Respecting the Autonomy of Elderly Patients in Switzerland:

Hindering and Promoting Factors in Clinical Settings

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Contributions

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This thesis consists of seven chapters: background (Chapter 1), journal articles (Chapter 2-6, each chapter comprising one article), and general discussion (Chapter 7). In the following, my contributions to each journal article as well as the contributions of the co-authors are presented in detail.

Rakic M, Wienand I, Shaw D, Nast R, Elger BS. Autonomy and Fear of Synthetic Biology: How Can Patients' Autonomy Be Enhanced in the Field of Synthetic Biology? A Qualitative Study with Stable Patients. *Science and Engineering Ethics.* Apr 2017;23(2):375-388.

I carried out the data analysis and drafted the initial manuscript. Dr. David Shaw, Prof. Dr. Bernice Elger and Dr. Isabelle Wienand supervised the data analysis, and supported me with the manuscript preparation. Rebecca Nast carried out the interviews. All authors provided critical revisions to the manuscript and approved the final version.

Rakic M, Dittrich T, Elger BS, Shaw D. Enhancing Patients' Autonomy by Involving Them in Research Ethics Committees. *International Journal for Quality in Health Care: Journal of the International Society for Quality in Health Care.* Nov 2017;29(7):896-900.

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Wienand I, **Rakic M**, Elger B, Shaw D. The Beneficence of Hope: Findings from a Qualitative Study with Gout and Diabetes Patients. *Journal of Bioethical Inquiry.* Jun 2018;15(2):211-218.

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Rakic M, Escher M, Elger BS, Eckstein S, Pacurari N, Zwahlen S, Wienand I. Feelings of Burden in Palliative Care: A Qualitative Analysis of Medical Records. *Journal of Palliative Care*. Jan 2018;33(1):32-38.

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Rakic M, Rost M, Wienand I, Elger BS, Escher M. Advance Care Planning in Swiss Acute Hospitals: A Retrospective Analysis of Medical Records.

Dr. Isabelle Wienand and I carried out data collection. Michael Rost and I analysed the data. I drafted the initial manuscript. Dr. Monica Escher, Prof. Dr. Bernice Elger, and Dr. Isabelle Wienand supervised the data analysis and supported me with the manuscript preparation. All authors provided critical revisions to the manuscript and approved the final version.

Summary

The steady increase in human life expectancy has been accompanied by a growing prevalence of patients with chronic diseases and multiple medical conditions, and the number of people in need of Palliative Care in Switzerland is expected to continue rising. Few people will die from a sudden death, whereas the majority will face an extended dying process, which will lead to a significant need for formal (e.g. hospital, retirement home) and informal care (e.g. family) throughout the course of a patient's illness. At the same time, autonomy has emerged as a crucial principle in our modern societies. It plays a significant role in the many domains of our lives in which autonomous decision-making is promoted, and autonomy is particularly relevant for elderly patients. Therefore, different approaches on how to improve patients' quality of life and promote their autonomy in clinical settings are increasingly important to discuss. The purpose of this PhD thesis is to integrate empirical and normative analyses using a qualitative and quantitative approach in order to promote respect of elderly patients' autonomy. This PhD thesis consists of seven chapters (background, journal articles, and discussion). The background chapter (Chapter 1) introduces chronic diseases, demographic shift, clinical trials, autonomy, and Palliative Care. Chapter 1 also discusses the research objectives and the methodological approach. Each of the chapters 2-6 consists of a deep dive into one journal article.

Chapter 2 analyses patients' views regarding potential participation in clinical trials of synthetic biology. Our results indicate that information should be communicated with great accuracy and transparency to allay irrational fears of patients and minimize the risk that researchers present facts too optimistically in an effort to persuade patients to participate in the trials. Patients must be adequately informed in order to be able to autonomously decide whether or not to participate.

Chapter 3 explores patients' thoughts about the idea of participating in research ethics committees. If the patients were allowed to participate in the decision-making process, their autonomy would be more respected. Analysis of the interviews revealed a patients' preference towards involvement in research ethics committees. The main motivation for the interviewed patients to participate was the improvement of therapeutic options in the future. Our study adds important knowledge about the idea of patients becoming research ethics committee members by exploring their perceptions of the prospective role.

Chapter 4 focuses on different aspects of hope in the context of human health and well-being and explores the varieties of hope expressed by patients. Three concepts of hope emerged from the interviews: hope as certainty, hope as reflective uncertainty, and hope as self-therapy. Health professionals ought to be more aware of the three concepts of hope and their great potential as a coping strategy for patients. Hope seems to be genuinely beneficent for patients' well-being in a therapeutic and in a research context.

Chapter 5 analyses patients' medical records to determine what is reported about burden and overburden and who seems to be mostly affected. Daily life situations reveal that the concept of autonomy is challenged when the two parties (e.g. patients and their families) have different interests, resources, and needs. Patients often felt burdened by their disease, financial problems, situation at home, and family members' reactions to their disease. Families felt burdened by issues related to patients' medical condition, providing home care, or financial and social aspects.

Chapter 6 discusses different factors determining the application of advance care planning and advance directives. By enabling patients to determine their medical treatments in advance and make their preferences known, advance care planning promotes respect for patients' autonomy. For most patients, a discussion about advance directives, values, and wishes was

documented in the medical records. Of those patients, almost two-thirds engaged in advance care planning. Knowing patients' preferences in advance is needed to base end-of-life decisions on the patients' values and wishes.

Chapter 7 provides a general discussion of the findings derived from the journal articles. More precisely, the discussion coalesces the empirical findings and discusses their ethical significance. Afterwards, limitations and implications for further research are discussed.

Zusammenfassung

Die zunehmende Lebenserwartung in der Schweiz wird von einer gestiegenen Prävalenz chronisch kranker Menschen und solcher, welche Palliative Care benötigen, begleitet. Nur wenige Menschen werden eines plötzlichen Todes sterben. Die Mehrheit wird nach langer Krankheit versterben. Dieser lange Krankheitsprozess des Patienten bedarf einerseits vermehrter formeller (bspw. Spital, Altersheim) und anderseits informeller (bspw. Familie) Pflege. Gleichzeitig hat der Begriff der Autonomie als wesentliches Prinzip der Medizinethik an Bedeutung gewonnen. Autonomie spielt eine wichtige Rolle in vielen Domänen unseres Lebens, in welchen wir Entscheidungen (bspw. medizinische Eingriffe) treffen müssen. Des Weiteren bleibt Autonomie für Patienten[1] auch im höheren Alter wichtig. Deshalb werden in den wissenschaftlichen Artikeln verschiedene Ansätze vorgestellt und diskutiert, wie man die Lebensqualität und die Autonomie von älteren Patienten in einem klinischen Setting verbessern kann. Das Ziel der vorliegenden Doktorarbeit ist es, mithilfe von qualitativen, sowie quantitativen Ansätzen, empirische und normative Analysen zu synthetisieren, um den Respekt der Autonomie älterer Patienten zu fördern. Diese Doktorarbeit besteht aus sieben Kapiteln: Hintergrund, fünf wissenschaftliche Artikel, Diskussion. Im 1. Kapitel (Hintergrund) wird näher auf chronische Krankheiten, demografischen Wandel, klinische Versuche und Palliative Care eingegangen. Ausserdem werden die Forschungsziele und Methoden diskutiert. Die Kapitel 2-6 bestehen je aus einem wissenschaftlichen Artikel.

[1] Aus Gründen der Lesbarkeit wird nur die männliche Form benutzt. Es sind jedoch alle Geschlechter gleichermassen gemeint.

Im 2. Kapitel werden die Resultate zur Partizipation von Patienten an klinischen Versuchen, welche synthetische Biologie beinhalten, diskutiert. Unsere Resultate deuten darauf hin, dass Informationen mit hoher Genauigkeit und Transparenz kommuniziert werden müssen, um einerseits irrationalen Ängsten seitens der Patienten vorzubeugen und um andererseits zu vermeiden, dass Forscher Fakten zu optimistisch präsentieren, um Patienten zu einer Teilnahme an einem klinischen Versuch zu überreden. Patienten müssen adäquat informiert werden, damit sie autonom entscheiden können, ob sie an einem klinischen Versuch mitmachen wollen oder nicht.

Kapitel 3 untersucht die Meinung von Patienten zu einer möglichen Teilnahme an Forschungsethikkommissionen. Eine aktive Teilnahme der Patienten an solchen Kommissionen würde ihre Autonomie angemessen respektieren. Die Ergebnisse zeigen, dass Patienten sich prinzipiell vorstellen können, Mitglieder einer solchen Kommission zu sein. Die Verbesserung der therapeutischen Optionen wurde als ein Hauptgrund für eine mögliche Teilnahme aufgeführt. Indem auf die Sichtweisen der Patienten eingegangen wird, liefert unsere Studie wichtiges Wissen bezüglich der Idee, Patienten in Forschungsethikkommissionen zu inkludieren.

Kapitel 4 beschäftigt sich mit der Hoffnung im Zusammenhang mit Gesundheit und Wohlbefinden von Patienten. Zudem wird die Vielfalt verschiedener Formen von Hoffnung diskutiert. Aus der Analyse der Patienteninterviews wurden drei Konzepte von Hoffnung herausgearbeitet: Hoffnung als Sicherheit, Hoffnung als reflektierte Unsicherheit und Hoffnung als Selbsttherapie. Gesundheitsfachleute sollten sich dieser drei Arten von Hoffnung bewusst werden und dem damit verbundenen Potential als Bewältigungsstrategie für Patienten. Hoffnung scheint wohltuend für das Wohlbefinden der Patienten zu sein.

In der in Kapitel 5 vorgestellten Studie werden Patientenakten analysiert, um zu eruieren, was über Belastungen und Überbelastungen geschrieben wird und wer am meisten davon betroffen ist. Patienten fühlen sich oft durch ihre Krankheit, finanziellen Probleme, die Situation zuhause und die Reaktion der Angehörigen auf ihre Krankheit belastet. Angehörige fühlen sich oftmals durch den Gesundheitszustand des Patienten, Pflege zuhause, sowie finanzielle und soziale Aspekte belastet. Alltagssituationen zeigen auf, dass das Konzept der Autonomie herausgefordert wird, wenn zwei Parteien (bspw. Patienten und deren Familien) unterschiedliche Interessen, Ressourcen oder Bedürfnisse haben.

Kapitel 6 zeigt verschiedene Faktoren auf, welche das Advance Care Planning, sowie das Ausfüllen einer Patientenverfügung beeinflussen. Durch das vorzeitige Ermöglichen, sich mit ihren medizinischen Behandlungen auseinanderzusetzen, fördert das Advance Care Planning die Achtung der Patientenautonomie. Bei den meisten Patienten fand eine Diskussion zu ihren Wünschen, Werten oder Patientenverfügungen statt. Jene wurden auch in den Patientenakten dokumentiert. Patientenwünsche zu kennen ist Voraussetzung, um Pflege und Behandlung am Ende des Lebens nach den Wünschen und Vorstellungen der Patienten zu gestalten.

Im Kapitel 7 werden die Resultate der wissenschaftlichen Artikel insofern zusammengeführt und diskutiert, als die empirischen Resultate synthetisiert und ihre ethische Signifikanz aufgezeigt wird. Abschliessend werden die Limitationen und Implikationen für weitere Forschung diskutiert.

Chapter 1 – Background

1 Introduction

1.1 Demographic shift and increase in chronic diseases

In 2050, almost 22% of the global population will be older than 60 years as compared to 12% in 2013. In developed countries, the number of people older than 60 years will increase from 22% in 2013 to 32% in 2050[1]. The growing number of elderly people can be traced back to a decrease in infant mortality, increase in life-expectancy, and a declining birth rate[1]. Consequently, this age group (60 years and older) is growing faster (2% per year) than other age groups[2]. According to the Swiss Federal Statistical Office, Switzerland is not excluded from this population trend, and it is expected that fewer than 20% of people will be younger than 20 years by the year 2060[3]. This demographic shift raises concerns about the increased national burden of chronic disease because such conditions are strongly correlated with older age[2,3].

The World Health Organization (WHO) defines chronic disease as disease that is not transmitted from one person to another, is of extended duration, and has a relatively slow progression. Cardiovascular diseases, cancers, respiratory diseases, and diabetes comprise four primary types of chronic diseases[4]. Less than 5% of the Swiss population will die from a sudden death; the vast majority of the population will die after a chronic disease. More precisely, 30-40% of patients will die after a disease duration of 8-10 years[3]. Cardiovascular diseases (32%) and cancers (26%) are the most frequent causes of death in Switzerland[5]. Furthermore, the number of elderly people suffering from more than one disease (multimorbidity) will increase[3]. According to statistical prognoses, the demographic shift will lead to an increase in number of people in need of care from 125,000 in 2010 to 182,000 in 2030 in Switzerland[3].

On the one hand, human life expectancy is steadily increasing, chronic diseases are on the rise, and the expected number of people in need of care in Switzerland will continue to increase[1-3]. On the other hand, only a minority will die from a sudden death[5], whereas the majority will face a lingering dying process, which will lead to an increase in both formal (e.g. retirement home) and informal care (e.g. family) throughout the course of the patients' disease[3]. Therefore, different approaches to improve patients' quality of life and promote their autonomy in clinical settings (throughout the course of their disease) will be discussed in the following sections as autonomy will become increasingly important and relevant to clinical care in the future[3].

1.2 Treatment options in light of chronic diseases

Patients who suffer from one or multiple chronic diseases do not die immediately[10]. Nevertheless, studies report a shorter life expectancy and decreased quality of life as compared to healthy persons[6,7]. A possible solution to address the decreased quality of life is the application of novel technologies, such as synthetic biology (SB), to synthetically reprogram metabolic systems in the body as shown in a preclinical study with mice[8]. SB is currently used to enable production of specific chemicals (e.g. antibiotics)[9]. With these developments[8], it may soon be possible to modify cells that are able to produce a certain substance that induces insulin production in the body and decreases the blood sugar concentration of a diabetic patient. With such a medical therapy, the patient does not need to regularly inject insulin and hence, would improve his quality of life. However, before a new treatment is approved and available for patients, it must be tested in first-in-human (FIH) trials to ensure safety and efficacy in humans[10]. To date, terminal cancer patients comprise the primary target population for FIH trials because of the absence of therapeutic alternatives and the hope that experimental treatments will help them to survive[10]. Given the limited remaining life spans of these terminal patients, clinical studies with severely ill patients (e.g.

refractory cancer) can never fully discern the long-term risks[11]. Additionally, patients with chronic diseases (e.g. gout, diabetes, and certain cancers) might benefit from the medications developed through clinical trials as compared to terminal cancer patients[6,7,12,13]. For this target group, it might be possible to treat some of the chronic diseases with synthetically reprogrammed metabolic systems[8]. This would lead to an increase in patients' life expectancy and quality of life.

Nonetheless, research ethics committees, which evaluate clinical trials, tend to reject studies involving stable patients because of high risk (e.g. risks of potential damage from clinical trial overweigh possible benefits) to these patients to participate[14]. This attitude has been criticized as unjustified paternalism[15]. Lack of consideration for patients' willingness to accept risks and the paternalistic attitude of research ethics committees[14,16] appear to create an anachronistic situation regarding autonomy. This fact could lead to a restriction of the patient's right to make autonomous decisions about participation in clinical trials (e.g. FIH trial). Therefore, shifting from paternalistic decision-making to a patient-centred, shared decision-making model that includes patients in research ethics committees would increase patients' ability to make fully autonomous health decisions[17]. Nevertheless, the possibility of unpredictable side-effects (e.g. long-term effects) of biotechnological interventions (e.g. SB) in humans needs to be articulated clearly to study participants, for example through informed consent (IC), to ensure autonomous decision-making.

1.3 Palliative Care

Another important aspect of the demographic shift is that chronic diseases often lead to complex physical and psychological end-of-life situations. Palliative Care (PC) addresses the whole spectrum of patients' needs and suffering[3]. Therefore, chronic diseases (e.g. cancers) will also increase the number of people in need of PC and thus, PC will become more important in the future[3]. According to the WHO, PC is an interdisciplinary and holistic approach that encompasses several domains of care (physical, social, psychological, and spiritual)[18]. Moreover, PC not only focuses on the requirements of patients but also on the needs of their families, friends, and significant others. Therefore, the aim of PC is to offer services to help patients and their families cope not only with the patient's illness, but also with the families' own needs[18]. Thus, patients suffering from a life-threatening disease should have the possibility to receive PC, which prioritizes quality of life and prevention of suffering[3].

The Swiss Federal Office for Public Health estimates that 40,000 people are currently in need of PC and that this number will increase to 53,000 people by 2032[3]. A representative poll showed that half of the surveyed people knew what PC entails. Moreover – when being asked about their attitude regarding PC – around 80% of the surveyed people could envision receiving PC treatment if they suffer from an incurable disease[19]. The wish for PC meets an important need, namely, the need to live as autonomous and self-determined a life as possible[3,20]. This increased request for self-determination has led to changes in the Adult Protection Law to promote PC and patients' autonomy[3,21]. However, a survey from 2011 indicated that the possibility to ensure patients' autonomy was seen as the main reason to justify assisted suicide[22], whereas PC or Advance Directives (ADs) were rather unknown as tools to promote one's autonomy[3,22]. To meet society's wish to live as autonomously as possible, but also to react to the demographic shift, Switzerland launched a national strategy

on PC with the goal to implement PC in the Swiss health care sector to make PC available for patients in need of it. Furthermore, with the launch of the national strategy on PC, patients should be given an alternative means to assisted suicide through which they can exercise their autonomy[3].

To support decision-making in PC situations, one common and recommended tool is the writing of legally binding ADs along with advance care planning (ACP)[23,24]. ACP ensures that the patient's wishes and preferences are known before the time at which the patient becomes unable to choose medical treatments (e.g. due to lack of mental capacity)[23,24]. By enabling patients to proactively determine their medical treatments in advance, ACP promotes respect for patients' autonomy[25], which is an important defining principle of PC[20]. Moreover, the new Adult Protection Law in Switzerland enables and encourages competent adults to write ADs and to appoint a surrogate decision-maker in case of their lack of mental capacity[21].

1.4 Theoretical Background: Autonomy

Autonomy means self-rule (Greek autos = self and nomos = rule)[26]. Since the 1960's, there has been a greater emphasis on the notion of 'autonomy' both in society and medical ethics[27,28]. As it is common among other researchers in medical ethics, I use autonomy/self-determination interchangeably[26,29].

The evolution of autonomy can be tracked back to mostly two developments. First, the increased rejection of paternalism in medicine due to public changes (e.g. the responsible citizen), and second, the plurality in common understandings as to what a good life entitles[28]. Therefore, every individual may decide upon his or her values on what a good life might be[28]. In practical philosophy, several concepts of autonomy exist based on different philosophical schools[29]. These concepts vary insofar as they have divergent criteria that must be fulfilled in

order to view a person as an autonomous being[29]. In what follows, two of these concepts are discussed, namely the Kantian and the Utilitarian philosophical views on autonomy, because these two models in modern philosophy have significantly shaped the current notion of autonomy[28].

Kant's understanding of autonomy (see *Grundlegung zur Metaphysik der Sitten*[30,31], 1785) posits that autonomous persons are fundamentally free, that is they are able to refrain their individual wishes and preferences and act according to the universal principles of rationality[28,30]. That is, the ability to orient their own will towards the Categorical Imperative, according to which free choices ought to be made based on universalizable maxims[29]. The first formula of the Categorical Imperative reads so: "Act only in accordance with that maxim through which you at the same time can will that it become a universal law."[30, p. 66]. Furthermore, the second formula of the Categorical Imperative underlines the priceless value of human persons: "So act that you use humanity, as much in your own person as in the person of every other, always at the same time as an end and never merely as means"[30, p. 66]. Taken together, no person should be merely instrumentalized and every person has intrinsic value[28]. These values still seem relevant in modern medical ethics, as shown by the indispensable utilisation of IC that aims to ensure patients autonomy[32].

The Utilitarian understanding of autonomy (see John Stuart Mill, *On liberty*[28,33], 1859) emphasizes the individual freedom of everyone to live in accordance to their own world views. Nevertheless, this freedom is restricted when a third party is being put at risk. According to Mill's definition of autonomy, putting oneself at risk is not a reason to neglect someone's autonomy and act paternalistically[28].

Depending on the philosophical approach (e.g. Kantian or Utilitarian), the definition of autonomy might differ. However, both agree that two prerequisites must be fulfilled for a

person to be autonomous: liberty and agency. The first condition means that a person can decide in an independent manner, that is, free from others' influence. Agency implies that a person has the capacity to act in an rational manner[26]. To find a consensus of these different ethical theories of autonomy, Beauchamp and Childress introduced four *prima facie* principles as guiding norms for the new discipline of bioethics: autonomy, non-maleficence, beneficence, and justice[26,34]. They have acquired an utmost importance in the field of medical ethics[28]. Beauchamp and Childress defined autonomy as follows: "At a minimum, personal autonomy encompasses self-rule that is free from both controlling interference by others and from certain limitations that prevent meaningful choice, such as inadequate understanding"[26, p. 100]. Nevertheless, it needs to be said that the individualistic approach (e.g. the patient is the sole decision-maker) of Beauchamp and Childress regarding autonomy has been widely criticized, mostly because it fails to consider the social and cultural determinants of one's autonomy, that is their importance on one's lives and decision-making processes[35,36]. This model is known as relational autonomy[36] – for an in-depth discussion on relational autonomy, see also chapter 7. A possible problem of the individualistic approach might be when elderly patients are faced with stereotypical assumptions regarding their autonomy (e.g. the older the patient, the less competent and less autonomous)[37]. Therefore, social, cultural, and existential aspects (e.g. patients' lifeworld) should also be taken into account, especially when patients face special situations (e. g. disease, ageing) that might affect their autonomy[37,38] (for an in-depth discussion on lifeworld, see also chapter 7).

In order to ensure the respect for patients' autonomy regarding medical treatments, IC has emerged as a prominent consideration in medical ethics since the late 1940s[26]. Moreover, IC empowers patients to decide for or against a certain medical treatment after being informed[26,29]. In addition, IC requires more than a sole provision of information regarding medical treatment[26]. In order to be able to make an autonomous decision regarding a medical

treatment, the following prerequisites of an IC must be fulfilled: “disclosure” (e.g. adequate delivery of information so that patients can make an informed decision), “understanding” (e.g. nature and purpose of treatment), “voluntariness” (e.g. patient agrees to certain treatment without undue influenced from another person), “competence” (e.g. capable of understanding consequences of the consent and able to make a free choice), and “consent”[26, p. 79].

Conclusion

The expected demographic shift toward older age will be accompanied by an increase in the prevalence of chronic diseases, multimorbid patients, and deaths in clinical settings (e.g. hospital, retirement home)[3]. At the same time, autonomy has become more crucial in our society[3] and plays a significant role in many domains (e.g. legal) that aim to promote autonomous decision-making[37]. For elderly patients, autonomy remains relevant, and they will likely not accept limitations placed on their autonomy[39]. Because autonomy has achieved great significance in society[3] and in medical ethics (e.g. right to make own decisions[26] or not being used merely as a means to an end[30]), the autonomous decision-making should be respected and promoted[35]. **Thus, the purpose of this PhD thesis is to integrate empirical and normative analyses in order to support respecting elderly patients’ autonomy in clinical settings.** More precisely, the thesis’ aim is to identify and discuss possible hindering and promoting determinants of autonomous decision-making to better ensure patients’ autonomy. One promoting factor of patients’ autonomy is active participation in decision-making processes (e.g. through research ethics committees). Research ethics committees facilitate patient access to and comprehension of medical information. Moreover, through precise and tailored information (e.g. specific IC), patients have the opportunity to competently decide on their own and give their consent whether to participate in clinical trials or to receive specific treatment. What is more, this process ensures voluntary participation of

patients. In case of lack of mental capacity, their future autonomy can be restored through the active promotion of ACPs[23,24] and thus, ensures that patients' autonomy will be respected.

Hindering factors include – amongst others – situation of dependence (e.g. fear of putting too much burden on family members), old age (e.g. lack of mental capacity), unrealistic hope (e.g. possible barrier to understand the medical situation and with that to give an IC) – in which it becomes difficult for the patients to express their preferences autonomously. Besides, disclosure, voluntariness or consent might be diminished. In addition, severe illness and fear of unknown treatments (e.g. within SB) could lead to deprivation of patients' autonomy as patients might not be able to decide in an independent manner.

2 Research Objectives and Empirical Methods

2.1 Research Objectives

This thesis is part of two larger research projects entitled *"Ethical issues of cutting edge biotechnology: Embedded interdisciplinary risk benefit evaluation of first-in-human trials in synthetic biology and nanomedicine"* and *"Respect for patient self-determination as quality indicator in palliative care: current state, problems and solutions in acute care hospitals*." The nature of each research projects has a clear ethical orientation and aims to contribute to a better recognition and respect for patients' preferences and values.

The first research project aimed to obtain information on how chronically ill patients perceive SB in general. Moreover, it sought to evaluate the willingness of patients to participate in FIH trials, including the arguments provided for and against such participation. As already discussed in the introduction, there is a research gap regarding patients' participation in clinical trials of new technologies and concerning attitudes of stable patients suffering from chronic disease with only slightly impaired life expectancy as compared to near-death patients[16]. Evidence of fears towards SB in the general population[40] should motivate research to study patients' attitudes towards clinical trial participation. These attitudes can be seen as an indicator for their preferences and tendencies to participate in research involving SB, as well as means to promote and ensure the respect of their autonomy.

The objective of the second research project was to evaluate the quality of PC in three acute care hospitals in Switzerland based on the respect for patients' autonomy (their values and wishes). The project aimed to describe and analyze autonomy-enhancing activities – provided by the hospitals (e.g. ACP) and desired by the patients (e.g. ADs) –, patients' characteristics (e.g. age, disease), and satisfaction with PC consultations. To our knowledge, there has been no systematic research to evaluate elderly patients' autonomy in PC in Switzerland. The few

existing studies focus on the lack of health care personnel in the evaluation of patients' values[41,42] or decision-making in intensive care units[43,44].

To fulfill these objectives, this thesis aims to answer the following research questions:

1. What are patients' opinions about synthetic biology and first-in-human trials using medical applications of SB?
2. What are patients' attitudes towards participation in RECs as established members?
3. What kinds of hope are being expressed by patients regarding first-in-human trials using medical applications of SB?
4. What kinds of burden are being expressed by PC patients in acute hospitals?
5. Which factors determine the application of ACP and/or the completion of an AD?
6. How does ACP occur in clinical settings?

2.2 Empirical Methods

The PhD project consists of 7 chapters that stem from two larger research projects, which were carried out between 2012 and 2018. The project employed a qualitative and quantitative methods design: a qualitative part from the first research project in which 36 patients suffering from diabetes or gout were interviewed to explore their views and preferences regarding participation in clinical trials (e.g. SB). For the second project, we performed a quantitative and qualitative analysis of retrospectively collected data from 300 PC patients' medical records. The exact methods are described in greater detail in the methods sections of each article included in this thesis (see Chapters 2-6).

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Chapter 2

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Autonomy and Fear of Synthetic Biology: How Can Patients' Autonomy Be Enhanced in the Field of Synthetic Biology? A Qualitative Study with Stable Patients

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Abstract

We analyzed stable patients' views regarding synthetic biology in general, the medical application of synthetic biology, and their potential participation in trials of synthetic biology in particular. The aim of the study was to find out whether patients' views and preferences change after receiving more detailed information about synthetic biology and its clinical applications. The qualitative study was carried out with a purposive sample of 36 stable patients, who suffered from diabetes or gout. Interviews were transcribed verbatim, translated and fully anonymized. Thematic analysis was applied in order to examine stable patients' attitude towards synthetic biology, its medical application, and their trial participation. When patients were asked about synthetic biology in general, most of them were anxious that something uncontrollable could be created. After a concrete example of possible future treatment options, patients started to see synthetic biology in a more positive way. Our study constitutes an important first empirical insight into stable patients' views on synthetic biology and into the kind of fears triggered by the term "synthetic biology." Our results show that clear and concrete information can change patients' initial negative feelings towards synthetic biology. Information should thus be transmitted with great accuracy and transparency in order to reduce irrational fears of patients and to minimize the risk that researchers present facts too positively for the purposes of persuading patients to participate in clinical trials. Potential participants need to be adequately informed in order to be able to autonomously decide whether to participate in human subject research involving synthetic biology.

Key words: synthetic biology, autonomy, stable patients, first-in-human trial

Introduction

There is not yet any standard definition of synthetic biology (SB) on which most scientists agree, but according to Balmer and Martin, the main aims of SB can be described as the following: "1) The production of minimal living genomes; 2) the design of interchangeable parts that can be assembled into pathways for the fabrication of novel components; 3) the construction of entirely artificial cells; and 4) the creation of synthetic molecules"[1, p. 3].

To sum up, SB uses engineering principles to consciously design biological systems or living organisms[1]. While several studies in animals have been promising[2,3], clinical trials of more advanced phases (especially clinical phases II, III) are not yet common[4]. A possible barrier to clinical trials could be diffuse fears of SB and other types of cutting edge biotechnology as we find by and large in society's reactions to these new technologies[5]. Although most of the new devices have been tested in preclinical phases only, some have already successfully completed clinical phase I trials: for example a drug-sensing hydrogel used to control the release of an antibiotic (novobiocin), which is thought to be important for cancer treatment[6,7].

What are the reasons for public fears of SB? In his analysis Hans-Jürgen Link explores the fears of SB. He shows that several types of fear are based on ethical considerations related partly to religious worldviews, and partly to fears of risks, as illustrated by the key words "playing God" and "creation of artificial life." These fears seem to arise from the following opinions: in popular publications related to SB, it is often mentioned that scientists are trying "to play God." The common understanding – based upon religious beliefs as well as ethical arguments – is that it is morally wrong, because humans are not supposed to create new forms of life. A common claim is that life, as a gift of God (God is the giver of life), is intrinsically valuable, and may not be altered. According to this theological point of view, humans are considered guardians of God's creation[8]. Therefore SB appears ominous, inasmuch as it disturbs the relation between creator and creature. What is more, SB blurs the

distinction between natural i.e. created by God and artificial i.e. fabricated by man[9]. Thus, scientists are asked to stop doing research based on SB in order to stay away from this slippery slope[9]. Moreover, the importance of unpredictable side-effects in biotechnological interventions in humans ought to be seriously taken into account, and explained clearly to the study participants. Otherwise, as the German philosopher Hans Jonas argues present and future generations will be restricted in or even deprived of their autonomy[10]. Indeed, respect for the autonomy of patients and research participants is central for modern bioethics. The ethical principle of patients' autonomy or self-determination is violated when participants are not given full and transparent information about the clinical trials. Beauchamp and Childress define autonomy as follows: "At a minimum, personal autonomy encompasses self-rule that is free from both controlling interference by others and from certain limitations that prevent meaningful choice, such as inadequate understanding"[11, p. 100]. Therefore, a patient's level of autonomy is intrinsically linked to the amount and quality of information she or he received about possible adverse events. That is, no "meaningful choice" can be made on the basis of partial, limited or inaccurate information. Lack of clear information could lead to ethically unjustified restriction or deprivation of autonomy[10]. Participants ought to be adequately informed in order to be able to decide autonomously whether they agree to participate in human subject research involving medication or devices developed by cutting edge biotechnology or SB[10,11]. Since the designation "SB" implies a specific type of modern biotechnology that is known to have solicited controversy[1,5], not mentioning SB to the patients would mean withholding information from them that could be relevant for their decision-making. To sum up, the ethical principle of patients' autonomy in connection with SB is a challenge for researchers, especially with regard to first-in-human trials (FIH) as well as more advanced clinical phases (II, III). Indeed, how can they both respect the participants' autonomy and proceed with their scientific research in SB? In other words, to which extent

are autonomy and research in unknown fields compatible? FIH trials are performed to ensure the security of interventions in humans[12]. The group of near-death cancer patients is a target group for FIH trials, given the absence of therapeutic alternatives and the hope that new treatments will help them survive[12]. However, in studies, involving end-stage cancer patients[6], long-term risks will never be fully known. There is a clear research gap concerning attitudes of stable patients suffering from chronic disease with only somewhat impaired life expectancy as compared to near-death patients[13]. More specifically, the evidence that fears exist in the general population[9] should motivate research to know more about stable patients' attitudes towards clinical trial participation. These attitudes can be seen as an indicator for their preferences and tendencies to participate in research involving SB. Indeed, false beliefs and non-justified fears are not only a barrier to patients' autonomy, but they may present serious obstacles to indispensable FIH studies on new SB devices.

In order to understand how patients' opinion about SB might affect their willingness to participate in FIH trials using medical applications of SB, we carried out interviews with 36 stable patients with the aim to a) analyze their opinion on research and technology in general, b) examine their opinion about SB that might affect their willingness to participate in FIH trials, and c) determine whether their views and preferences change after having received more detailed information about SB and its potential clinical applications.

Methods

We employed an empirical research design to explore stable patients' attitudes towards SB and clinical trial participation using medical applications of SB. After a literature search for translational research in cutting edge biotechnology (including in particular SB), we developed an interview guide. Based on the previous literature research, we selected the topics which should be included in our interview guide (e.g. examples of clinical trials,

patients' current health status, etc.). We were then able to develop a realistic example of a hypothetical medical application in the field of SB.

Study tool

The semi-structured interview guide consisted of ten open questions, each with several sub-questions. This paper investigates the following questions and sub-questions as featured in Tables 1, 2 and 3.

Table 1. Question and sub-questions about research and technology in general

1. To increase treatment options for diseases, much research is done in laboratories and hospitals. Let us go a step back. Research is done in almost every area of life. What do you think of technical development and research in general? Are you more neutral or how would you consider yourself?
1.1 Would you consider yourself rather critical or supportive of technology?
1.2 Are there areas of life, where you welcome technology development and others, where you reject such development?

Semi-structured interview about research and technology in general.

Table 2. Question and sub-questions about knowledge of and opinion on SB.

2. A very new research branch is SB. Have you already heard the phrase "synthetic biology?"
2.1 If yes: How do you imagine it? How did you hear about SB? *Afterwards explain briefly*.
2.2 If not: I wrote an explanation that you can read through. *Give patient „card 2" for illustration*.
2.3 *Subsequently, give patient „graphic 1" for illustration and explain shortly*.
2.4 Have you questions about this?
2.5 Reading about it [SB], what do you think? What do you find good, and what not?
2.6 If not mentioned: What do you think of SB as a treatment option for diseases? What do you find good, and what not?

Semi-structured interview about knowledge of and opinion on SB (Readers can request Fig. 1 [Fig. 1 displaying manipulation of human cell] from the corresponding author).

Table 3. Question and sub-questions about possible future treatments in the field of SB.

3. I would like to do a short thought experiment with you. a. hypothetical example for gout patients (see Annex) b. hypothetical example for diabetes patients (see Annex) 3.1 When you hear it [hypothetical example of a medical treatment in the field of SB], what kind of thoughts go through your head? What do you find good about it, what not so good?

Semi-structured interview about future treatments in the field of SB.

The hypothetical medical application presented during the interview depicted the implantation of autologous cells that had been modified by using SB technologies. Patients were informed that the implanted cells might be able to cure diabetes or gout. In that case, no further medication would be needed.

Ethical approval was obtained from the cantonal research ethics committee (Ethikkommission Nordwest- und Zentralschweiz: Nr. EK 193/12). We carried out a pilot study in 2013 to ensure participants' comprehension. As a result, two slight modifications were made. First, the interview structure was put in a chronological order, and second, wording of the questions was adapted to improve accurate understanding.

Sampling and data collection

The qualitative study involved a purposive sample of 36 patients. We recruited participants directly in the hospital during their routine check-ups. The recruitment duration lasted six months in 2014/2015. Written informed consent was obtained from each individual participant included in the study. Average interview duration was 44 minutes (min. 16 minutes; max. 1 hour and 42 minutes). All interviews were conducted in Swiss-German by the same researcher. Interviews were conducted at the patient's home, our Institute or in the hospital, where a separate room was available. Interviews were transcribed verbatim,

translated into High German and fully anonymized. Quotes were later translated into English. Finally, patients' names were anonymized.

Analysis

Thematic analysis was applied to the interview transcripts. We did not use a pre-existing theoretical framework while reading the interviews, as we were aiming for a bottom-up method. A bottom-up approach means that the themes we identified in our interviews were explicitly linked to the data we analyzed. Possible themes were identified via a stepwise procedure. First, all authors read the interviews in order to obtain preliminary themes in an inductive way. Afterwards, these themes were discussed among the authors. Second, we discussed the previously identified themes. We discussed further, and agreed on the selected themes, thereby narrowing the overall research question. In a third step, we reread all interviews with a particular focus on the themes we had chosen (Tables 1, 2, 3). Next, themes (e.g. fear of SB, attitude towards SB, willingness to participate in clinical trials with SB devices) were refined into fully elaborated themes that are presented in the results section[14].

Results

Most of the included patients tended to have a positive attitude to research and technology in general (a). The term "synthetic biology" was either unknown or only vaguely known or feared (b). After a concrete example of possible future treatment options, patients started to see SB in a more positive way (c).

a) Patients' views on research and technology in general

Most interviewed patients held positive attitudes about research and technology in general. For example:

> **Ulla:** Yes I think it [research] is good that there is maybe something, where you have sort of a box with insulin, which automatically injects [insulin] or such things. (…) I found it [research] good.

> **Frieda:** We are not in the Middle Ages. No I find it [technology] good, (...) because mankind has always new diseases and new problems and technology causes these [problems] on one side, on the other it [technology] also helps. I have great opportunities, because if I cleaned [my] blood without technology (…), I would not be living anymore.

> **Otto:** Yes, it [research] must be. Otherwise you cannot try new drugs. Without research there is no curing.

In these patients' opinion, research needs to be done in order to improve health conditions and to develop new medical therapies which could facilitate patients' everyday life. Most acknowledged that they themselves would need new drugs or therapies. Patients knew that a chronic disease often leads to a worsening of their health condition. Therefore, patients are aware of the fact that they would more likely need, and profit from these developments.

Nevertheless, some patients had a more nuanced picture of research and technology. According to them, research is only permissible if it is likely to lead to an improvement.

> **Hanni:** If there is a good improvement for this disease, why not? But if there is no real improvement, you start to question the sense of the whole.

Few patients seemed to realise that it usually takes a long time until drugs are developed, approved and finally used to improve health or therapy. Only a few interviewees mentioned that they would not profit immediately from new findings.

> **Erik:** In general, yes that [research] is very good. I am also for research (…). If you just think, how long it takes (e.g.) with cancer [research]; how long they have done research. In principle, they did not bring it [cancer research] to the end yet. That is tremendous the research nowadays.

b) Patients' knowledge of and opinion on SB

Most patients expressed worries about and criticism of SB. In several interviews, it appeared that patients had no or only vague knowledge of SB or mixed it with other research branches.

> **Frieda:** For me that [SB] is a closed book. I can imagine something. (But) at the end it [the human] will be a robot. I am not for these kinds of things.

> **Erik:** Is there agriculture within? It is tremendous the research nowadays.

Time and again, the interviewees misunderstood SB as genetic engineering. The association seemed to generate a negative picture among patients (e.g. "to play God").

> **Noah:** Well, if you can cure any disease with genetic engineering, I am for it. But if you manipulate the genes that – how can I say – you only have blonde people [I would say] rather not. If somehow a superhuman gets created [the interviewee is against genetic engineering]. For the improvement of diseases, sure [positive adjusted towards genetic engineering]. Make that they [diseases] disappear. As long as you do not want to play God I find everything good."

> **Petra:** With genetic engineering we should slowdown, in my opinion. Otherwise we will have like in a science fiction movie all the same babies in the world: artificially

generated. That [artificially generated] is [something] we do not want. We have still limits and if you cannot continue, we have reached our limit. Rather say: okay I am sorry, but we cannot help you anymore, we have reached our limit.

The idea of genetic modification seemed to evoke the fear of creating something uncontrollable, similar to Frankenstein's monster. Hence, some of the patients expressed a sceptical opinion about what is going to happen, if researchers want to create a so-called "perfect human" with the help of SB.

Anna: I see disadvantages in breeding a perfect human some day or that something is bred, which cannot be controlled anymore (…).

Noah: Theoretically it [SB] is good, but since they [scientists] are not (…) far with it [SB], it is arguable that they [scientists] already want to start with it [SB] in humans. One could make a gene (another gene), which produces something weird. You can see it with plants. They are very good (…), but they [plants] produce something that they should not.

c) Patients' attitudes towards possible future treatments based on SB

Using a concrete hypothetical example we explained to patients how a possible medical treatment based on SB could look like (see Methods). After this, most of the patients started to see SB in a more positive way.

Ines: (...) it [example of a possible SB treatment] would be good, if it were possible. Hopefully, they [SB modified cells] will get along with the old cells in the body (…); [Thank to SB] you would have to pay less attention to your diet and that would be a progress.

> **Yves:** Yes, instead of measuring [blood sugar] and injecting [insulin] (if they were already that far?) (…) the body would get back its actual function, which is not working well at the moment.

The concrete example we used seemed to help most of the interviewees get a clearer picture of what SB actually is. With this increased knowledge, most of the patients were able to better distinguish between SB and other research branches (e.g. genetic engineering or other types of biotechnology) that they had previously mixed up. They also expressed better understanding of their own possible benefits regarding new therapies or improvement of their own health. For example Erik, a patient who did not know in the beginning what SB exactly was, felt very positive about SB after he received a concrete example of a possible future treatment based on SB.

> **Erik:** Yes, is that it? If one can do that [example of possible SB treatment], I am in favor, sure. (…) Because human beings will be better off afterwards.

Discussion

To our knowledge this study is unique in that we are the first to conduct an empirical study with stable patients in order to understand how their opinion about SB might affect their willingness to participate in FIH trials. (A Pubmed search for the combined terms "synthetic biology" AND "patient autonomy" or “first-in-human trial” or “stable patients” obtained zero results.) Patients’ opinions about research and technology in general, the subject of SB and treatment options in this field could be useful in the future, when the FIH trials pass into more advanced clinical phases (II and III)[2,3]. While studies exist on the theoretical background of the general public’s fear of and opinion about SB[9] and media coverage on SB[15,16], to date none has been carried out on an empirical level with stable patients. Therefore, a further novelty of our study is the fact that we explore the attitudes of those who could actually be directly involved in this type of research, namely stable patients for clinical trials in the field of SB.

Stable Patients: Possible target group for clinical trials with SB

These first findings are of substantial importance, because previously only near-death cancer patients have been targeted for this type of study[13]. Given the absence of therapeutic alternatives, it is debateable whether these patients can autonomously choose to participate in clinical trials[12]. In contrast, stable patients suffering from a chronic illness such as diabetes are not near death. However, many of them report a decreased quality of life[17]. Even if they have not yet presented symptoms of cardiovascular disease, they have an overall decreased life expectancy compared to non-diabetic populations[17]. Similar observations have been made for gout patients[18]. Stable patients could profit from SB treatment, which is currently under development. For example, Kemmer et al. constructed a synthetic mammalian gene circuit to regulate uric acid homeostasis *in vivo*[19].

Enhancing patients' autonomy by providing sufficient information

Therefore, it is important to obtain a first impression of stable patients' opinion about SB in order to better understand why they would participate or refuse to participate in FIH trials. By improving, completing and correcting the patients' knowledge about SB researchers will thus be able to act at an early stage to ensure patients' autonomy while also facilitating FIH trials. According to Ong et al., patients who received more information from the physician were more satisfied overall[20]. From this finding one might conclude that providing information and thereby influencing patients' perspective is nothing new. However, there is a distinction between providing information on something which is relatively common for patients (e.g. cancer and cancer treatment) and providing information on something new and unknown (e.g. SB) where patients are not familiar with, or suffer from biases regarding, the presented subject as reported in the results. To a large part, participants' fears of and negative attitudes towards participation in clinical trials involving SB were due to misconceptions of what SB entails (e.g. creation of a "perfect human" or "something that cannot be controlled anymore").

Changing Attitudes towards SB

Even though most of the patients did not know exactly what SB was in the beginning, their attitudes towards SB changed to a more positive direction after they were provided with accurate information. It is important to note that people who are scared of SB can nonetheless envisage having a medical SB intervention. Therefore, our results also indicate a change in patients' opinion after they received information regarding medical treatments in SB. This is an important finding which is likely to be generalizable to patients in other countries, where sceptical attitudes about biotechnology and genetically modified organisms have also been identified[21]. We have good reason to believe that the changes of Swiss patients' opinions about SB would also occur in patients from other countries. The interviewees' answers

showed that negative attitudes were most often related to lack of accurate knowledge and confusion over various technologies. The media often convey a negative view on these new technologies, by invoking religious and environmental arguments[9,15]. It is important to note that most of the participants in our study expressed rather positive attitudes to research and technology in general. They stated, for example, that research must be done in order to improve their own health and everyday lives.

Reasons for patients' ambivalent attitudes towards SB

Participants' ambivalent attitude – both negative and positive – towards SB reflects the theoretical background, which has already been described in the research literature regarding fears related to SB but also the possibilities of medical improvements thanks to SB[1,5,6,9]. In addition, SB is often compared with biotechnology, since it deals with similar issues (e.g. the construction of life). Moreover, some scientists see SB as the next step of biotechnology[15,22] and that comparison also leads to a rather negative picture of SB. There is a general tendency in society to distrust new technologies, especially biotechnology[5,15]. Schmidt et al. argue that a new debate about genetically modified organisms (GMOs) should be avoided. Since SB is often associated with GMOs in public opinion, overstating both the risks and benefits of SB, even outside any GMO context, might generate a new debate. Moreover, the authors outline that transnational companies should not dominate the conversation. In previous debates about GMOs the transnational companies did not consider social and moral concerns expressed by a wider community (e.g. consumers). They conclude that with promotion of an open dialog, mistakes from the past could be avoided[23]. These above discussed findings give our study additional importance, since we have included patients in the discussion about SB.

Public debates about SB

Nevertheless, it seems that SB is still in a phase where the public has particularly poor and sometimes mistaken knowledge about the topic[15]. There seems to be considerable uncertainty among the public regarding what to think about SB. The comparison of SB with biotechnology (which appears to be associated with negative connotations) could lead to a continuation of old debates[5,15]. Another possibility is that the public pays less attention to SB, because it is not seen as something distinct or new. The media, in spite of generally mentioning SB, do not in general discuss the very concrete healing potential of SB (technology) in patient care in an elaborate way[5]. Therefore, it is important to encourage more specific discussions about SB to avoid possible spill-over from the abundantly negative media coverage of biotechnology[5,15,22]. These specific discussions could be achieved with an accurate set of information about SB. As already mentioned, after the interviewer informed patients in more detail about SB and its clinical applications with hypothetical examples for gout or diabetes treatment, most patients developed more positive opinions about SB. This observation clearly shows that accurate information can correct misconceptions and positively influence patients' opinion. Such information is a prerequisite for respecting and encouraging patients' autonomous decision-making[24,25] whether to participate in human subject research involving medication or devices involving SB.

In Switzerland, Schmid-Petri et al. showed that the public has little or no knowledge about SB. It is a complex field, and extensive explanation is needed in order to clarify its definition and main aims. As already noted, discussions in newspapers tend to be superficial and reports about SB are often neutral or even positive. Reports about potential risks and dangers have so far been rare. In contrast to the French-speaking part of Switzerland, in which possible regulations for SB have already been discussed in newspapers, SB is not reviewed in the German-speaking newspapers[16]. It can be said that SB is misrepresented, because of its

heterogeneous definition and association with biotechnology[1,5]. This makes it to explain to a broader public[16].

Limitations

Our study has some limitations. We included patients only from the German-speaking part of Switzerland and therefore the question arises as to whether our results are generalizable. Some regions in Europe are known to be relatively critical towards biotechnologies and genetically modified organisms[21]. In 2015 a popular petition for pre-implantation diagnostics was accepted by a great majority in the French-speaking part (e.g. Geneva; 82.2% votes of "yes" vs. 17.8% of "no"), whereas the acceptance was clearly lower in the German-speaking parts of Switzerland (e.g. Lucerne; 54.7% vs. 45.3%)[26]. These facts could partly explain the negative views of our Swiss German patients about SB as well as their diffuse fear of SB. Moreover, cultural differences between the German- and French-speaking parts of Switzerland have been discussed in other studies and are related among others to the influence of German-speaking technology opponents[27,28].

Furthermore, we cannot exclude the possibility of a social desirability bias. Social desirability means that people tend to behave in a way they believe to be culturally acceptable[29]. Overall we have reasons to believe that the results of our study are relevant and representative for important trends in Europe. Indeed, it has been shown that fears of cutting edge biotechnologies (e.g. nanotechnology) exist throughout all countries[30,31].

Our study has also the typical limitations of qualitative studies, i.e. that people who already have a strong interest in the particular field tend to participate[32]. The answers between patients varied and were sometimes even conflicting with one other. This could indicate that we were able to capture a sufficiently broad and heterogeneous sample.

However, our study also points to the risk that patients can be influenced by unrealistic hope or incomplete information where potential risks are underestimated. This could be due to inaccurate presentation of the information, but also due to a misconception regarding future treatment options (e.g. FIH trials)[12]. According to Appelbaum et al. the "therapeutic misconception" means that patients do not understand the setting of equipoise that defines research as such. Especially, if research takes place in a clinical setting such as hospitals, patients tend to deny the possibility of major disadvantages and are more likely to mistakenly assume a benefit, if they enroll in a clinical research study[33]. Clearly, a lack of information and accurate understanding undermines patients' decisional autonomy[11,24,25]. As Cialdini has shown, under uncertain circumstances, people tend to trust authorities (religious, political, media, etc.) even more than usual .These powerful figures greatly influence people's opinion and decision-making[34]. Therefore, a detailed knowledge of SB is crucial to guarantee patients' sufficient autonomy to make informed decisions (e.g. for possible future FIH trials)[11,12]. Research ethics committees have to examine very carefully the content of consent forms to make sure that information is detailed and accurate. Patients need to be able to appreciate the advantages as well as the disadvantages of clinical trials[12].

Conclusion

Our study contributes an important first insight into what stable patients think of SB and what kind of fears arise (e.g. "playing God") when SB is mentioned, and the effect on these fears once patients have received more detailed information. We have showed that some patients - when hearing about SB - might associate SB to those transhumanist dangerous experiments with humans ("playing God"). Therefore it is important to mention to the patient that the clinical use of SB is not related to these Promethean dreams. The patient's informed consent has little ethical value if it is based on loose associations and emotions. Similar recommendations were made in the field of nanotechnology. Satalkar et al. noticed too that

these terms trigger exaggerated fears in patients, but that these fears should be discussed openly with the physician as part of an adequate information process for research participants. They conclude that the word "nanotechnology" should be mentioned in the informed consent sheet in order to gain patients' trust but also to provide them a transparent discussion on clinical trials in this field[35]. Bromwich et al. discuss that informed consent should be adapted to the risks which the participants are taking. The authors argue that the concerns about the validity of informed consents increase with the risk of research in which the patients are involved[25]. Fagerlin et al. show that using plain language or pictographs can enhance patients' understanding the risk-benefit ratio[24]. The above discussed literature and our results reveal that providing accurate information is crucial for enhancing patients' autonomy. Researchers must present facts in a fair and balanced way. Therefore, detailed information about SB and its clinical applications are important in terms of future FIH trials[11,12].

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Appendix

Hypothetical Example for Gout Patients:

„I will guide you into Mr. Müller's world in the year 2025. Mr. Müller suffers, as you, from gout, but he is not taking any drugs. He needs to go rarely to his GP to get his uric acid level controlled. Mr. Müller has a capsule implanted under his skin. This capsule contains human cells. These cells are from Mr. Müller himself. They were removed and modified in the laboratory.

These modified cells from Mr. Müller are able to produce a certain protein that removes the surplus uric acid in the blood. Additionally, a sensor was integrated that constantly measures the uric acid levels in the blood. If it [uric acid level] increases too strongly, the protein production is stimulated. She [cell] produces more of the uric acid degrading protein. Mr. Müller notices nothing of this. Everything happens automatically and alone.

Hypothetical Example for Diabetes Patients:

„I will guide you into Mr. Müller's world in the year 2025. Mr. Müller suffers, as you, from diabetes. Mr. Müller has a capsule implanted under his skin. This capsule contains human cells. These cells are from Mr. Müller himself. They were removed and modified in the laboratory.

These modified cells from Mr. Müller are able to produce a certain substance that stimulates the insulin production in the body and decreases the blood sugar concentration. Mr. Müller is wearing a plaster with incorporated LED-lamps on his skin. After food intake, Mr. Müller switches the LED-lamps on via touch of a button. The light ensures that the substance gets produced in the cells and distributed in the blood.

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Chapter 3

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Enhancing Patients' Autonomy by Involving Them in Research Ethics Committees

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Abstract

Objective Although clinical trial participants are the most affected by research ethics committee's decisions, they are not formally represented on Swiss committees. We aimed to find out what patients think about the idea of being members of such committees.

Design Latent thematic analysis was used to analyse the interviews.

Setting Patients were recruited in a Swiss university hospital.

Participants The study involved 26 patients suffering from diabetes or gout.

Interventions We conducted semi-structured interviews.

Main Outcome Measures We explored what patients think of being established members of research ethics committees.

Results We identified three different attitudes among our participants regarding participation in research ethics committees: (i) positive attitude regarding the idea of being members of such committees (ii) ambivalent attitude and (iii) negative attitude. Patients belonging to the first group (i) often mentioned that they wanted their health condition to be more visible. Patients from the second group (ii) mentioned positive as well as negative aspects. Patients from the third group (iii) said that patients in general did not have enough background knowledge to be able to gain an overview of a whole clinical trial.

Conclusions Our study adds important knowledge about the idea of patients becoming research ethics committee members by exploring their perceptions of being members. Stable patients tended to be interested in the idea of participation and some specific recommendations could be derived (patients could have an advisory instead of a decision-making role on committees). However, further studies with more patients and further quantitative research are needed.

Key words: research ethics committee, autonomy, stable patients

Introduction

According to the Declaration of Helsinki, every trial involving human beings must be approved by a research ethics committee (REC) in advance. Each committee member must be independent of the researcher and sponsor and must operate free of any other inappropriate influence[1]. RECs are constituted by members of different specialities (e.g. physicians, statisticians, ethicists). In the UK, RECs need to include so-called "lay members" who are independent of health services. Half of them are required to never have worked in the healthcare sector. Some RECs also include patient representatives[2]. Swiss RECs are similar as they include experts from different scientific disciplines, but they are not required to include lay members[2,3]. Nevertheless, each state (canton) of the federalist Swiss Confederation can decide whether its REC needs to include lay persons, defined as any person who is not a physician. However, the lay person is not necessarily a representative of patients[4]. While three cantonal RECs (Zurich, St. Gallen, Vaud) employ patient representatives, only 1.6% of Swiss REC members are patient representatives[4]. In contrast, 41.5% are physicians[4]. This means that although clinical trial (CT) participants are the group most affected by the REC's decisions, they are not formally represented on Swiss RECs[3]. Including patient representatives on RECs, however, is not necessarily enough to support patient interests. The question is whether patient representatives are able to speak for patients who suffer from other diseases. Therefore, it might be helpful to include patients rather than patient representatives or lay members in RECs and decision-making regarding CTs to ensure that patients' voices are heard[2].

A possible disadvantage of having patients as REC members could be the whole process of recruiting appropriate patients (e.g. stable patients), which could be very costly and time consuming[2]. CTs involving novel technologies (e.g. synthetic biology) and stable patients (i.e. not terminally ill), are more likely to be rejected because RECs consider it highly risky to

enrol stable patients in (e.g.) first-in-human (FIH) trials. In these cases, the potential damage to health outweighs the potential benefit for volunteering participants[2]. Terminally ill cancer patients are a common target group for CTs, given the absence of alternative treatment options. However, decisions of patients who have a life-threatening illness may be strongly affected by the lack of treatment alternatives[5]. Indeed, patients with a high degree of psychological strain might be more likely to accept possibly high risks and be victims of the therapeutic misconception (i.e. lacking awareness of the difference between clinical research and therapeutic treatment)[6]. Moreover, the informed consent process itself can be exhausting for severely ill patients and be considered as too harmful[7]. Enrolling stable patients in FIH trials (e.g. diabetes patients) could be a way to avoid these ethical issues. Stable patients have more treatment options than near-death cancer patients. Hence, they are more likely to make free choices[5] and less likely to fall victim to the therapeutic misconception[6]. Additionally, they might benefit from the medications developed through CTs since despite limited quality of life, life expectancy is only slightly decreased[8,9]. Therefore, RECs' tendency to reject high-risk studies involving stable patients could be criticized as unjustified paternalism[10,11]. It has been argued that stable patients are capable of giving reflective „independent" answers[5] and should be allowed to decide whether to take trial related risks. McKinstry concludes that paternalism, especially with respect to competent patients, is rarely justified[12]. Respect for patient autonomy is one of the four principles of modern biomedical ethics[13]. Two prerequisites for a person to be autonomous are identified: liberty and agency. This means that a person can decide independently, free from others' influence and has the capacity to act in an intentional manner[13]. Autonomy has acquired increased importance in medicine[7]. Failing to consider patients' willingness to accept risks, i.e. the paternalistic attitude of RECs[2,11], seems to create an anachronistic situation regarding autonomy. This situation could lead to the patient's right to make autonomous decisions regarding participation in clinical

research being restricted. Therefore, shifting from paternalistic decision-making to a patient-centred and shared decision-making by putting patients on RECs increases patients' ability to engage in autonomous decision-making[14]. Thus, patients should have the opportunity to participate in decision-making regarding CTs.

Aim of the Study

Given the identified advantages and disadvantages of a system where RECs include patients as members[2], we aimed to find out what stable patients think about being members of RECs. Therefore, we explored this issue using qualitative interviews from a broader study on FIH trials with stable patients.

Methods

We employed an empirical research design with the overall goal of exploring stable patients' attitudes towards participation in RECs as established members. The data were gathered as a part of a larger interview study where patients were asked about their attitudes towards synthetic biology and related CTs[15]. A pilot study was carried out in order to ensure patients' understanding. We used the 32-item checklist from consolidated criteria for reporting qualitative research (COREQ)[16]. We obtained ethical approval from the local REC.

Sampling and Data Collection

The interview study involved a purposive sample of patients suffering from diabetes or gout. Inclusion criteria for this study were that patients were (i) > 18 years, (ii) stable, and (iii) suffered either from diabetes or gout. The recruitment was carried out in the hospital during a time period of six months in 2014/2015 while patients were there for a routine check-up. Our recruiting physicians approached suitable patients and asked if they would be interested in participating in an interview study. Subsequently, a research assistant (trained in qualitative research) went to the hospital and asked patients if they agreed to participate. In case of agreement, patients received a participant information sheet, and an informed consent form

and were given time to consider whether to consent. Afterwards, the research assistant approached the patients via phone or email and made an appointment. The interview took place at the patient's home, our research institute, or in the hospital. During the interview only the interviewer and the interviewee were present in the room. All interviews were conducted by the same research assistant. Written informed consent was obtained from all participants. On average, the interviews lasted for 44 min (range: 16 to 102 min). All interviews were conducted in Swiss German, transcribed verbatim and fully anonymized.

Interview Guide

After a literature search for research on cutting edge biotechnology, we developed an interview guide. Based on the previous literature research, we selected topics which should be included in our interview guide (e.g. examples of CTs, patients' current health status). The semi-structured interview guide provided a short explanation of our study and of RECs, followed by two questions regarding patients' opinion on RECs (Table 1). These two questions were specifically analysed in this paper.

Table 1: Questions about research ethics committees

Before a new type of treatment (e.g. gout or diabetes capsules) can be tested on patients within clinical trials, a committee of experts decides whether this trial may to take place at all. This committee assesses the possible risks and benefits related to this trial, and weigh them up against each other. In Switzerland there are many different ideas about who should be represented in such a committee.
1. What do you think about this? Who should be represented in such a committee and why?
2. How do you see the participation of patients in such committees?

Analysis

Of the 36 patients, 26 answered the question about the topic of patient representation in RECs. Ten patients responded that due to not knowing the concept of RECs they could not give an appropriate answer. Here, we present and analyze the responses of the remaining 26 patients. We used latent thematic analysis as it is independent of a particular theory or epistemology. Therefore, it can be applied across different approaches[17]. The project did not intent to develop a theory or understand the experiences of the patients, but to study their opinions on participation on RECs. First, all authors read the interview-transcripts in order to inductively obtain preliminary themes that are not a priori defined based on a theory[17]. The authors discussed the preliminary themes. Afterwards, we agreed on themes and coded the transcripts according to the agreed themes. Member check was done by the co-authors. During the analysis for the questions analysed for this paper, data saturation was reached according to Guest et al.[18]. The final themes are presented in Results.

Study Population

Eighty-eight percent (*n*=23) of the patients were male; age ranged from 26 to 91 years. Other demographic information is presented in Table 2.

Table 2: Descriptive statistics of our study population (n = 26)

Gender (male)	88.5%
Age (M*; *SD**) (1 missing)	64.9 (16.599)
Education (1 missing)	
• University	19.2%
• Apprenticeship	76.9%
Household (1 missing)	
• ≤ two person	88.5%
• > three person	7.7%
Disease	
• Diabetes Mellitus I	23.1%
• Diabetes Mellitus II	38.5%
• Gout	38.5%

*M = mean; *SD* = standard deviation

Results

We identified three different attitudes regarding participation on RECs: (i) exclusively mentioning positive aspects (ii) ambivalence about the idea, and (iii) exclusively mentioning negative aspects.

Positive aspects of being members of RECs

The majority were very positive about patient participation in RECs. Participants often mentioned their own benefit as a reason to participate as members. More precisely, patients saw a chance of a long-term benefit on their own health condition from participating in RECs and perhaps allowing more CTs. Another frequent reason was that patients wanted their situation to be visible. Patients also said that they have experience with the disease and therefore they can tell what it is like to live with it. For this reason, they should be able to integrate their opinions on whether a CT should be performed within an REC. Another reason for patient participation in RECs was that they possibly add different perspectives on a certain aspect of the disease (Table 3).

Table 3: Positive aspects of being members of RECs

Patient 8: This would be good. [Good] in the sense that they [patients] talk from experience, they know what happens in the body [e.g.] of a diabetes patient. In my opinion there should be both types of diabetes patients in there [committees]. This would mirror the reality very well (...), because they [diabetes patients] know what they are talking about and you can rely on their opinion. This would be the main goal that these kinds of people [patients] are represented in such committees (…), people who know the problem (diabetes diagnosis 10 years ago).
Patient 1: To be able to see the patients' situation. He/she can, only he/she can, say how hard the disability is, caused by the disease. He/she can estimate the agony caused by the disease. A physician is not able nor is a psychologist, right. That is something only the patient can (…) and I think that [patients] should be heard and incorporated [in RECS] (gout diagnosis one year ago).
Patient 7: Because they [patients] are interested that science gets on (…), because there are a lot of things that do not work 100% yet. This could be a reason that they [patients] are interested in being part of such committees and maybe they can positively influence the whole thing (gout diagnosis less than one year ago).

Patient 16: Because he/she [patient] can maybe add some things, which might get forgotten by more educated people (diabetes diagnosis 3 years ago).

Ambivalent aspects of being members of RECs

A smaller second group of patients was ambivalent. Participants mentioned both positive (e.g. to see what is happening; patients experience) and negative aspects (e.g. patients may not have enough knowledge; they only see their own benefit) of being on RECs. Some patients said that it does not necessarily have to be patients but independent people who are on the committee (Table 4).

Table 4: Ambivalent aspects of being members of RECs

Patient 25: There are pros and cons (…) which speak for and against it, right. Patients have some experiences as well. (…) if there are more [patients], there is an exchange of ideas and they could talk together and accordingly influence something in a positive or negative way (diabetes diagnosis 15 years ago).
Patient 36: I think that is delicate, because the "ego-thinking" comes up again, yes that could bring something or it [drug, treatment] could help a little bit. I do not think so (gout diagnosis 12 years ago).
Patient 23: For this [patient participation in RECs] that they can see what is being done. Against it [patient participation in RECs] that there will be maybe a pushing [due to own profit] in order to get it [drug] developed.

Negative aspects of being members of RECs

Finally, a few patients did not see any positive aspects of making patients members of RECs. The main reason cited regarding why patients should not be part of RECs was that they do not have enough expertise to be able to gain an overview of the whole study. In addition, participants mentioned that they did not understand the purpose of having ordinary people on a REC (Table 5).

Table 5: Negative aspects of being members of RECs

Patient 13: He/She [patient] does not have the overview of the whole thing [study], of what was and what might come (…). The patient cannot determine this (diabetes diagnosis 40 years ago).
Patient 24: They [patients] cannot decide, because they [patients] have no knowledge. They [patients] only can say if this [treatment, drug] would be something for me, but if it [treatment, drug] is really good, that is something they cannot decide (…) (diabetes diagnosis 41 years ago).
Patient 28: Because I think that we as ordinary mortals do not really have an idea what really goes on [Diabetes diagnosis 12 years ago].
Pat 29: (…) I need to leave this [decision] to the experts (Gout diagnosis one year ago).

In summary, our analysis showed that most participants were positive about the idea of being members of RECs. Interviewees illustrated their experience and their comprehension of the disease, but also their interest in propelling research. Many patients think that present RECs do not pay enough attention to their health condition, and that only patients are able to assess it.

Discussion

To our knowledge, this is the first empirical study to specifically explore stable patients' perceptions of being REC members. The most commonly mentioned advantageous aspects were: (i) potential benefit for affected patients and (ii) the disease burden of the patients, which enables them to add new perspectives on certain aspects of the disease.

Surprisingly, although the interviewees were informed that participation in CTs does not lead to any personal benefit in terms of changes in therapy, they still anticipated personal benefit as one of the main incentives for the involvement of patients in RECs. This might be seen as a biasing factor affecting proponents of this idea, because the hope of long-term benefit for oneself might make one overlook the risks of participating. Considering this as an indicator for a persistent therapeutic misconception disqualifies this as an argument for involving patients in RECs.

However, this biasing factor does not seem to operate on a broader scale. This presumption is supported by the data of a large cross-sectional survey exploring community understanding of medical RECs[19]. According to this study the majority of the respondents were aware of the role of RECs.

The second most-mentioned motivation was disease-related knowledge, particularly regarding the accompanying psychological and physical strains, which could allow RECs to obtain additional insight into a specific medical condition. Generally, patients believed themselves to be most familiar with their specific medical issue and this specific aspect has not yet been addressed by RECs.

Interestingly, our cohort, with a relatively high average age of almost 65 years, had similar views to participants in a study investigating young participants' views on composition of RECs (mean: 16 years). Overall, participants expressed the need for a broader view provided by lay people[20].

Amongst the negative aspects mentioned in our cohort were patients' lack of knowledge compared to experts, and potential difficulties in assessing the consequences of decisions made in the context of complex studies. Similarly, professional expertise was considered important among young people[20].

Nevertheless, the argument that lack of medical knowledge could count against patients' inclusion in decision-making is not tenable. As stated by Edwards et al.[10], it is not the task of RECs to judge the competence of patients. As in the shared decision-making model, participating patients would have to be properly provided with all relevant information (e.g. risks, potential benefits) before engaging in REC decisions.

Overall, stable patients seem to be particularly appropriate decision-makers as they suffer from a chronic disease with a significant burden[21-24]. Due to the relatively slow progression and associated mortality of e.g. diabetes compared to acute diseases, stable patients are more likely to benefit from future research[23,25]. Therefore, REC decisions on CTs might affect them indirectly over the medium-term, and the problem of 'therapeutic misconception' could have a less prominent role[6]. The most important ethical consideration favouring the inclusion of stable patients is the need to respect patient autonomy. In order to meet this requirement, affected patients should have the opportunity to participate in decision-making in RECs through their representatives. It has been claimed before that qualified individuals are in the best position to decide which risks are acceptable for them[10]. From this point of view, the exclusion of competent patients from RECs can be seen as a form of paternalism, contradicting the concept of shared decision-making. Shared decision-making – in a clinical setting – means that neither the physician ("paternalism") nor the patient ("informed choice") on his own decide what is going to be done (e.g. what kind of treatment etc.). Instead, the decision is made together[26]. This requires the ability of an individual to make his or her own, independent choices and respecting patients' perspectives as being just as valuable as experts'

perspectives[26,27]. The impression of RECs as a paternalistic characterized decision-making body[10,28] could be countered by enhancing patients' autonomy through involving them in decision-making.

Limitations

The limitations of this current study relate to its qualitative design and relatively low number of participants: the subjectivity of data analysis and the limited generalizability of the results that we obtained from German-speaking patients. Furthermore, 10 out of 36 persons could not say anything about the idea of patients as members of RECs because they were lacking respective knowledge. Since our investigation only focused on stable patients, generalizable statements about other patient groups are limited. Another possible limitation could be the overrepresentation of male patients (88.5%). However, an epidemiological study showed that 80% of gout patients were male[29]. Also, a review showed a male excess in diabetes mellitus I, whereas diabetes mellitus II seemed to be fairly distributed among both sexes[30]. Generally, it cannot be ruled out that supposedly healthy lay members suffer from a chronic disease themselves, in which case their decision-making may also be affected.

Conclusion

From the previous considerations we conclude that stable patients appear to be suitable as REC members in the field of clinical research. This is particularly true for CTs in which novel treatment technologies will be evaluated in affected but stable patients. The reasons for this are various: First, it can be argued that respect for patients' autonomy as one of the four fundamental principles of medical ethics requires the involvement of patients instead of healthy third parties (e.g. physicians, ethicists, lay members). Furthermore, the interviews revealed a tendency towards the idea of involvement of stable patients. The primary stated motivation for this was the improvement of therapeutic options in the future. This seems to be supported by the fact that chronic diseases such as diabetes commonly have a slowly progressive clinical course over several years and do not pose an acute threat to life compared

to, for example, advanced stages of cancer. In addition to this idea of being able to influence new therapeutic options in the future, there are presumably further reasons why it could be appealing for stable patients to be part of RECs. Taking part in decision-making regarding CTs could create a feeling of inclusion and respect for patient perspectives. In this way, early integration of persons affected could influence the general acceptance of research in a positive manner. In contrast to terminally ill patients, stable patients are more likely to be able to fulfil the demanding work of a REC member because of their better health condition. Relatively slow disease progression with possible stable phases under therapy, comparatively good life expectancy, and diverse treatment options especially in early stages may prevent stable patients from experimental treatment approaches.

The improvement in quality of life in the long-term instead of a short-term prolongation of life expectancy appears to be the primary objective for many of the stable patients. Therefore, the possible objection that stable patients could generally have a bias towards approving research on novel treatment technologies is not applicable. Patients could play an important role when it comes to the benefit-risk assessment of future therapeutic interventions. The main additional benefit of this patient group, compared to healthy REC members, is the disease-burden that these patients are aware of and the direct insight into patients' perspectives that they could provide.

For practical purposes it could generally make sense to reach out to stable patients that match the inclusion criteria of the planned study. The patients included in RECs should not take part in the study themselves in order to avoid biased opinions. Another important point is that patients would have to be properly informed about their role in the REC as affected patient representatives. By excluding patients from taking part in the trial and by providing detailed information the influence of therapeutic misconception should be reduced. A point of concern in this context could be that patients who take part in decision-making but do not participate

in the study themselves, may overlook potential risks to participants of the trial by attaching greater weight to potential long-term benefits. To counter this, patients could have an advisory instead of a decision-making role on RECs.

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Chapter 4

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The Beneficence of Hope: Findings from a Qualitative Study with Gout and Diabetes Patients

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Abstract

This paper explores the importance of hope as a determining factor for patients to participate in first-in-human trials for synthetic biology therapies.

This paper focuses on different aspects of hope in the context of human health and well-being and explores the varieties of hope expressed by patients. The research findings are based on interview data collected from stable gout and diabetes patients. Three concepts of hope have emerged from the interviews: hope as certainty (H1); hope as reflective uncertainty (H2); hope as self-therapy (H3).

The purpose of the paper is twofold. First, it aims to underline the significance of hope in patients' medical decision-making, as well as the beneficence of hope for patients' well-being, and for progress in research. Second, it shows how philosophical investigations – in particular Descartes' – explore the phenomenon of hope, and provide medical empirical research with profitable insights and tools.

Keywords: Hope, Certainty, Optimism, Self-therapy, Virtue, Well-being

Introduction

Hope is crucial for human lives and particularly for those affected by ailments[1,2]. And yet, it is not easy to determine the specific nature of hope, as it is a diffuse phenomenon. Indeed, researchers have identified forty-nine different definitions of hope[3]. As Eliott has noted, the perception of hope differs markedly across time and culture. For instance, Ancient Greece defined hope as a divine evil "that encourages foolish optimism"[4, p. 2]. In the Latin Christian tradition (e.g. 1 Corinthians 13:13) hope (*spes*) is a virtue among the three theological virtues (faith, hope, and charity). It is viewed as a God-given disposition – or infused virtue – to direct us to God and thus guides us through our journey on earth. Whereas the Medieval thinker Aquinas insisted that without this infused virtue, we would not feel the emotion of hope[5], modern philosophers such as Camus[6] (1942) and Bloch[7] (1959) conceive hope in immanent terms. Psychologists and medical scholars do not generally explain hope as an effect of divine grace. However, they do not completely give up the idea that hope is a virtue[8]. Miller reminds us that, for the 19th century English physician Thomas Percival, the physician is a "minister of hope and comfort to the sick". Miller endorses this view as "still apt"[8]. In general, researchers focus their attention upon the psychological mechanisms that generate emotions of hope[9]. Indeed, in the last four decades an increasing number of empirical studies – conducted mainly in psychology and psychiatry – have developed tools for measuring hope, for example "The Hope Scale" (see[10]). This measures the effect of hope on bodily ailments and illnesses (see[11]). Andresen et al. demonstrate that hope can play a role in shortening recovery processes[12]. Huguelet adds that hope may be both a motivating *factor* for healing more promptly and a *consequence* of healing[13]. Maier and Shibles (2012) define hope as an emotion which produces positive bodily feelings[14]. Maier and Shibles also establish a direct link between hope and humor:

Both hope and humor take and run around life's problems. A negative situation may not be within our control, but humor is. […] The most hopeless situation is death, which is why humor is one of the few ways in which it can be coped with or explored[14, p. 150].

Rivka Jacoby[15] shows that hope is also a resourceful aid for coping in stressful situations. Particularly for terminally ill patients, the significance of hope has been abundantly documented (see[16,17]). As Cotter and Foxell note, health professionals in palliative care widely agree that,

…although hope tends to change in people with terminal illness, maintaining a delicate balance of death and hope for a cure often remains an important task up until the time of death, even when people acknowledge that cure is virtually impossible. The dying person needs to envision future moments of happiness, fulfilment, and connection[18, p. 7].

In a similar vein, recent empirical research in psychiatry has showed hope to be important for the recovery process of schizophrenia patients, even when their chances of reintegration into society are limited (see[19]).

The significance of hope can also be identified in the context of first-in-human (FIH) trials, as we observed in thirty-six interviews conducted with stable gout and diabetes patients. The aim of the interviews was to have a better understanding of patients' attitude towards hypothetical participation in cutting edge biotechnology research with a special focus on synthetic biology. Hope emerged as a distinctively rich theme – explicitly or tacitly present in many interviews with stable, but chronically ill patients with decreased life expectancies. The present paper attempts to clarify the importance of hope for patients who participate in clinical research, and particularly in FIH trials. This article thus explores a novel research

question that has hardly been discussed in the literature[20,21]. Based on the patients' narratives we identified three kinds of hope: hope as certainty (H1); hope as reflective uncertainty (H2); hope as self-therapy (H3). As the interviews illustrate hope can express a strong confidence in the goodness or beneficence of the scientific research's outcome, whether for the patient, or for future patients (H1). Yet, hope can also imply scepticism, fear, and concerns about the outcome of scientific research (H2). Finally, hope can also function as self-therapy allowing patients to remain positive despite uncertain health outcomes (H3). The purpose of the paper is twofold. First, it aims to underline the significance of hope in patients' decision-making and to encourage the promotion of hope, as beneficent not only for patients' well-being, but also as a component of research. Second, it shows how philosophical investigations – in particular Descartes'– explore the complex phenomenon of hope and provide medical empirical research with useful theoretical insights and methodological tools. Descartes emphasizes the plasticity of hope: hope is a psychological coping strategy; hope can coexist with uncertainty; and hope is a great incentive to recover health.

1. Various Understandings of Hope

As Albert Camus writes in his philosophical essay *The Absurd*, hope arises when meaningfulness is at stake, that is, when we have to deal with purposeless events, or more fundamentally when we try to make sense of the vulnerability and finitude of our lives: "Absurdity, hope and death carry on their dialogue"[6, p. 25], (our translation; see also[22]). In a similar vein to the existentialist way of evaluating hope as a way to comprehend the apparent absurdity of human existence, the atheist Marxist-inspired conceptions of hope such as Ernst Bloch's utopic model shares with Camus that hope is an immanent principle of moral agency. In his influential book *Das Prinzip Hoffnung*[7] (1959) Bloch shows that hope is a strong

motivating force of political actions. Without hope for a more just society, no dialectic change in history would be thinkable, no political reform would ever take place.

Despite their evident contrasts, the transcendent religious and the immanent atheistic models of hope agree on hope as confidence in the good that humans can potentially achieve. Being hopeful seems to be *prima facie* a beneficial trait of character, for it encourages committing oneself to noble causes such as childcare, education and healthcare in the world. In this regard, hope has a critical normative dimension as it challenges unfair conditions: for example insufficient childcare, and societal exclusion of people with mental conditions[19]. As well as being a strong motivational drive to positively change aspects of one's own life or to contribute to modify the course of history for the better, hope also generates a generally positive outlook on the potential of humans. An interesting consideration of hope raised by Aquinas concerns whether one can teach and learn hope. Aquinas thinks it is the effect of divine grace, whereas Bloch defends the views that it can be acquired by human efforts. Recent literature reports that a variety of hope-therapy programmes have been designed[23].

In contrast to despair, hope turns us into optimistic people. However, the idea of "hope" is not fully interchangeable with "optimism"[1]. Averill, Caitlin, and Chon[9] suggest we should distinguish hope from optimism. Hope is a positive attitude toward desirable but unlikely events, whereas optimism expresses confidence in events which are likely to take place. So for instance we do not need hope for tomorrow to come, but we need hope in order to think that a fairer distribution of medical care is possible. More importantly, one needs hope, and not optimism, to defend a lost cause, for hope is not about evaluating the world as it is in a positive way, but about believing that the world could be better than what it is. Optimism is a

[1] We are not speaking here about the classical form of metaphysical optimism, as it is defended by Leibniz in his *Theodicy* (published in 1710 [24. Leibniz G.W. *Theodicy. Edited by A. Farrer and translated by E.M. Huggard.* New Haven: Yale University Press1952.]). Optimism is understood here in a more psychological sense, that is as a tendency to interpret positively what happens and will happen to others and oneself.

Weltanschauung which considers the world as predominantly good. In contrast, hope is a belief that the world as it is, is not predominantly good and that it could (or should) be different. Another difference highlighted by Averill and colleagues is that the events we are hoping for *matter* a lot to us. This personal involvement need not be the case for optimism. This latter distinction is harder to substantiate and we tend to disagree with Averill on the point, as both hope and optimism seem to imply a certain amount of personal engagement with the world. Indeed, a favourable course of events matters as much to the optimist as to the hopeful person. Hope differs from optimism in that hope implies that certain states of affairs should be avoided, even if it seems *prima facie* unlikely, if not impossible, to change them. In contrast, an optimist would typically look for the positive in any state of affairs, on the premise that the world as it is, is fundamentally good. In other words, hope has a stronger utopian dimension that is more critical of cultural, social, and political affairs than mere optimism. Hope evaluates the present in view of a possible and better future, while the optimist is content with the existing condition, the *status quo*. Our suggestion is that these distinctions between hope and optimism can also be relevant within a medical context. Consider this sentence from a physician to her/his incurable patient: "although there is little reason for optimism, don't lose hope"[9, p. 96]. Smith et al. (2011) confirm the common occurrence of this statement in their study. The authors explain that the more honest and precise information patients receive, the more hopeful they can be (see[25]). A recent study shows also that "disclosure of prognosis by the physician can support hope, even when the prognosis is poor"[26, p. 5636]. For certain persons, to be hopeful means to believe in miracles. Cooper et al. also remind us that "many people, including healthcare providers, believe that miracles can and do happen, even in the most traumatic experiences"[16, p. 2]. The authors add that the belief in miracles can refer to at least two different conceptions:

Some writers note that the belief in miracles is based on irrationality, meaning that something will occur despite the laws of sciences. Others frame the belief in a miracle as a statement of faith or piety. (p. 2)

However, there is also good reason to doubt whether hope can be given any epistemic value, and has any quantifiable use at all, since even the optimist recognizes the medical fact that the patient is incurable. So what is the point of hope? In certain ways hope seems to be the last evil in Pandora's Box, an illusion which we should fight against, as recommended by Hesiod and Aesop[4]. Should we not be more suspicious about the psychological twist of hope, as Ludwig Feuerbach[27] showed in his critical analysis of religion? For the German philosopher, hope, particularly Christian hope is an infra-conscious projection of our desires for divine immortality (see[28]). Seen in this light, hope is a kind of defiance and denial of our finitude.

Indeed, there are some cases in which hope seems to be an inadequate or even bad habit, a self-deceptive behaviour[9]. Psychologists speak of "false hope"[4,29]. The English language has a word to depict this out-of-place confidence: "pollyannaism". The *Oxford English Dictionary* defines pollyannaish as "naively cheerful and optimistic; unrealistically happy" (OED Online 2018[30]). Ruddick[31] emphasizes that physicians should avoid supporting patients' false hopes, as this attitude amounts to a "paternalistic violation of patient autonomy"(p. 343). In the field of research ethics, unrealistic optimism can lead to what is called "therapeutic misconception", when the patient conflates research with therapy; when s/he believes that "every aspect of the research project […] is designed to benefit him [or her] directly"[32, p.12], see also[21].

To sum up, hope plays a key role in human lives as it helps us face uncertain or fatal outcomes and interpret them in a pro-active sense. We have seen that philosophers and ethicists are wary of the potential harm of hope, as it rests on belief about improbable events and can lead to self-deception. However, our empirical data illustrate that the epistemic poverty of hope does not seem to be a problem for the interviewed patients. First, the medical knowledge that there will be little or no improvement in the patients' condition can coexist with the hope for a better outcome for future generations. Second, patients use hope as a measurable good ("little hope"), i.e. to indicate a low level of knowledge. Third, they seem to conceive of hope as a kind of therapeutic tool helping them to get through the day and envisage their near future cheerfully. While trying to identify the different combinations of hope in our collected material, we realized that Descartes made similar distinctions regarding hope in his private correspondence with Princess Elisabeth of Bohemia. The next section analyses our empirical data on hope in light of the philosophical insights of Descartes. We suggest that (1) the phenomenon of hope, as expressed in the interviews with gout and diabetes patients, is complex, even paradoxical; (2) the finesse of Descartes' descriptions of hope seems to capture the complexity of hope and makes him in that regard a valuable resource for today's debate in medical ethics; and (3) health professionals should be perhaps more aware of the plasticity of hope: hope can be an expression of self-deception but also of moral certainty, reflective uncertainty, and mental health.

2. Three Kinds of Hope

Methodological Remarks

In the thirty-six interviews conducted with stable patients suffering from gout and diabetes, we analysed how patients reacted to hypothetical participation in FIH trials using synthetic biology devices. The interview guide consisted of ten open questions; each with several sub-

questions prompting patients on particular details. During the interview, the interviewer provided information about potential medical applications of synthetic biology and FIH research. Each interviewed patient was provided with the hypothetical example of the implantation of synthetically modified cells. Patients were informed that the hypothetical implanted cells would cure diabetes and gout and make other medication redundant. The average interview duration was forty-four minutes. Interviews were transcribed verbatim and quotes were translated into English. We applied a bottom-up, rather than a top-down approach: we did not use an existing theoretical framework of hope while reading the interviews. Hope emerged as one of the themes from the interview material (see[33]).

This main theme was divided into three subcategories as patients referred to different kinds of hope in the medical setting[2]: hope as certainty (H1); hope as reflective uncertainty (H2); hope as self-therapy (H3). In the final phase the chosen theme, hope, including the empirically identified three sub-forms of hope – H1, H2, and H3 – were analysed in the context of Descartes' moral philosophy. Finally, a recommendation was made for clinical settings: hope is not only a positive attitude towards a particular event but can even entail fear and doubt. However, hope implies an essential confidence in the ultimate outcome of events which matter to us. As such, hope should be promoted for the sake of both patients' well-being and clinical research. Details of the methods are described elsewhere[33].

3.1 Hope as Certainty

For a number of patients, hope expresses an unshakable confidence in the effectiveness of medical treatment for themselves, and/or for future generations of patients. Hope expresses the patients' trust that clinical research will contribute to human well-being in the long run.

[2] The paper does not claim that the kinds of hope occurring in the interviews are the only existing kinds of hope. For an overview of hope theories, see Rand and Cheavens 2009.

Consider for instance patient Danielle's answer to the question of whether she has hope that the trial can be helpful: "Yes, absolutely. Yes, I have the hope that it will be of help in the future." See too the general statement from patient Yves about confidence in future therapies: "One hopes that there will be better therapies in the future to help others."

The certainty which these patients envisage is not based upon scientific research, or upon complicated statistics. Neither is it the result of a long and metaphysical meditation or a blind faith in medical progress[34]. Rather, it is a kind of *moral certainty*, that is, a *positive evaluation* of present and future human potentialities as well as a strong faith in the overall goodness of things. In other words, hope is a conviction that things will turn out for the best. This seems to be a *spiritual resource*[3] that is available to us in adverse situations, particularly in the case of serious illnesses[4]. The view that hope is a coping strategy, a form of medicine for the soul, is not a new idea. It was a widespread view in early modern moral philosophy, which was strongly advocated by Descartes[35,36]. For Descartes, spiritual fortitude does not only relate to the mental part of the human: being strong affects both mind and body. Thus, according to the Cartesian doctrine of the mind–body union, thoughts can produce improvement or deterioration of bodily health, and vice-versa. Conceived as a certainty about an ultimately good outcome, hope is a medicine for the soul and for the body, as the Latin adage says *mens sana in corpore sano* (a healthy mind in a healthy body)[2]. Ultimately, the conviction that all will be for the best, despite present pains and worries, helps protect us from interpreting our own fate and death (as well as the fate and death of other human beings) as something inherently negative.

[3] "Spiritual" is used here in its etymological meaning: of the, related to the spirit (*mens*, *anima*).

3.2 Hope as Reflective Uncertainty

Hope can also imply the awareness of uncertainty or doubt regarding the chance of recovery. As patient Chris replies to the interviewer, he would participate in the trial for the following reason: "Yes there is a chance that the treatment is efficacious. Efficacious and supportable. That there is meaning in it."

Chris states further that the reason why a paralyzed patient participates in a clinical trial is that he hopes and does not know whether he will feel better. Chris then concludes that it is an instinctive decision:

…also if it is a paralyzed or damaged [patient], who then says: "Yes", this and that I hope, then I do not know. Then, it is a gut feeling based decision (*Bauchentscheidung*)."

Patient Danielle speaks of there being "little hope":

> And therefore there can always be something, when something foreign enters the body, which causes a reaction. Of course you hope that there will be always positive reactions, but the contrary can happen as well. […] There is little hope that it [treatment] is already useful, because it is an experiment/trial.

The fact that hope can formulate uncertainty about future outcomes is not idiosyncratic to gout and diabetes patients. On the contrary, the patients interviewed tend to illustrate a recognizable pattern in human psychology. Folkman[37] notices a similar kind of hope among cancer patients. They learn how to live well despite the fact that the outcomes are only "plausible". The French philosopher too compares hope as a speculative form of knowledge in *The Passions of the Soul* (published in 1649) and his moral correspondence. In his letter to Princess Elisabeth of Bohemia from 3 November 1645 Descartes points out this reflective dimension of hope: hope includes uncertainty, or as he writes "conjectures" and "no assurance":

> As for the state of the soul after this life, I have much less knowledge of it than M. Digby. For leaving aside what faith teaches us, I confess that, by natural reason alone, we can make many conjectures to our benefit and have some high hopes, but no assurance[38, p. 126].

Hope is not a blind denial of what human reason cannot control. The particularity of hope as reflective uncertainty is that it does not make us fall into despair. Hope occupies this very subtle position in our self-awareness which *compensates* for our cognitive weaknesses and *reminds* us of them.

We can now better understand the plasticity of the concept referred to earlier: hope implies both *certainty* in the sense of overall faith in the ultimate actuality of goodness and *uncertainty* in the sense of recognition of human limits. In our view, there is no necessary contradiction in stating that hope can have both meanings, since *certainty* is not on the same level as *uncertainty*. *Certainty* here relates to the moral conviction that values which matter to us (such as health and well-being) will materialize one day. *Uncertainty* relates to the awareness of lacking factual knowledge (e.g. medical knowledge). This distinction between moral certitude and reflective uncertainty, which Descartes develops in his *Principles of Philosophy*, is particularly useful here[39]. Not only does it remind us that human life belongs to a great extent to the realm of uncertainty; it also emphasizes that metaphysic certainty – which is a divine attribute – is not a prerequisite for human lives to fare well. Hope is the awareness of lacking this absolute knowledge; it is reflective positive knowledge of one's limits. Thus hope is not an unclear concept with self-contradictory elements. On the contrary, hope has a sound self-therapeutic function when it combines both planes, that is, certainty and uncertainty.

3.3 Hope as Self-therapy

It would be a harmful kind of hope if a terminally ill patient hoped that s/he could be cured. An example of a realistic hope would be the wish to die at home. A further justifiable form of hope is that the same terminally ill patient hoped that some treatment could be found for future patients suffering from the same incurable illness. In this hypothetical example, hope produces *consolation*. In other words, the positive emotion of hope provides comfort and therefore compensates for the grief that this patient feels when facing imminent death[40,41]. A similar psychological mechanism can be observed with diabetes and gout patients, albeit with the difference that these patients are not in life-threatening conditions. A way to cope with their illness is to hope that research will cure them or future generations. The statement of patient Ines indicates how hoping can be self-therapeutic: she does not consider her illness as an immutable fate but something which can potentially create change for the better: "I always have the hope that they [scientists] will develop something that could help me someday too." Patient Yves shares the view too that research will contribute to better health for himself or future generations. "They [patients] hope to get a better therapy with time."

The significance of hope functioning as self-therapy seems to apply for life-threatening illnesses, such as cancer[42]. In his letter to Elisabeth of Bohemia from May or June 1645 Descartes emphasizes too the importance of hopeful thoughts for the sake of recovering health:

> In this regard [the curing of sadness], I judge the waters of Spa very appropriate, especially if your Highness in taking them observes what the doctors usually recommend, and clears her mind entirely of all sorts of unhappy thoughts, and even also of all sorts of serious meditations concerning the sciences. She should occupy herself by imitating those who convince themselves they think of nothing in looking at the greenery of a wood, the colors of a flower, the flight of a bird, and such things that

require no attention. This is not to waste time but to employ it well. *For one can, in doing this, satisfy oneself by the hope that by this means one will recover perfect health, which is the foundation of all the other goods that one can have in this life*. ([38, p. 92]; our italics)

Descartes' suggestions that Princess Elisabeth treat her depressive states by diverting her mind to pleasant activities are still valuable insights for today's range of therapies offered to cancer patients, such as music therapy[43].

3. Conclusion

Based upon thirty-six interviews conducted with diabetes and gout patients, this paper shows the significance of hope in the context of clinical research. The findings presented and discussed are original in as much as research on hope has been focusing, until now mainly on palliative care and terminally ill patients. Our study aimed at finding out the reactions of diabetes and gout patients to hypothetical participation in FIH trials. In their answers, the interviewees used hope in a cognitive sense: hope can imply certainty (H1) and reflective uncertainty (H2). In our view, the affirmation of H1 and H2 does not amount to a self-contradiction. On the contrary, the patients' answers showed the useful nature and plasticity of hope: as a coping strategy against uncertainty and anxiety (H1 and H2) and as self-therapy (H3). These results are positive in the sense that they confirm the therapeutic potency of hope. They also corroborate the surprising functioning of our mental resources: being ill does not make one necessarily despaired, but prompts one to be hopeful for a treatment to be found. Moreover, these findings show how philosophical investigations – in particular Descartes' – explore the phenomenon of hope and provide medical research with useful resources to interpret the seemingly paradoxical nature of the empirical data on hope.

Finally it is important to stress that the three aspects of hope (H1, H2, and H3) are compatible with modern standards of bioethics in therapy and in research, in particular related to respect for patient autonomy. A traditional myth stemming from the era of medical paternalism has been that patients should not be fully informed by doctors or researchers in order to preserve hope. However, empirical studies from the past fifty years prove the contrary (see[44]): these studies have shown that full and clear information is beneficial. Patients suffer psychologically the most from uncertainty and deception. Using the three aspects of hope identified both in patients' answers and reflected in the works of Descartes helps to understand why the traditional paternalistic understanding of hope is a misconception. Indeed, the combination of H1 and H2 coexists with honest information as hope is an innate certainty that is not the same as optimism following information about a good prognosis. Physicians can and should reinforce hope as self-therapy (H3) in the same way that it exists in dying patients: hope is able to cope with the worst case, the end of life. Hope in these three senses does not mean exaggerating benefits to future patients or reinforcing therapeutic misconceptions in patients participating in research and it does not mean hiding information from a dying patient.

In short, health professionals should be more aware of the great potential of hope as a coping strategy for patients. Despite its apparent contradiction, hope seems to be genuinely beneficent for patients' well-being in a therapeutic and in a research context.

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Chapter 5

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Feelings of Burden in Palliative Care: a Qualitative Analysis of Medical Records

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Abstract

Background Care for palliative care patients is often provided by unpaid caregivers (e.g. family members) who take care of the patient's daily needs (e.g. bathing, dressing). Family members of palliative care patients are involved in numerous ways. These tasks and responsibilities can make them feel burdened and even overburdened.

Aim We specifically looked at patients' medical records to determine what is being reported about burden and overburden and who seems to be mostly affected. Burden was understood as a weight or task that is difficult to accept or carry, whereas overburden indicates that this weight or task cannot be carried anymore.

Methods We looked at 300 medical records of palliative care patients written by health-care professionals. Written notes were analysed using latent content analysis as it helps to analyse large amounts of textual data qualitatively and to understand the underlying concepts of what was said.

Results Most patients (73.5%) had a cancer diagnosis. Mean age was 67.6 years (range, 22-98 years). Burden and overburden were identified as main categories and further divided into the following sub-categories: for patients and families. According to the written notes, patients often felt burdened by their disease, financial problems, situation at home and families' reactions to their disease. By and large, patients felt overburdened by their own disease. Families often felt burdened because of issues related to patients' medical condition, providing home care or financial and social aspects. Families mentioned homecare and the decision-making process as being overburdening.

Conclusion Findings in the palliative care patients' medical records are inasmuch important, as they point at the health-care staff's awareness of possible weights and tasks that might be burdensome for patients and their families. Attention should be drawn to the documentation of medical records in order to identify recurrent difficulties and to help discuss these.

Keywords: palliative care; burden; qualitative research; caregivers

Introduction

The Swiss Federal Office for Public Health (FOPH) estimates that 40,000 people are currently in need of palliative care (PC), and this number will increase to 53,000 people by 2032[1]. According to the World Health Organization, PC encompasses an interdisciplinary and holistic approach focusing on several domains of care, such as physical, social, psychological and spiritual care of patients and their families[2]. Another important defining principle of PC is the promotion of autonomy[3]. Palliative care offers a range of support services to help families cope with the patients' illness, but also with the families' own problems[2]. Care for PC patients is often provided by unpaid caregivers[4], or someone (e.g. family member, friend, neighbor) who takes care of the patient's daily needs (e.g. bathing, dressing)[5]. Family members of PC patients are involved in numerous ways: They care for the patients' daily needs, are in close contact with health professionals, and sometimes act as the patients' surrogates. These multiple roles can affect their own health, as Kristjanson and Aoun suggest[6]. Older caregivers most often provide care to partners, friends, and neighbors, whereas younger caregivers typically provide care to their parents[4]. Emanuel et al. suggest that even for care that requires qualification (e.g. nursing) patients generally receive care from family members or friends rather than from paid caregivers[7]. However, family members often indicate a lack of self-confidence in providing care for their relatives[8].

The FOPH states in its report on the PC situation in Switzerland that the inclusion of informal caregivers in the provision of care is a central need of PC patients. The report also emphasizes that patients fear that they could be a burden for their family caregivers[9]. According to a generally accepted definition, a burden is a weight or task – in a physical and psychological sense – that is difficult to accept or carry, whereas overburden indicates that this weight or task – in our case caring for PC patients, their families and friends – cannot be carried anymore[10,11].

Compared to younger PC patients, older patients are more frequently isolated (e.g. loss of partner) and have a limited informal care network. Family caregivers who provide care for older patients may feel burdened by such a challenging task[12]. Furthermore, the ethical principle of autonomy, which is highlighted by the FOPH, might be difficult to respect and implement fully because of possible barriers regarding the provision of home care[9]. For example, patients want to spend their last days at home, but their relatives cannot provide the desired homecare as it is too burdensome[13]. The family's needs should also be recognized and taken into account, so they can support their loved one. Hence, it is important to address possible hindering factors – such as burden and overburden of patients and of their families

Since the number of patients in need of PC will increase in the future[1] and caregivers often feel burdened by caring for them[12], our study focused on the different notions of burden and overburden in a PC context. More precisely, we looked at patients' notes to determine what is being reported about burden and overburden in the medical records and who seems to be mostly affected according to these notes. To do so, we focused on written notes of the health-care staff working in a PC setting. Using latent content analysis, we analysed 300 medical records of patients who received PC at 3 Swiss university hospitals.

Methods

Study design

We employed a qualitative research design since it helps to investigate patients' attitudes and preferences in more depth than quantitative research[14]. We used content analysis to analyse the large amounts of textual data (notes or comments in medical records)[15]. Moreover, in order to ensure high quality in reporting qualitative research, we have applied – where possible – the 32-item consolidated criteria for reporting qualitative research (COREQ)

checklist[16]. In total, we examined 300 medical records from 3 university hospitals in Switzerland using a self-developed data extraction sheet.

Data extraction sheet

The data extraction sheet focused on patients' conditions, and specifically on their attitudes and preferences regarding PC. The extraction sheet covered the following aspects: (1) demographics, (2) diagnosis, (3) information about advance directives, and (4) all notes written by the medical team about patients' attitudes and preferences regarding PC. The extraction sheet consisted of items with categorical responses (e.g. gender), continuous variables (e.g. age), and open-ended items (e.g. notes about patient wishes and preferences). Items were developed from the research team's knowledge in the field (M.R., I.W., B.S.E.) and based on discussions with collaborating physicians (M.E., S.E., S.Z.).

Study population

Inclusion criteria were (1) patients received PC at one of the three Swiss university hospitals, and (2) patients were older than 18 years of age. The necessary information (lists of patients) was provided by the research partners at the 3 university hospitals (A, B, C). Exclusion criterion was if a patients' medical record had already been collected and the same patient appeared again later on in the list, because of multiple visits in the hospital during the period of data collection. In such a case, this patient was excluded in order to avoid a duplicate. All information that could lead to an identification of patients was deleted after data collection.

Data collection

Data collection took place between April and September 2016 and was carried out by 4 research team members. Ethical approval was obtained from the local research ethics committee (EKNZ; Nr. EK 2015-197). Because only routine non-genetic data were collected, informed consent from each patient was not needed (providing an opt-out), based on the Swiss federal law of human subject research[17]. Patients are routinely informed that health-

related data may be collected for research purposes during their hospital stay, and those who refuse such data collection must actively request exclusion. Before starting with data collection, the responsible physicians and data managers from each university hospital provided access to patients' medical records. All medical records were available in digital format. We collected data throughout the patients' medical records (e.g. cover page with mostly demographic information, such as age, sex, and diagnosis), PC reports (special focus on advance care planning, patient's wishes, discussions which took place with the patient), and discharge reports (which provided a good summary of the whole hospitalization of a patient). We searched the notes written by all the health-care professionals (e.g. physicians, nurses, psychologists). We included in the analysis summarized discussions, which took place between patients and health-care professionals (e.g. case manager, social worker, physician, nurse) and between physicians and families (and patients). We used the information written between the first PC consultation and the day the patient either left the hospital or died. Each patient received a special code, which ensured anonymity regarding the gathered data. Researchers who extracted the data discussed the first 5 extractions to achieve standardization of extraction, and continuously discussed their extractions, when needed. Patients were included sequentially. More specifically, we started with the patient who received PC on January 1 2016, and continuously went back until the year 2015, thereby extracting 100 medical records per hospital. The same procedure was followed in all three university hospitals resulting in a final number of 300 extractions. Patients' demographics and characteristics are presented in Table 2.

Data analysis

Data were analysed using software for qualitative research (MAXQDA 12). Content analysis was chosen as it helps develop categories and analyse large amounts of textual data qualitatively[15]. We were particularly interested in the underlying concepts of what was written. This approach is known as latent content analysis[18]. The analysis process started with several readings of all extracted data by 1 researcher (M.R.), aiming for an overview of the data. In the next step, 2 members of the research team (M.R., I.W.) agreed on the main themes that emerged from the data. In this paper, we report on one of them: health-care staff's perception of burden and overburden. This topic was considered important as it was found recurrently across the medical records. M.R. started with an initial open coding and then organized the codes into main categories as well as sub-categories. I.W. crosschecked the coded passages. Then, based upon the text material, they made a distinction between "burden" and "overburden". We used the generally accepted definition of burden and overburden, that is, a burden is a weight or task – in a physical and psychological sense – that is difficult to accept or carry[11]. Overburden, indicates that the weight or task – in our case caring for PC patients, their families and friends – cannot be carried any more[10]. As found in the literature, the term 'family' was understood in a broader way[19] and we therefore also included the category 'friends' in our analysis. The research team defined "burden" and "overburden" as the 2 main categories, after checking that both terms were used in the research literature[20,21]. M.R. started with the coding regarding "burden" and "overburden". To guarantee accuracy and consistency of the coded segments, I.W. re-read all the previously coded text passages and cross-checked them. All transcripts were analysed in the original languages (French, German). Quotes were translated into English, and this translation was edited by a native English-speaking researcher. All authors agreed on the conceptual map of main categories and sub-categories presented in the results section (see Table 1).

Results

Our analysis identified burden and overburden as main categories which were further divided into 2 sub-categories: patients and families (see table 1).

Table 1. Main categories and sub-categories from content analysis

Main categories	**Sub-categories**
1. Burden	(a) for patients (b) for families
2. Overburden	(c) for patients (d) for families

Study sample

Forty-seven percent (143/299) of the patients were female. Mean age was 67.6 years, ranging from 22 to 98 years. Cancer was diagnosed in seventy-three percent (211/287) of the patients (see Table 2).

Table 2. Demographics of palliative care patients for each hospital (n = 300)

University hospital	A	B	C
Age (M*; *SD**)	70.55 (14.77)	63.02 (14.87)	69.11(14.54
Min., max. age	23-98	22-91	27-94
Gender (female)	51%	39%	53%
Diagnosis (cancer)	73%	78%	70%

*M = mean; *SD* = standard deviation;

Cause of burden for patients

Patients' perceived burden was mostly related to obligations they felt towards their own family. Diseases were also often mentioned as a cause of burden for patients. Other less mentioned burdens were related to financial problems or to current domestic situation.

Family

Examining possible causes for why patients felt burdened, we found that patients experienced a feeling of burden, as they had insufficient time and space to be alone without family being constantly around them. Moreover, patients were said to have problems talking about diagnosis with the family, because they were worried about the family's reaction. Other patients were described as being afraid to express their emotions because they were embarrassed and because they wanted to protect their family and friends: Sometimes, patients were reported to be more worried about other family members than themselves. At times, the health-care staff noted that this could cause burden for the patients. In these difficult moments, the notes indicated that patients felt the need to clarify their relationship with their children (see Table 3).

Table 3. Family
"He also means that he is glad that his family is not always with him, as he also needs time for himself" [Patient record (PatRec) 1]
"(…) [Patient] reports difficulties in informing her family about the disease and its progression. She [patient] fears that everyone will cry, actually she wishes for strong people" [PatRec 2]
"She [patient] said that she was ashamed to cry and she didn't do it in order not to worry her close family and friends" [PatRec 3]
"The patient was very sad and scared, he wanted to meet the whole family in the presence of the psychologist in order to discuss about his father role. He had had his first son with his ex/first wife and he was feeling guilty towards this first son" [PatRec 4]

Disease

The notes indicated that patients seemed aware that their disease was continuous and life-prolonging measures were counterproductive and, as such, felt burdened by the illness. We found that patients were described as feeling helpless regarding their own illness. Moreover, pain and lack of physical autonomy were sometimes noted as burdensome (see Table 4).

Table 4. Disease
"Patient loves her family, but she knows that the disease has progressed and that life-prolonging measures are just a prolongation of suffering" [PatRec 5]
"Psychologist noticed that this anger was related to a feeling of helplessness regarding his disease" [PatRec 6]
"Patient feels burdened by pain and the associated immobility" [PatRec 7]

Financial problems

According to the notes of health-care personnel, an additional reason that patients felt burdened was monetary concerns. It was also evident that worrying about money issues sometimes caused additional anger for patients (see Table 5).

Table 5. Financial problems
"The patient was worried about financial problems" [PatRec 8]
"[…] this anger was related to a feeling of helplessness regarding his disease, his financial and family situation" [PatRec 9]

Fear of putting too much burden on the partner

Some patients were reported as scared of asking too much from their partners. Patients seemed to realize that their partners also needed some help at home and consequently wished for supervision at home. Sometimes, patients did not want their care to be continued at home

because they knew that their partner could not provide the needed support for them (see Table 6).

Table 6. Fear of putting too much burden on the partner
"Patient wishes for support at home, also to relieve his wife" [PatRec 16]
"Patient knows that she cannot go home, because her partner relies on her "guidance". Partner cannot take care of her" [PatRec 17]

Situation at home

An important finding was that the current household situation could lead to further burden not only for partners but also for patients. For instance, the illness of their partner is noted to create an additional burden for the patient (see Table 7).

Table 7. Situation at home
"Patient reports about difficult domestic situation, because his partner is suffering from Parkinson's disease" [PatRec 10]

Cause of burden for families

Issues related to patients' medical condition

The notes in the medical records mentioned patients' condition and issues related to it (e.g. being in the final stage of the illness) as the most frequent reason why partners felt burdened. Family members mentioned that they needed some space for themselves. Sometimes, they seemed to feel burdened because of the patients' imminent transfer to a hospice. Moreover, relatives were described as having expressed the difficulty of accepting the patient's current medical condition and treatment. Nevertheless, it must be underlined that an initial burden could turn into relief for the family (see Table 8).

Table 8. Issues related to patients' medical condition
"Discussion with spouse and daughter of patient; they are told why patient is in a terminal stage. Spouse finds difficult to accept the situation (…)" [PatRec 11]
"Wife expresses the wish to sleep in a separate room from her husband in order to be able to have some space for herself" [PatRec 12]
"Wife reports about difficult past weeks. In the beginning, she had difficulties with the transfer to the hospice, because of the fear of an "end station". "However she does not feel that way anymore and is looking forward to the transfer" [PatRec 13]
"Husband sees situation critically: He has big hope that patient will stabilize, to be mobile. On the other hand it was always clear for the patient: "Not at all cost" [PatRec 14]

Home care

Another recurring aspect was the burden related to caring for patients at home. More specifically, the most frequent feeling of burden was the inability to take care of the patient at home because the patient was too disabled (see Table 9).

Table 9. Home care
"Patient and wife are discussing the transfer to the hospital [name of hospital]. Wife seems to be relieved not to have to take patient home in this condition" [PatRec 1]
"Conversation with wife, physicians, and patient: Wife cannot presently imagine a return home, because patient is too much in need of care" [PatRec 15]
"Conversation with long-standing friend of patient: patient has always been stubborn; she lives in a shabby flat, if the patient returns home, her friend will hand over her keys, she only sees the patient in a hospital etc." [PatRec 20]

Patients' wishes to die

Additional reasons for a partner's feeling of burden were when the patient wished to die with an organization that supports assisted suicide (e.g. EXIT) and the difficulty to accept or deal with this wish (see Table 10).

Table 10. Patients' wishes to die
"Partner wants to help her satisfy this wish, but seems to struggle with this" [PatRec 18]

Financial and social aspects

Another aspect of burden of care was the burden that partners felt when they had to make non-medical decisions on behalf of the patient, such as bureaucratic or monetary questions. The wife of one patient was worried that she and her son would be left alone after her husband's death (see Table 11).

Table 11. Financial and social aspects
"She was also dealing with many administrative and financial issues related to the patient's inheritance" [PatRec 19]
"She was aware of the severity of the situation and very affected by the speed of the disease and that she was going to be alone with her son in [name of the city], knowing that her social network was little developed in [name of the city]" [PatRec 19]

Cause of overburden for patients

Disease

Overburdening was most often caused by patients' disease. Often, the fast disease progression made them feel overburdened. Disease aggravation could also lead to the inability to cope with the disease. Moreover, a poor symptom management could represent a source of overburden (see Table 12).

Table 12. Disease
“Patient is heavily burdened by the course of the disease (neurological deterioration)” [PatRec 21]
“Because patient cannot continue to live like this, he was in contact with EXIT, he wants to go this way” [PatRec 18]
“Discussion with patient and nursing assistants from institution: Patient’s symptoms are not well-managed, [patient] cries a lot: “I cannot anymore; I cannot stand it any longer” [PatRec 22]

Cause of overburden for families

Issues related to patients’ medical condition

The most frequent cause for feeling overburdened was patients’ medical condition. Moreover, relatives had great difficulties dealing with patients’ present circumstances and their constantly deteriorating health status. Partners sometimes mentioned that patients did not receive extensive medical treatment (see table 13).

Table 13. Issues related to patients’ medical condition
“Discussion with wife, cousin and cousins’ husband at patient’s bedside: Wife reports that she is overburdened with the current situation” [PatRec 23]
“Discussion with husband without patient; [husband] reports about overstrain; the constant aggravation of the patient’s situation was a shock for him” [PatRec 24]
“Discussion with wife (alone); she is heavily burdened, she has the impression that patient is not receiving comprehensive care and that he is now ‘abandoned’” [PatRec 25]

Home care

Partners often mentioned that they could not take care of patients anymore because they needed continual support. Some patients realized that their partners could not take care of them because of the amount of care they needed. Sometimes partners who were already taking care of children felt overloaded by additionally taking care of patient (see Table 14).

Table 14. Home care
"Partner considers taking care of the patient and his dog as overburdening, because she [patient] needs care around the clock" [PatRec 26]
"Patient tells that she hopes to get back home, but she also knows that her partner would be overburdened" [PatRec 17]
"Situation at home for wife and two little children no longer tenable" [PatRec 27]
"Patient cannot take care of herself at home anymore, an acquaintance who is supporting her feels overburdened" [PatRec 20]

Decision-making

Partners who needed to make a decision regarding the patient's medical treatment sometimes felt overburdened by this role. Another report shows that not only medical decisions but all kinds of decisions were overburdening for the patient's partner (see Table 15).

Table 15. Decision-making
"Husband reports that he was overburdened, when the assistant doctors wanted to know from him if an infection should be treated with antibiotics" [PatRec 24]
"Wife reports that she was overburdened with the current situation and also with all the decisions that were brought to her" [PatRec 23]

Discussion

Our objective was to highlight documented information about burden and overburden in the medical records of PC patients. More precisely, we wanted to analyse the possible challenges faced by patients and informal caregivers as documented by health-care staff. Furthermore, we aimed to understand the possible underlying reasons which made these stakeholders feel burdened and sometimes even overburdened. So, we analysed how burden and overburden of patients and their families were documented in the patients' medical records. The distinction between burden and overburden was evaluated to analyse when burden becomes overburden. Burden can be further divided and refined into caregiver burden (CB) (e.g. burden which arises of taking care for patients) and self-perceived burden (SPB) (e.g. patient's perception of being a burden to their family members). Moreover, Lee et al. showed a connection between both kinds of burdens and PC treatment. They conclude that patients could choose certain treatments to avoid putting burden on their informal caregivers or if they have the feeling to be a burden (SPB) to their family members. On the other hand, burdened informal caregivers could influence patients' decision regarding certain treatments. Finally, the authors demonstrate that higher CB or SPB could lead to a deprivation of patient autonomy[22]. These findings align with our results. Our analysis showed that it was recurrently written in the medical records that patients expressed the fear of putting too much burden on the partner. A study suggest that CB and SPB can be decreased through several interventions, such as support programs for informal caregivers, advance care planning for patients, promotion of communication[22], and the organisation of "family conferences" to discuss matters important to patients and their relatives[23]. Our results also suggest that particular attention should be given to families because of their role as informal caregivers. More specifically, we found that home care was often mentioned as being a cause of burden and overburden for patients' families. Our findings agree with current literature. Interview studies with informal

caregivers pointed out that they faced a high risk of being burdened as a consequence of caring for their loved one[24,25]. Proot et al. concluded that caring for a patient at home could be both, a mental and physical burden[24]. Given et al. summarized that the burden on informal caregivers was different from anxiety or depression. As a possible reason for this burden, the authors listed disease progression and the subsequent greater need of care[26]. This topic was also found in the medical records, as it was noted that issues related to patients' medical condition (e.g. disease progression) act as a possible factor for patients' families to feel burdened and overburdened.

Our results show that disease, home care, patients' wishes, financial concerns, and social issues were objective things that patients and families had to deal with and which might let them to feel burdened and even overburdened. Findings regarding what was documented in the medical records are inasmuch important, as they point at the health-care staff's awareness of possible weights and tasks that might be burdensome for PC patients and their families. Moreover, these issues documented by health-care staff appeared to confirm findings from other empirical studies regarding causes of burden and overburden in PC[22,24-26].

Limitations

Medical notes were written by health-care professionals, but these notes might not be exhaustive. What is more, if health-care staff are not sensitive enough to the burden issue, the feelings expressed by patients and their families and friends might not be fully recorded in the notes. Furthermore, the medical team might superficially misinterpret signs of burden (e.g. tiredness or physical exhaustion). Finally, these notes might not always give the details or verbatim wording of the dialogue. Sometimes, documentation in medical records of communication leaves out important verbal and non-verbal information.

Conclusion

Our results indicate that, according to the written notes, patients felt burdened or overburdened because of their own disease, the situation at home or their own family. Moreover, the analysis of medical records suggests that families often seemed to mention issues related to the patient's medical condition, the decision-making process, as well as social and financial issues as being burdensome. To conclude, our analysis showed that – according to the FOPH[9] – the central aim of including informal caregivers in the provision of care for PC patients might be difficult to implement. Attention should be drawn to the documentation of medical records in order to identify recurrent difficulties - such as feelings of burden and overburden documented in the medical records - and to help discuss these difficulties (e.g. "family conferences[23]).

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Chapter 6

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Advance Care Planning in Swiss Acute Hospitals:

A Retrospective Analysis of Medical Records

Rakic M, Rost M, Wienand I, Elger BS, Escher M. Advance Care Planning in Acute Hospitals: A Retrospective Analysis of Medical Records.

Abstract

Objective We wanted to describe how advance care planning occurs in major Swiss acute hospitals that have established mobile palliative care teams. Moreover, we wanted to identify different factors determining the application of advance care planning and advance directives.

Methods We collected data retrospectively from medical records of palliative care patients. We analysed the data descriptively and employed inferential statistics (Chi-square test of independence, generalized linear mixed model).

Results For most patients (98.3%) a discussion about advance directives, values and wishes was documented in the medical records. Almost two thirds of the patients (62.6%) engaged in advance care planning and around one quarter (26.3%) laid down their preferences in an advance directive. Moreover, we found that engaging patients in advance care planning resulted in higher odds of having an advance directive by a factor of 17.5.

Conclusion Knowing patients' preferences in advance is needed to base end-of-life decisions on the patients' values and wishes. Our analysis of patients' medical records showed that engaging patients in advance care planning increases the number of advance directives. Patients should be supported to state their goals and preferences by involving them in advance care planning.

Keywords: advance care planning, advance directives, palliative care, end of life, quantitative research

Introduction

In 2014 around 64,000 persons died in Switzerland and 26,900 of them (42%) were older than 85 years[1]. More than 41% of total deaths occurred in a hospital and the average age of patients who received Palliative Care (PC) was 68 years[2]. In a clinical setting, older patients often lack decisional capacity and half of the decisions are made by patients' surrogates[3]. Empirical data show that one third of patients with an acute illness aged ≥ 75 years suffered from a delirium. Delirium is an acute and confusional state, linked to an increased mortality rate[4]. Furthermore, the incidence of dementia increases with age[5]. These statistics reflect the importance to provide advance care planning (ACP) as the elderly population increases[6] and many may not be able to decide for themselves[3]. By promoting ACP early in the course of disease, patients' autonomy can be respected, even if patients become unable to decide for themselves what kind of treatments they want or not[7].

PC is a holistic approach that centres on quality of life of patients and their families[8]. End-of-life decisions can be burdensome, especially for incapacitated patients when family members do not know their wishes[9]. ACP is recommended to support decision-making in these situations, along with the writing of legally binding advance directives (ADs)[10,11]. By enabling patients to determine their medical treatments in advance and make their preferences known, ACP implements the ethical principle of respect for patients' autonomy[7]. Previous data show that ACP can help respect patients' wishes at the end of life[12] and that physicians comply with patients' advance directives[13]. Furthermore, ACP not only increased patients' but also families' satisfaction with PC (e.g. satisfaction with dying process, decreased level of stress and anxiety) during the last hospital stays[12].

ADs are considered an important component of ACP[14]. Empirical evidence showed that the most important reason for patients to write ADs was promotion of their autonomy[15].

Similarly, the Mental Capacity Act in the UK and the Adult Protection Law in Switzerland enable and encourage to write ADs. Moreover, adults can appoint a surrogate decision-maker[16,17].

However, in Switzerland only 11% of PC patients had written an AD prior to hospital admission[18]. Rao et al. reported that the main reason for not having an AD was a lack of awareness among patients[19]. Studies focusing on determinants for completing an AD indicated that patients who died at home or in a retirement home were more likely to have an AD than patients who died at hospital[20].

Switzerland is facing an increase in deaths occurring in hospitals with complex end-of-life situations[2,3]. Knowing patients' preferences is needed to align end-of-life-care with their values[15], and to alleviate the family's burden in decision-making[12]. Therefore, the main aim of this study is to find out how clinical practice takes place in a PC setting of an acute care hospital. More precisely, we want to a) describe how ACP occurs in major Swiss acute hospitals that have established mobile PC teams and, b) identify different factors determining the application of ACP and/or the completion of an AD in Switzerland. By employing a retrospective approach focusing on PC inpatients cared for by mobile PC teams, we captured variables likely to influence patients' self-determination, such as socio-demographics and illness.

Methods

Study design

We collected data from three Swiss university hospitals which have hospital-wide palliative care consultations ("mobile specialised team"). We reviewed the medical records of the patients seen by the PC teams. Ethical approval was obtained from the responsible ethics committees in Switzerland (EKNZ; Nr. EK 2015-197).

Study population

At the time when a patient's medical situation was seen as a palliative one, the treating physicians contacted the hospital's mobile PC team in order to discuss the possible PC approaches (e.g. pain management, spiritual or psychosocial support) with the patient. PC patients who met the following criteria were included: (a) ≥ 18 years, (b) having received PC treatment in one of the three participating hospitals. Eligible patients were identified from the consultation lists established by the collaborating physicians. We exclusively searched the electronic files of those patients. Patients who had more than one hospital stay during the inclusion period were included only once.

Data extraction sheet

The data extraction sheet included patients' characteristics (e.g. gender, nationality, age), palliative care related variables (e.g. diagnosis, treatments), and variables related to patients' autonomy (e.g. ACP, AD). Information on burden in PC are discussed in another paper that used the qualitative data of the medical records [blinded for peer review]. The notes in the patients' files were written by all the health-care team. The digital extraction sheet consisted of items with categorical responses (e.g. gender), continuous variables (e.g. age), and open-ended items (e.g. notes about patients' wishes and preferences). All items were developed from the interdisciplinary research team's knowledge in the field and based on discussions with the collaborating physicians.

Data collection

Data collection was carried out between April and September 2016. We started collecting the data of the first patient who was referred to a palliative care team on 1st January 2016 and we then continuously went back to the year 2015 until we had included 100 patients at each hospital. The medical records were available in digitalized form. We collected data throughout the medical records. This included the cover page, PC reports, and discharge

reports. We searched the notes written by all the health-care professionals (e.g. physicians, nurses, psychologists). We included all the information written between the first PC consultation and the day the patient either left the hospital or died.

Data were entered in the previously developed extraction sheet. The research team discussed the first five extractions aiming for standardization of extracting and continuously discussed the extractions, when needed. Since not every variable of the extraction form was contained in all medical records or could be found, sample sizes for most of the variables were less than the number of included patients (N = 300). Patients' anonymity was ensured by using a predefined algorithm employing numbers unrelated to birth date or other personal identifiers. Furthermore, all identifying information was deleted after data collection.

Statistical analysis

A research assistant entered all extracted records into SPSS.22 (SPSS Inc, Chicago, IL) and a second researcher checked for correctness of data entry. Statistical analyses were performed using SPSS.22. In accordance with the aim of this study, variables related to PC (e.g. diagnosis, place of care, several PC treatments) and patients' autonomy (e.g. ACP, AD, discussion about wishes and values) were analysed. Regarding ADs and ACP: the research team searched in the medical records for documented discussions on ACP between the mobile PC team and the patient (PC treatment, in particular resuscitation, artificial nutrition; patient's wishes; values; preferences of family members and of the patient's general practitioner, nurses and other relevant care givers). Moreover, the research team examined the medical records for any documented information on patients' ADs (long or short form, if the patient received advice during hospitalisation, and if the patient had preferences for or against specific treatment). In a first step, variables were analysed descriptively. In a second step, we employed inferential statistics, namely Chi-square test of independence and Generalized Linear Mixed Model (GLMM). Reported P values were 2-sided and statistical

significance level was set at $P < .05$. In cases of multiple testing Bonferroni-Holm correction was applied to control for the increased likelihood of a type I error. The GLMM adjusted for centre clustering.

Results

Characteristics of the sample

Fifty-two percent of the patients were male (Table 1). Mean age was 67.6 years, ranging from 22 to 98 years. Seventy-three percent of the patients were diagnosed with cancer. Among the non-cancer patients, nearly one fifth had a neurological disease (19.74%).

Table 1: Sample characteristics (N = 300)

Demographics and Diagnosis	Mean (Mdn, SD) Percentage
Age (n = 299)	67.6 (69.0, 15.0)
Sex (male; n = 299)	52.2 %
Diagnosis (cancer; n = 287)	73.5 %
Nationality (Swiss; n = 298)	77.2%
Marital status (married; n = 242)	72.3%
Living place (urban, n = 204)	68.5%
Children (yes; n = 198)	72.7%
Retirement (yes; n = 300)	48.0%
Religious affiliation (yes; n = 295)	91.9%

For most patients (98.3%, 238 out of 242) a discussion about ADs, values and wishes was documented in the records. Almost two thirds of the patients (62.6%, 154 out of 246) engaged in ACP and around one quarter (26.3%, 52 out of 198) laid down their preferences in an AD (see figure 1). Eighteen percent of the patients (39 out of 215) had a Do Not Resuscitate (DNR) order.

Factors influencing advance care planning

Relation between ACP and AD

Almost every patient had a discussion about his or her values and wishes regarding ACP (98.3%). Moreover, sixty-three percent of the PC patients engaged in ACP (154 out of 246). Exploring whether ACP actually predicted whether or not a patient had an AD, GLMM revealed that patients who engaged in ACP more often had an AD than those patients who did not engage in ACP (Figure 1; Table 2). To illustrate, in our sample engaging in ACP resulted in higher odds of having an AD by a factor of 17.5 (p = .000)

Table 2: GLMM of advance directives (n = 172)

	B	SE	t	P	Odds Ratio	95% CI for Odds Ratio Lower	Upper
Intercept	-3.004	0.938	-3.202	.002			
ACP	2.863	.055	5.670	.000	17.506	6.437	47.613
Age	0.002	.013	0.115	.909	1.002	0.975	1.028
Gender	.083	.406	.205	.838	1.087	.486	2.429

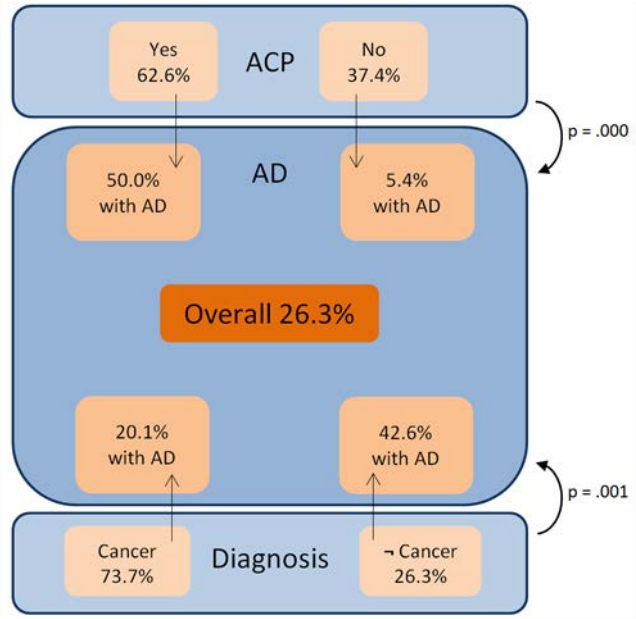
Note. The dependent variable in this analysis is "advance directive" so that 0 = no and 1 = yes. Results were adjusted for centre clustering.

In the following, further variables that might influence either advance care planning or having an advance directive are tested.

Diagnosis

Forty-three percent of non-cancer patients (23 out 54) and twenty-one percent of cancer patients (29 out of 144) had an AD. Results of a Chi-square test of independence indicated that the relation between diagnosis (cancer versus non-cancer) and whether or not a PC patient had an AD was significant, that is, non-cancer patients more often than cancer patients had an AD, X^2 (1, N = 198) = 10.2, p = .001, V = .23 (see figure 1).

Figure 1. Advance care planning and advance directives



Partner

A Chi-square test of independence revealed no significant relation between whether or not a patient had a partner, and whether or not a patient had an AD, X2 (1, N = 191) = .082, p = .863, V = .02. Similarly, there was no significant relation between whether or not a patient had a partner, and whether or not a patient engaged in ACP, X2 (1, N = 195) = .087, p = .769, V = .02.

Children

The relation between whether or not a patient had an AD and whether or not the patient had children was tested. Chi-square test of independence revealed no significant relation, X^2 (1, N = 144) = 2.5, p = .113, V = .13. Thirty-eight percent (14 out of 37) of patients without children had an AD and only twenty-four percent (26 out of 107) of patients who had at least one child, had an AD. The same pattern was observed for the relation between whether or not a patient had engaged in ACP and whether or not the patient had children. Again, Chi-square test of independence did not reveal a significant relation, X^2 (1, N = 168) = 2.5, p = .110, V = .12. However, descriptively differences existed, with sixty-eight percent (32 out of 47) of

those childless patients had engaged in ACP and only fifty-five percent (66 out of 121) of those patients who had at least one child.

Place of care

Chi-Square tests for independence (Bonferroni-Holm correction was applied) neither revealed a significant relation between whether or not a patient engaged in ACP and the place of care, X^2 (1, N = 239) = 3.0, p = .086, V = .11, nor between whether or not a patient had an AD and the place of care, X^2 (1, N = 184) = .09, p = .768, V = .02.

Discussion

In our study, we analyzed data about wishes and values of PC patients hospitalized in an acute care setting. Almost every patient had a discussion about his or her wishes and values and six out of ten engaged in ACP. In addition, we focused on patients who were seen by hospital-wide mobile palliative care teams. Hence, we do not know if the proportion of discussions among other patients – who were also diagnosed with an advanced disease but not referred to a specialized palliative care team – is similar. There are studies from other countries that compared PC units and mobile PC services within hospitals regarding economical and patient related outcomes[21,22]. Our results revealed that around three quarters of patients for whom hospital units contacted the PC team were diagnosed with cancer and mean age was approximately 70 years. Similar findings were reported in studies that focused on specialized PC institutions or mobile PC teams[2,21,23,24].

Discussions about advance care planning and advance directives

A study from the United States showed that the incidence rate for patients requesting ACP was 39%[25]. In our study, 63% of patients engaged in ACP. An intervention study showed that for patients who actively obtained ACP, wishes were more often known and respected (86%), as compared to those receiving only standard care (30%)[12]. For our sample, results of the

GLMM showed that those patients who engaged in ACP more often had an AD. At the same time – even though ACP entails discussions about ADs[12] – only every second patient who engaged in ACP had an AD.

Moreover, since we analyzed medical records, it was not always possible for us to retrospectively determine whether patients had an AD prior to ACP or if they filled out an AD after they engaged in ACP. This gives rise to two different interpretations, namely, first, that a high number of patients who engaged in ACP finally completed ADs and, second, that health-care professionals more easily engage patients in ACP when patients already had an AD. However, based on the results of the GLMM, we can say that the first interpretation is more accurate: ACP increases the number of patients with ADs. As previously shown, ADs can gain importance once patients are unable to articulate their wishes and preferences regarding medical treatments[7,14]. Therefore, it is important to provide every patient with the opportunity to engage in ACP and to make an informed decision on filling out an AD. Ultimately, this process promotes autonomous decision-making of patients[7].

Advance directives

Overall, 26.3% of the PC patients in our sample had an AD. However, a study from Switzerland from 2015 reported a lower percentage of PC patients regarding existence of ADs prior to hospital admission, namely 11%. Nevertheless, it needs to be said that this number slightly increased during hospitalization[18]. The higher percentage in our study represents an encouraging finding as it suggests that the number of patients with ADs increases during hospitalization and has increased over the past years. There are several explanations for this. First, the increase could be caused by a raised public awareness in the last years through the launch of the national strategy aiming to promote PC[26]. Another explanation for the increase in ADs could be the new Adult Protection Law (since 2013) in Switzerland. The aim of the new law is to promote patients' right for self-determination and

to enable and encourage competent adults to write ADs[16]. Finally, the increase could be attributed to the fact that, in our sample, a comparably high number of patients engaged in ACP (compared to the Swiss study from 2015, where only 11% of the patients had an AD prior to hospitalization[18]) which resulted in a higher number of patients with ADs.

Children

Although the relation between having children and the presence of an AD or ACP was statistically not significant, descriptively childless patients more frequently engaged in ACP and had ADs. Subject to further research exploring this relation, such a finding might be explained by a greater certainty among patients with children that, in case of becoming unable to consent to medical treatments, children can and will decide on their behalf. Confidently assuming that your child(ren) will make decisions on your behalf diminishes the necessity to think about ACP and to sign an AD. However, it is important to note that these differences were not significant and that this relation, therefore, need further careful examination in order to draw robust conclusions.

Limitations

First, medical notes are written by health-care professionals and they might have different ways of writing and reporting. Therefore, medical notes are not exhaustive, and they may not always render verbatim the exact dialog which took place between the patient and health-care professionals. Second, the analysis of medical records is necessarily limited to both, the written information, but also to the quality of this information found in the records. Although the information in the medical records might not be complete, it is this information the health-care professionals have at their disposal when they have to discuss with the family and/or make a decision.

Conclusion

Our analysis revealed that almost every patient had discussions about values and wishes and almost two out of three patients engaged in ACP. Moreover, 26.3% of the patients in our sample had an AD. Knowing patients' wishes is needed to base the decisions on patients' values[15], and to alleviate the family's burden in the decision-making process[12]. Therefore, PC patients should be supported to state their goals and preferences by engaging them in ACP and, eventually, filling out ADs.

Conflict of interest

The authors have no conflict of interest in the authoring of this manuscript.

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Chapter 7 – General Discussion

This PhD thesis aims to integrate empirical and normative analyses in order to promote respect for elderly patients' autonomy in various *clinical settings*. More specifically, the purpose is to explore and evaluate possible *hindering and promoting factors* of autonomous decision-making in research and Palliative Care (PC) contexts (section 1 and 2). The empirical results were obtained from i) in-depth interviews regarding clinical trial (CT) participation involving synthetic biology (SB) with 36 patients suffering either from diabetes or gout, and ii) 300 medical records of PC patients regarding quality of PC. These results are discussed from a bioethical perspective. The final sections of this chapter present the *research limitations, implications for further research*, and *conclusion* (section 4, 5, and 6).

Hindering and promoting factors in a research context

Clinical trial participation

Chapter 2 examines patients' willingness to participate in CT's involving SB and evaluates the extent to which their views and preferences change after receiving detailed information about SB. Our results indicate that patients are anxious and lack understanding of SB when discussing possible CT participation. Our results revealed that the most prevalent concern of patients is a general anxiety that SB creates something that cannot be controlled (one interviewed patient was afraid that "somehow a superhuman gets created"). Nevertheless, after a concrete example was given on how a future medical treatment involving SB could look, patients began to see SB in a more positive light:

> "(…) Mr. Müller suffers, as you, from gout, but he is not taking any drugs. He needs to go rarely to his GP to get his uric acid level controlled. Mr. Müller has a capsule implanted under his skin. This capsule contains human cells. These cells are from Mr. Müller himself. They were removed and modified in the laboratory. These modified

cells from Mr. Müller are able to produce a certain protein that removes the surplus uric acid in the blood. Additionally, a sensor was integrated that constantly measures the uric acid levels in the blood (…)." (See Chapter 2, p. 49)

Therefore, it is important to educate patients and give them realistic expectations about the synthetic biology CT's. Achievement of each of these recommendations would promote patients' autonomy in decision-making. Although providing adequate information is not novel[1], we think that providing information on something relatively common (e.g. cancer and treatment) is different from providing information on SB, which is often foreign to or misconceived by patients. Most interviewed patients did not know the purpose of the new technology and viewed it as a risky procedure (one interviewed patient thought that the researchers are "playing God"). Patients appeared to have difficulty understanding the purpose of medical research given that the future applications are still hypothetical. The patients' incomplete and inaccurate picture of SB could lead to therapeutic misconception by which patients believe that enrolling into the CT will treat their disease[2] and therefore, might prompt them to make decisions based on mistaken beliefs. This lack of accurate information contradicts the requirements of an informed consent (IC), which requires (among other things) an understanding of the purpose of the research[3].

Patients who do not understand the purpose of medical research (i.e. difference between research and treatment[2]) or lack information regarding the main aims (e.g. one patient noticed that "[SB] is a closed book") might be misled in their decision-making on CT participation.

To reduce this bias, the provision of information must be as accurate as possible and avoid misconceptions. If clear information about SB is not delivered, then patient autonomy is undermined, as the principle of autonomy relies on informed patient understanding of the objectives and potential consequences of the CT[3]. Furthermore, IC has little value if a

patient's decision whether or not to participate in a CT is mainly based on emotions (e.g. one patient feared that "something that cannot be controlled anymore" will be created) evoked by an inaccurate understanding of the CT. Because SB is not widely understood by patients, providing sufficient knowledge for IC is of particular relevance for these CT's.

To address the challenge of misunderstanding the aim of SB, the use of simple language or graphics instead of difficult medical jargon[4] would enhance patients' understanding. Our study found that patients viewed SB and CT participation more positively after they were given a concrete example of a hypothetical patient suffering from diabetes/gout and how SB might be able to help that patient (see example, p. 49). Given that example, most patients were able to distinguish SB from other technologies (e.g. genetic engineering) and expressed a better understanding of SB and the possible benefits to their own health.

Research ethics committees

Another possible approach to overcome the obstacle of patient misunderstanding in SB CT's is to have research ethics committees (RECs) examine very carefully the content of ICs to ensure all information presented is detailed, accurate, and understandable, as information is one of the key elements of ICs[5]. Cassileth et al. stress that patients have difficulties to understand ICs (e.g. the purpose or possible complications related to medical procedures)[6]. To overcome these challenges discussed by Cassileth et al., IC information could be reviewed and tailored by patients who are actively involved in this process. This could make the information more easily accessible for possible CT participants. Results from our study, which aims to explore how patients perceive their own participation as active members of RECs (Chapter 3), indicate a positive attitude towards participating in RECs.

Patients in our study often mentioned benefits to their own health as a reason for their participation in RECs. More precisely, patients saw a chance for a long-term benefit on their own health condition from participating in RECs and perhaps allowing more CTs. In other words, if these CTs show a positive effect, patients could profit from an optimization for their own treatment over time[7].

Even though these patients suffer from chronic diseases with a decreased life expectancy and lower quality of life[8,9], they are not imminently near death[7]. Therefore, they have a realistic opportunity to profit from medical developments[10] in the near future. Thus, the risk of therapeutic misconception[2] does not seem to be applicable in this situation, since this is not their last hope[7]. Another reason mentioned by patients was that they wanted their situation to be visible (see patient's quote p. 61). Therefore, not involving patients in RECs might be seen as unjustified paternalism[11].

> "To be able to see the patients' situation. He/she can, only he/she can, say how hard the disability is, caused by the disease. He/she can estimate the agony caused by the disease (…)." (See Chapter 3, p. 61)

Patients mentioned in our study that they wanted to express their experiences of the disease, acquired knowledge about the disease, and their unique perspectives to be taken into consideration within RECs. Our results align with other studies, which indicate that patients' perspectives on their disease, use of language, and experiences of their diseases differ from those of health-care professionals[12]. Thus, health-care professionals should take patients' lifeworld into account to improve the comprehensibility of written medical information (e.g. by using graphical symbols)[12]. Lifeworld is understood here as patients' individual

experiences and problems in their everyday lives[13,14]. Moreover, Barry et al. point out possible consequences, if patients' lifeworld is not taken into account by physicians:

> "Here the patients talked either exclusively or for a large amount of the consultation in the voice of the lifeworld. However, the doctors completely ignored this and conducted the whole of their communication in the voice of medicine. Most of these patients had chronic physical problems and this group had the worst outcomes of any group […] Patients and doctors seemed to be operating at odds to each other. Patients often seemed relaxed and happy to chat away in the voice of the lifeworld about their concerns while doctors stayed rigidly inside the biomedical format."[13, p. 494-495]

Miscommunication between patient and physician can result in a poor outcome if health-care professionals are not sensitive to the patient's experiences and narratives[13,14]. Therefore, health-care professionals should take patients' illness narratives into account during medical discussions to integrate more fully the first-person perspective of patients. Involving stable patients actively in RECs and letting them participate in decision-making processes could enhance their autonomy and ensure that ICs are more accurately and understandable for prospective CT participants.

Hope

As discussed in Chapter 4, we explore the importance of hope as a determining factor for patient participation in CTs for SB therapies. Our results suggest that hope can act as a 1) coping strategy in the face of either anxiety or 2) uncertainty, or as 3) self-therapy.

Health-care professionals might be hesitant to provide full information (e.g. about a patient's condition) out of fear of taking away the patient's hope[15]. However, hope does not mean exaggerating benefits for future patients, nor does it entail reinforcing therapeutic misconceptions in patients and hiding information from them[15]. Based on our findings, health-care professionals should be more aware of the resources of hope as it seems to be beneficial to patients' well-being. Moreover, these three kinds of hope can coexist with fully informing patients and thereby respecting their autonomy. Our results are supported by other studies. For example, Milna et al. concluded that informing patients about the side effects of their disease and helping them find strategies to manage these side effects helped patients acquire specific knowledge about their disease. This acquired knowledge relieved them to restore their hope and become more autonomous regarding their own care[16]. At the same time, we have shown that hope can also imply the awareness of uncertainty regarding the chance of convalescence, and this aspect of hope does not sink us into despair.

Hindering and promoting factors in a Palliative Care context

Advance care planning and advance directives

Patients are encouraged to record their preferences – e.g. through advance care planning (ACP) or advance directives (ADs) – and determine their medical treatments in advance[17,18]. By encouraging patients to do so, the bioethical principle of respecting patients' autonomy is implemented[19]. Moreover, knowing patients' preferences is a prerequisite to align care with patients' values[20]. Chapter 6 discusses how ACP/ADs are approached in a PC setting in Switzerland using data from medical records. Our results indicate that almost every patient discussed his or her values and wishes regarding ACP with a health-care professional. Furthermore, patients who engaged in ACP more often had an AD than those patients who did not engage in ACP. Therefore, patients should be supported to state their goals and preferences by involving them in ACP[21]. This becomes even more important for patients with an expected decline in mental status because these patients might not be able to decide for themselves anymore[22], creating a large burden on the family to make decisions in their place[23].

Burden

Respecting patients' autonomy and including informal caregivers (e.g. family members) in the care plan are central needs of PC patients[24]. Nevertheless, patients fear that they might be a burden to their informal caregivers[24], and conversely, informal caregivers feel burdened by providing care for patients[25]. In Chapter 5, we analyse what was reported about burden in PC patients' medical records. Our results reveal that patients felt often burdened by their own disease, their family being constantly around them, and the situation at home. Families felt burdened by issues related to patients' medical condition, home care, and decision-making. These common situations illustrate that the individualistic concept of autonomy is challenged

when the two parties have different goals, interests, resources, and needs. For example, some patients want to spend their last days at home, but their relatives cannot provide the desired homecare as it is too burdensome for them[26]. The apparent incompatibility of views might be minimised under a less individualistic framework of autonomy. Indeed, the standard understanding of autonomy as self-determination in Western modern society[27] might neglect important cultural, social, and practical aspects that undergird patients' sense of autonomy[26,28]. Walter et al. conclude that the individualistic understanding of autonomy puts an emphasis on health-care professionals as the sole information providers for patients that base their decisions only on rationality. Furthermore, emotions are seen as counter-productive to this rationalistic understanding of autonomy because they undermine the rational decision-maker[28].

Relational autonomy

Relational autonomy can be seen as a promising alternative to the individualistic understanding of autonomy because it emphasizes the significance of the social network in our lives[28,29]. The claim behind relational autonomy is that human beings are embedded in a social context. Identities are significantly impacted by social and emotional relationships to other persons and are shaped by social determinants (e.g. education, gender, language). The main focus of relational autonomy is to underline the impact of these social relationships and determinants on ourselves and our decision-making and reciprocally, our influence on other members of the social network[29]. Within the framework of relational autonomy, asking family members to participate in the decision-making process of patients does not necessarily undermine patients' autonomy, as patients' preferences are embedded within a larger network of relationships with family members and others[28]. Within a PC context, patients' autonomy can be enhanced if the family supports and recognizes their decisions[30]. Furthermore, Lavoie

et al. explain that PC patients describe autonomy as something that not only has to do with the individual, but also involves a relationship with others[31]. This aspect of patient, as well as family centred care is also emphasized by the WHO definition of PC[32].

Families too need to be assisted in dealing with their own burden and needs, in order to be able to support and respect patients' decisions. Thus identifying and reducing hindering factors, such as burden or overburden of patients and their families, could foster patients' autonomous decision-making, as pointed out in the literature[30]. Therefore, we suggest that health-care professionals should be more sensitive to a relational understanding of autonomy because this would facilitate a more holistic understanding of patients' and families' needs[32].

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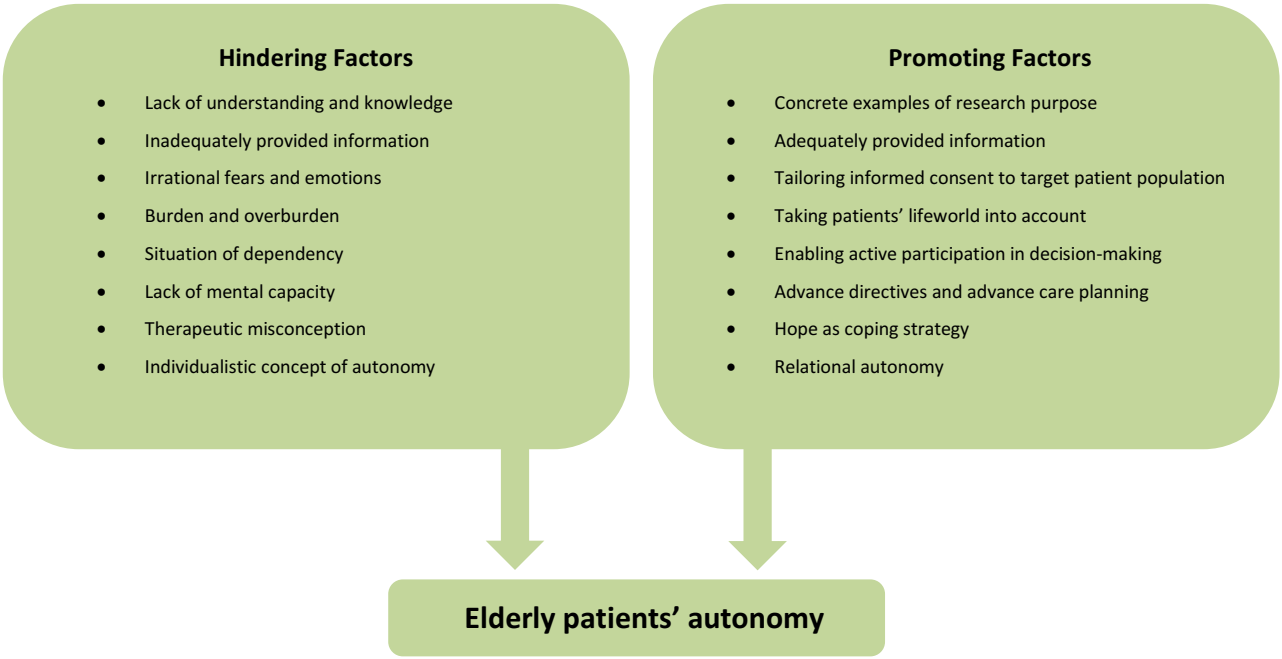
3 Overview


Hindering Factors
Lack of understanding and knowledge
Inadequately provided information
Irrational fears and emotions
Burden and overburden
Situation of dependency
Lack of mental capacity
Therapeutic misconception
Individualistic concept of autonomy
Promoting Factors
Concrete examples of research purpose
Adequately provided information
Tailoring informed consent to target patient population
Taking patients' lifeworld into account
Enabling active participation in decision-making
Advance directives and advance care planning
Hope as coping strategy
Relational autonomy
Elderly patients' autonomy

4 Research Limitations

Limitations that apply to each paper included in this PhD thesis are discussed in the corresponding Chapters (2-6). The thesis merged theoretical and normative concepts (autonomy) and empirical findings (promoting and hindering factors of autonomy in a clinical setting). It has been repeatedly argued that ethics focuses too heavily on normative claims rather than reaching out for the real-life experience[33].

> "While ethicists contribute normative judgments relying on secondary, distant information or vignettes made available to them by others, normally clinical staff are completely involved in the phenomena described and provide, thus, first hand statements in the mode of self-report and subjective, personal experience."[33, p. 27]

In order to reduce the gap between prescribing what should be (normative level) and describing what is (empirical level), medical ethicists should use empirical methods to apply their normative concepts to clinical challenges[33]. Without committing a naturalistic fallacy[33], we believe it is possible to bridge these two approaches, and moreover, that they can mutually enrich each other. The discipline of bioethics is in this regard very useful insofar as it attempts to bridge the empirical and normative approach, thereby acknowledging the importance of empirical research to mirror the reality (e.g. patients in a clinical setting and their autonomy). Bioethics also emphasizes the importance of a normative approach to identify the ethical issues at stake and find solutions based on a real-life approach[33-35].

Limitations of this PhD thesis include the partially qualitative nature and thus, its lower degree of generalizability. The quantitative part of the thesis focused exclusively on Switzerland and therefore, it is unclear to what extent these results are applicable to other countries. Nevertheless, our findings provide interesting and important insights on how elderly patients' autonomy can be promoted in a clinical setting.

5 Implications for further research

Respect for elderly patients' autonomy remains important throughout the illness course and especially during the end of life. First, more qualitative research (e.g. interviews with patients) is needed to understand more precisely what patients understand under the term "autonomy". Second, our initial qualitative findings could be expanded through additional quantitative research to make more generalizable statements regarding patients' willingness to participate in CTs involving novel technologies or being part on RECs.

6 Conclusion

The ethical imperative of respecting patients' autonomy is not new. Nevertheless, in the light of an increase in chronic diseases, new medical developments (e.g. SB), and complex end-of-life situations (e.g. PC), it remains of utmost importance to examine what might hinder patients' autonomy in these situations and what can be done to promote it. This PhD thesis aimed to discover hindering and promoting factors of patients' autonomy throughout their course of disease.

Moreover, our results indicated that there is not a single concept of autonomy valid for everyone at any time. These findings point to the culturally determined nature of autonomy and serve as a reminder that health-care professionals should be aware that the perception of what a patient understands under autonomy might shift throughout the disease and patients' life narrative. Therefore, communication among the different parties involved in decision-making (e.g. patient, physician, family member) should be consistently and rigorously

pursued. Through frequent discussions (e.g. family conferences), a shared understanding of what autonomy means for each individual can be built. Health-care professionals should not focus solely on the individualistic definition of autonomy, but also take into account patients' network of relations and their lifeworld to best promote their autonomous decision-making. Relational autonomy and inclusion of patient's lifeworld into the clinical setting can act as promoting factors to their autonomy.

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Appendix

Questionnaire for Patients (Chapter 2, 3, and 4)

Leitfaden für Gicht- und Diabetespatienten zur Wahrnehmung von Risiken und Nutzen früher klinischer Studien im Bereich der synthetischen Biologie

(Bewertung des Risiko-Nutzen-Verhältnisses und Teilnahmebereitschaft)

Allgemeine Angaben

Interviewnummer:

Grunderkrankung: ❑ Gicht ❑ Typ-2-Diabetes

Interviewer(in):

Datum:

Uhrzeit:

Dauer:

Begrüßung

Vorstellung der eigenen Person

Danke für Teilnahme am Interview

Zeitrahmen: ca. 45 bis 90 Minuten, Pausen und Unterbrechungen möglich, Abbruch ohne nachteilige Konsequenzen

Ziel des Gespräches: persönliche Vorstellungen und Wünsche in Bezug auf innovative Behandlungsmethoden, vor allem aus dem Bereich der synthetischen Biologie ermitteln. Beantwortung dieser Frage sehr wichtig, da bisher noch nicht bekannt ist, was chronisch kranke Patienten über Forschungsstudien zu diesen neuen Therapien denken, Interviewpartner als Experte für die Sichtweise der Patienten; Herausstellen, dass IP sich frei äußern kann, es nicht um Wissensermittlung, sondern um pers. Meinung geht; wenn Frage nicht beantwortet werden kann, kein Problem, Zeit zum Überlegen; selbst: neutrale Befragung, keine Diskussion, eigene Meinung zurückstellen.

2 Teile: ihre jetzige Behandlung und Entwicklung neuer Behandlungsmethoden

Bitte um Aufzeichnung des Gesprächs (damit keine wichtigen Informationen verloren gehen) & Zusicherung Anonymität und Datenschutz

Allgemeine Fragen: Gesundheitszustand und momentane Behandlung

1. Wie würden Sie ihren jetzigen Gesundheitszustand beschreiben?

1.1 Wann wurde Gicht/Typ-2-Diabetes bei Ihnen diagnostiziert?

1.2 Haben Sie noch weitere Krankheiten? Wenn ja, welche?

1.3 Ich werde Ihnen jetzt ein paar konkretere Fragen zu ihrem Wohlbefinden stellen.

Standardform SF-36 vorlegen und gemeinsam ausfüllen (Dauer: ca. 5 Minuten)

2. Wie werden Sie zurzeit behandelt?

2.1. Wie geht es Ihnen denn mit ihrer Behandlung?

Wenn Leid erwähnt oder beschrieben wird: Worunter leiden Sie persönlich am meisten? Wie gehen Sie hiermit um? Hat sich das im Laufe ihrer Krankheit verändert?

2.2. Haben Sie vorher bereits andere Behandlungen erhalten?

2.3. Was würden Sie sich für ihre Behandlung wünschen?

Einstellung gegenüber Forschung/technischer Entwicklung

3. Um die Behandlungsmöglichkeiten für Krankheiten zu verbessern, wird in Laboren und Spitälern viel geforscht. Gehen wir noch einmal einen Schritt zurück. Forschung findet ja in fast allen Lebensbereichen statt. **Was denken Sie denn über technische Entwicklungen und Forschung ganz allgemein? Sind Sie da eher neutral eingestellt oder würden Sie sich hierzu positionieren?**

3.1. Würden Sie sich selbst eher als technikkritisch oder als Technikbefürworter bezeichnen?

3.2. Gibt es vielleicht Lebensbereiche, in denen Sie technische Entwicklungen eher gutheißen und andere, in denen Sie so etwas generell ablehnen?

Einstellung gegenüber synthetischer Biologie

3. Ein sehr neues Forschungsgebiet ist die Synthetische Biologie. Haben Sie das Wort „Synthetische Biologie“ schon mal gehört?

4.1. *Falls ja:* Was stellen Sie sich denn darunter vor? Wie haben Sie denn von Synthetischer Biologie gehört? *Anschließend noch einmal kurz erklären.*

4.2. Falls nein:

Ich habe Ihnen hier einmal eine Erklärung aufgeschrieben, die Sie sich in Ruhe durchlesen können.

Dem Patienten/der Patientin Karte 1 zur Veranschaulichung übergeben (Anhang 2).

Anschließend dem Patienten/der Patientin Grafik 1 zur Veranschaulichung übergeben und kurz erklären (Siehe Anhang 1).

4.3. Haben Sie Fragen hierzu?

4.4. Wenn Sie das so lesen und hören, was denken Sie denn hierüber? Was finden Sie hieran gut, was eher nicht?

4.5. *Falls es nicht erwähnt wird:* Was denken Sie denn über synthetische Biologie als Behandlungsmethode für Krankheiten? Was finden Sie hieran gut, was eher nicht?

Fallbeispiel: synthetic circuit

4. Ich möchte mit Ihnen nun ein kurzes Gedankenexperiment machen.

a. <u>Fallbeispiel für Gichtpatienten</u>

Ich werde Sie nun in die Welt von Herrn Müller im Jahr 2025 entführen. Herr Müller leidet wie Sie an Gicht, nimmt aber keine Medikamente ein. Er muss nur selten zum Arzt, um seinen Harnsäurespiegel kontrollieren zu lassen. Herr Müller hat sich eine Kapsel unter die Haut implantieren lassen. In dieser Kapsel befinden sich menschliche Zellen. Diese Zellen stammen von Herrn Müller selbst. Sie wurden ihm entnommen und im Labor verändert. Die veränderten Körperzellen von Herrn Müller sind in der Lage ein bestimmtes Eiweiss herzustellen, das die überschüssige Harnsäure im Blut abbaut. Zudem wurde noch ein Sensor in die Zellen eingebaut, der konstant den Harnsäurespiegel im Blut misst. Wenn dieser zu stark ansteigt, wird die der Zelle. Sie produziert dann mehr von dem harnsäureabbauenden Eiweiss. Hiervon merkt Herr Müller nichts. Alles geschieht automatisch und ganz von allein. Sie können sich das hier ansehen.

b. <u>Fallbeispiel für Diabetespatienten</u>

Ich werde Sie nun in die Welt von Herrn Müller im Jahr 2025 entführen. Herr Müller leidet wie Sie an Diabetes. Herr Müller hat sich eine Kapsel unter die Haut implantieren lassen. In dieser Kapsel befinden sich Zellen. In dieser Kapsel befinden sich menschliche Zellen. Diese Zellen stammen von Herrn Müller selbst. Sie wurden ihm entnommen und im Labor verändert. Die veränderten Körperzellen von Herrn Müller sind in der Lage eine Substanz herzustellen, welche die Insulinproduktion im Körper anregt und die Blutzuckerkonzentration senkt. Auf der Haut trägt Herr Müller ein Pflaster in das LED-Leuchten eingearbeitet sind. Nach dem Essen schaltet Herr Müller per Knopfdruck diese LED-Lämpchen an. Das Licht sorgt dann dafür, dass die Substanz in den Zellen produziert und ins Blut ausgeschüttet wird. Sie können sich das hier ansehen.

4.1. Wenn Sie das so hören, welche Gedanken gehen Ihnen hierzu durch den Kopf? Was finden Sie gut und was finden Sie nicht so gut?

4.2. Diese Behandlungsmethode wurde vor ein paar Jahren hier in Basel entwickelt. Bis diese neue Behandlungsmethode Patienten verschrieben werden kann, muss deren Wirksamkeit und Ungefährlichkeit nach fest vorgegebenen Regeln getestet und bewiesen werden. Das geschieht in Studien.

Meinung zu klinischen Studien

5. Damit Sie eine bessere Vorstellung von solchen Studien haben, habe ich hier eine Erklärung aufgemalt

Dem Patienten/der Patientin Grafik 2 zur Veranschaulichung übergeben (Anhang 1).

Wie Sie sehen können, beginnt man zunächst damit den Wirkstoff in Zellen zu testen. Dann testet man ihn im lebenden Organismus aus. Zunächst an verschiedenen Tieren und dann schließlich im Menschen. Die Studien mit Menschen bezeichnet man auch als klinische Studien. Sie verlaufen in 3 Phasen. Ich habe Ihnen hier ein paar Karten mitgebracht, auf denen Sie ganz in Ruhe nachlesen können, bevor wir darüber sprechen. Sie können mir jederzeit Fragen stellen.

Dem Patienten/der Patientin Karten 2 bis 7 zum Lesen übergeben (Anhang 2).

5.1. Was ging Ihnen durch den Kopf, als Sie eben die Karten gelesen haben? Inwiefern war Ihnen dieses Prozedere vertraut oder ganz neu?

5.2. Gibt es etwas, dass Sie überraschend finden?

5.3. *Falls sich ergibt, dass der Patient/die Patientin Vorwissen hat*: Wo haben Sie denn schon einmal vor unserem Gespräch von klinischer Forschung gehört?

5.3.1. Inwiefern haben Sie mit Ihrem Arzt über Studien zur Erprobung neuer Behandlungsmethoden gesprochen und falls ja, was hat er Ihnen hierüber erzählt? *Falls nicht, unbedingt erklären:* Das kann ich verstehen. Je nach Spital wird mehr oder weniger Forschung durchgeführt, d.h. Forschung gehört nicht zum regulären Behandlungsplan.

5.3.2. *Nur, falls es sich aus dem Gespräch ergibt:* Haben Sie schon einmal an klinischen Erprobungen, sogenannten klinischen Studien, teilgenommen? Wenn ja, wie oft, wann und was wurde wie getestet? Können Sie es mir etwas genauer erzählen?

5.3.3. Warum haben Sie sich entschlossen, mitzumachen?

5.3.4. Wie sehen Sie diese Entscheidung heute, wenn Sie zurückblicken?

5.3.5. Falls nein: Wurde Ihnen schon einmal eine Teilnahme angeboten? Falls, ja: Weshalb haben Sie damals abgelehnt?

Teilnahmebereitschaft und Risikowahrnehmung

6. Stellen Sie sich einmal vor, die Gicht-/Diabeteskapsel, von der ich Ihnen vorhin erzählt habe, soll erprobt werden. Inwiefern können Sie sich denn grundsätzlich vorstellen hieran teilzunehmen?

6.1. *Falls der Befragte eine Teilnahme vollständig ausschließt:* Können Sie sich vorstellen an einer Medikamentenstudie teilzunehmen, wenn ein neues Gicht-/Diabetesmedikament erprobt wird? *Falls ja, weiter mit 6.2., falls nein:* An wem sollten neue Behandlungsmethoden ihrer Meinung nach erprobt werden? Wer wäre denn ihrer Meinung nach gut geeignet?

6.2. *Falls der Befragte sich eine Teilnahme grundsätzlich vorstellen kann:* Können Sie sich eine Teilnahme in allen Phasen gleichermaßen vorstellen oder gibt es Unterschiede? Wenn ja, warum?

6.3. Was denken Sie über den allerersten Schritt, d.h. Behandlungsmethoden, die zum ersten Mal am Menschen getestet werden?

Wie ich Ihnen schon erzählt habe, wurde diese Therapie hier in Basel entwickelt. Die Wirksamkeit und Sicherheit wurde bisher im Labor und in Versuchen mit Mäusen belegt. Bis zur ersten Erprobung mit Menschen kann es aber noch etwas dauern. Stellen Sie sich aber bei den nächsten Fragen einmal vor, die ersten Studien zur Erprobung dieses Implantats am Menschen würden tatsächlich jetzt durchgeführt. Es geht uns hierbei nicht darum, Sie für eine Versuchsteilnahme zu gewinnen. Wir möchten nur untersuchen, was Sie und andere Patienten hierüber denken.

6.4. Was wären denn für Sie Gründe an einer solchen Studie als PatientIn teilzunehmen/nicht teilzunehmen? Welche Ziele würden Sie mit einer Teilnahme verfolgen? Wie sehen Sie eine Teilnahme für sich persönlich?

Gesucht werden Hinweise zur Wahrnehmung und Bedeutung von persönlichem Nutzen (aktuell oder mittelbar, direkt, indirekt), therapeutic misconception, Risiken

6.4.1. *Falls der Patient/die Patientin therapeutischen Nutzen nennt: Die Graphik erneut anschauen*: Wie wir vorhin angeschaut haben, ist in den frühen Phasen eher nicht mit Heilung zu rechnen, sondern wird eher überprüft, welches die richtige Dosis ist und ob es Nebenwirkungen gibt. In der Regel profitieren Patienten von frühen Testphasen deshalb in der Regel nicht. Was würde Sie dennoch zu einer Teilnahme bewegen?

6.4.2. Wenn Sie an einer solchen Versuchsreihe teilnehmen, helfen Sie, eine neue Behandlungsmethode auf den Weg zur Zulassung zu bringen. Inwiefern spielt es für Sie eine Rolle, später einmal vom zugelassenen Medikament zu profitieren?

6.4.3. Wie wir vorhin gesehen haben, ist es schwer, wenn eine Therapie noch nicht am Menschen getestet wurde, eventuelle Risiken oder Nebenwirkungen vorherzusagen. Sie haben sich sicher schon einmal den Beipackzettel ihrer Medikamente angesehen. Alles, was dort steht ist irgendwann einmal als Nebenwirkung ihres Medikaments in Studien beobachtet worden. Probiert man eine neue Therapie zum ersten Mal am Menschen aus, ist es besonders schwierig, eventuelle Nebenwirkungen vorherzusagen. Wenn Ihnen ihr Arzt erklären würde, dass man nicht genau vorhersagen kann, ob und welche Nebenwirkungen auftreten und wie stark sie sein werden, wie würden Sie hiermit umgehen?

Gesucht werden Hinweise zum Entscheidungsprozess, zum Umgang mit Unsicherheit, zum persönlichen Verständnis von Risiken und Nebenwirkungen

6.4.4. Wenn Sie einmal an Ihren Beipackzettel und Nebenwirkungen, die Sie kennen denken, wie sehen Sie das? Bis wohin wäre es denn für Sie in Ordnung mitzumachen?

Gesucht werden Hinweise zur Persönlichen Risikoschwelle/zu inakzeptablen Risiken und zum Umgang mit unbekannten Risiken

6.4.5. Wenn Ihnen ihr Arzt erklärt, dass die kurzfristigen Nebenwirkungen sehr gering sind und relativ genau bekannt sind, eventuelle späte Nebenwirkungen nach 2, 5 oder auch 10 Jahren aber gänzlich unbekannt sind, welche Rolle würde das bei Ihrer Entscheidung spielen?

6.5. Gerade im Bereich innovativer Behandlungsmethoden dauert es mitunter sehr lange bis eine Medizinanwendung wirklich im ärztlichen Alltag ankommt. Es ist deshalb möglich, unter ganz strengen Voraussetzungen auch sogenannte Phase-0-Studien mit besonders niedrigen Wirkstoffdosen durchzuführen, bei denen ein Teil der Vorversuche mit Tieren ausgelassen wird. Ziel ist es, schneller herauszufinden, wie verträglich und nützlich das Medikament bei Menschen ist. Was denken Sie hierüber?

Wer soll über Ihre Studienteilnahme entscheiden?

7. Stellen Sie sich einmal vor, ihr Hausarzt erzählt Ihnen von dieser Studie und schlägt Ihnen eine Teilnahme vor. Was würden Sie dann machen? Wie würden Sie mit diesem Vorschlag umgehen?

7.1. Wie schätzen Sie sich selbst ein, wenn es darum geht über die Studienteilnahme zu entscheiden?

7.2. Was denken Sie ist für Sie wichtig, wenn es darum geht über eine eventuelle Studienteilnahme zu entscheiden?

7.3. Inwiefern würden Sie dies mit jemandem besprechen? Mit wem? Oder würden Sie ihre Entscheidung ganz allein treffen wollen?

7.4. Inwieweit spielen hierbei die Aussagen ihres Arztes eine Rolle?

8. Bevor eine neue Behandlungsmethode wie zum Beispiel die Gicht-/Diabeteskapsel in klinischen Studien an Patienten erprobt wird, muss ein Expertengremium entscheiden, ob die Studie überhaupt stattfinden darf. Dieses Gremium bewertet hierfür den möglichen Nutzen und die möglichen Risiken, die mit der Studie verbunden sind und wägt diese Positionen gegeneinander ab. In der Schweiz gibt es viele unterschiedliche Vorstellungen darüber, wer in einem solchen Gremium vertreten sein sollte. **Was denken Sie denn dazu? Wer sollte in diesem Gremium vertreten sein und warum?**

8.1. Wie sehen Sie denn die Teilnahme von Patienten in solchen Gremien?

Abschlussfrage

9. Wie sehen Sie denn den Zusammenhang zwischen ihrer Erkrankung und ihrer Bereitschaft an einer Studie teilzunehmen?

9.1. Wenn Leidensdruck als Hauptfaktor erwähnt wird hinterfragen: Finden Sie das problematisch? Wie sehen Sie das?

„Noch was loswerden?“

10. Gibt es etwas was Sie noch sagen möchten, auf das wir im Gespräch noch nicht eingegangen sind?

Angaben zur Person

Geschlecht:	❑ weiblich	❑ männlich		
Haushaltsgröße:	1-Person ❑	2-Personen ❑	3-Personen ❑	> 3-Personen ❑
Geburtsjahr:				
Höchster Bildungsabschluss				

Vielen Dank für das angenehme Gespräch und dafür, dass Sie sich die Zeit genommen haben, heute hier mit mir über diese Fragen zu sprechen.

Medical Records Data Extraction Sheet (Chapter 5 and 6)

Data Extraction Sheet Palliative Care Patients

I Sociodemographic variables

- Month and year of birth: Date of death:
- Gender:
- Nationality:
- Country of origin:
- Religion:
- Marital status:
- Place of care after hospital (at home, retirement home, hospital):
- Living place (urban, countryside):
- Number of children:

  ☐ 1-4; if more than four children please indicate:
- Profession:
- Mother tongue:

II Diseases

Diagnosis:

Year and month of main diagnosis:

Begin of Palliative Care (year, month and day):

Treatment and duration:

- Disease modifying treatment:
- Symptom- and problem-related treatment:

- Complexity of palliative case: (Phase 1-5 PCOC)

  Phase 1: Stable ☐

  Phase 2: Unstable ☐

  Phase 3: Deteriorating ☐

  Phase 4: Terminal ☐

  Phase 5: Bereaved ☐

III Advance Directives

Is /was there

-discussion about Advance Care Planning:

☐ no

☐ yes; if yes, what kind of discussions?

-written statement of goals of care:

☐ no

☐ yes; if yes, what kind of goals?

-Is/was there an AD (Advanced Directives)

☐ no; are/were there any indications why not?

☐ yes; if yes, oral or written AD?:

☐ yes; if yes, long or short form?:

☐ yes; if yes, did the patient receive advice (doctor, nurse, lawyer)

☐ yes; who signed the AD?

Motivation and personal values for AD:

No special motivation to fill in the AD:

-If yes, specify:

- This AD is applicable to the following situation:

  -All situations:

  -Specific situations (specify):

- Was there an adaption of the AD during the hospitalization?

  ☐ no ☐ yes

  ->If yes, please specify what kind of adaptions:

- Preference for or against specific treatments:

-I do not wish to give any instructions concerning specific medical measures, but I would ask the health care team to act as far as possible in accordance with my wishes:

- I wish to give specific instructions for the following situations:

  Artificial hydration and nutrition

  ☐ yes ☐ no

  Resuscitation in the event of a cardiac and/or respiratory arrest

  ☐ yes ☐ no

  Comments:

- Trusted person:
  ☐ no

  ☐ yes:
  ->specify:
  Proxy:
  GP:

- Organ donation: ☐ yes ☐ no

- ->If yes, specify which organ(s):

- Did/does the patient call for pastoral/spiritual care?
  ☐ yes ☐ no

  ->If yes, specify how often did/does the patient receive pastoral/spiritual care?

- When did discussions take place regarding PC treatment, patient's wishes, values, preferences and Ads with family members, the patient's GP, Spitex nurses and other relevant care givers?
  ☐ at admission ☐ during hospitalization ☐ after hospitalization

  ☐ after patient's death ☐ never

- Were there conflicts within the health care team or among family members and HCPs about patient's values and preferences?

  ☐ yes ☐ no

  >If yes, specify:

General wishes of patients during hospitalization:

Other information:

Contact person: