables and therefore an abandonment of the possibility to come back to the patient in question. Some initiatives (such as UK Biobank [18]) openly state that they neither come back to the participants in case of accidental adverse findings, nor to inform them of future discoveries for their benefit.

Besides these ethical perspectives, staying in contact with the patients can contribute a lot to the scientific value of the collected data because researchers can update old data and ask for new information that might be needed [7].

2) Legal difficulties

When discussing legality of secondary use of medical data, the starting point is that the patient should be protected from the non-tangible risks arising from the use of his or her personal data. In Europe the Data Protection Directive [20] (and the implementing national laws), protect personal data of the individual. The Directive in principle forbids any processing of personal data, but provides exceptions. The basically preferable way to render data processing legal is through obtaining informed consent of the patient (Art. 8 (2a)), because of the maintenance of the individuals autonomy.

According to Art. 2(h) of the Directive consent for data processing needs to be freely given, informed and specific. Further clarifications are offered by Art. 29 Working Party (an independent body responsible for interpretation of the Data Protection Directive). This body has argued that: "To be specific, consent must be intelligible: it should refer clearly and precisely to the scope and the consequences of the data processing. It cannot apply to an open-ended set of processing activities. This means in other words that the context in which consent applies is limited" [21]. Accordingly, broad, prospective consent has to be deemed insufficient, but there is no common stance on the validity of broad consent across Europe. The UK [18], for example, allows broad consent, which is opposed in other states, requiring specific consent like Germany [22]. This creates confusion, especially when considering that research now is often done by multi-national consortia, where the applicable laws differ significantly between jurisdictions.

IV. Technical Solutions in Support of Patient Empowerment

Against this background, it is unsurprising that relevant stakeholders (including the research community supported by European Commission) are seeking to reform the consent procedures for the benefit of both the patients and the physicians.

One of the emerging trends in this respect is the move towards technological solutions to help in obtaining meaningful consent. Technical developments relevant here develop on various plains:

Firstly, technical solutions to improve the patient's comprehension of complex medical information by means of videos, applications, quizzes or others are developed, (see IV. A.)

Secondly, applications which aim at obtaining the patient's consent on each subsequent occasion when data (and/or samples) shall be used for a new reason are developed (IV.A.).

Thirdly, security solutions aiming at coupling the access rights of physicians, investigators, sponsors and the whole of the trial team to the exact consent which was given by the patient (so that by technical design the data provided by the patient can be only used for the research the patient has actually consented to) are under investigation(IV.B.).

A. p-medicine

The p-medicine project is developing an innovative and integrated technological solution to enable personalized medicine. It is seeking for an Interactive Empowerment Service (IEmS) for a better integration of the patient in the clinical trial procedure. Patients will be able to view all their data, receive patient-understandable information and make decisions for an optimal consent-management, so that they are always in control of their data. Clinicians on the other hand, will be able to ask for new consent and additional data whenever needed. Moreover, IEmS will provide a tool that will enable patients to monitor and implement decisions on research to be performed with their samples. In order to be able to develop a user friendly portal, patients' demands need to be thoroughly analysed. This has been done in p-medicine by questionnaires and interviews [24]. For improving communication processes between doctors and patients, the nature of the interaction between health staff and patients has been investigated as well. P-medicine considers a linguistic structure on different levels according to preferences and abilities [25] to ensure the understanding of the patient and to give him or her the chance to make an informed choice. It is envisaged that the IEmS will be connected to the p-medicine metabiobank (p-BioSPRE) which will function as a search engine for patients' samples and related data for approved users. Researchers will be able to get a synchronized overview of patient's consent with other scientific information on the samples. Such tools have to be evaluated and validated. Therefore a series of experimental tests will be performed on individuals classified by age, computer skills and specific expertise through empirical user-based tests.

B. EURECA

Trust is one of the most important values for the research community. It is because of trust that individual patients agree to take part in research and donate their time, samples, or other resources. When patients give consent it is not only important to convince them of the aims of research, it is equally relevant to prove that sensitive information about

them and their families (as genetic data is often at stake, too) is in safe hands. For that reason, security solutions in place within the clinics, research facilities for sharing patients' data are of utmost importance.

The consortium of the EURECA project aims at tackling this objective by closely pairing the legal procedures of consent and the access policies installed within the sharing infrastructures. A policy based authorization tool will verify whether the researcher wishing to access the data may do so, dependent on the patient wishes. Therefore if the patient gave consent for a particular form of research (e.g. research on lung cancer, but not on heart disease) the researcher can only access the data if the research is on the stipulated topic. Similarly if the patient agreed on usage by a specific research institute, only members of that institute will be allowed to access the data.

By closely connecting consent procedures and access policies the EURECA consortium aspires to reflect and respect the preferences of individual patients. The expected outcome is to give every patient a multiplicity of choices and still reduce the bureaucratic burden on the physicians and researchers – both only possible with technological approaches.

V. Conclusion

The research environment is filled with conflicting interests - it is often society and patient's interests to weight against each other. There are the physicians and researchers struggling not only with difficult research questions, but even more with the conflicting and complex formal and legal issues. Finally there is a complex patient-physician relation, where both autonomy and dependence exist. Achieving patient empowerment in this constellation is not easy but it becomes evident that technology can change this arrangement for the better.

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