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Title
Advance Research Directives: Avoiding Double Standards

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Abstract

Background: Advance research directives (ARD) have been suggested to facilitate research with incapacitated subjects, in particular in the context of dementia research. However, established disclosure requirements for study participation raise an ethical problem for the application of ARDs: While regular consent procedures call for detailed information on a specific study (“token disclosure”), ARDs can typically only include generic information (“type disclosure”). ARDs, therefore, run the risk of introducing an ethically problematic double standard. Methods: This paper provides an ethical analysis of ARDs, taking into account the results of numerous empirical studies that have been performed so far. It will be argued that a revised understanding of informed consent can allow for context-sensitive disclosure standards. As a consequence, ARDs that include “type disclosure” can be acceptable under suitable circumstances. Discussion: Such an approach raises objections, two of which are especially important. A thorough examination shows, however, that they are not sufficient to justify a rejection of the approach. Conclusion: The approach presented in this paper avoids introducing a double-standard for particular types of research such as dementia research. It is, therefore, more suitable for the implementation of ARDs than established approaches.

Keywords

Advance research directives, informed consent, dementia research, research ethics
Background

Introduction

Informed consent is one of the core principles of medical ethics and research ethics. While this is widely acknowledged, both in theory and in practice, it is equally acknowledged that the principle of informed consent is not always directly applicable. A case in point is research with incapacitated subjects, in particular with those suffering from neurodegenerative diseases. From a certain point in time on, such persons are no longer able to give full informed consent. Suitable modifications or amendments to the principles of informed consent are, therefore, needed in this case. Since the 1980s, the model of advance consent has been suggested as a solution for some conditions, in particular for dementia research. The basic idea is simple enough: Patients are recruited before a predictable loss of capacity occurs [1, p. 521]. Their wish to participate in a medical study at a later time is recorded in a special document, an advance research directive (ARD), comparable to a living will or advance healthcare directive which registers future health care decisions.

An important argument in favor of ARDs is that they can help to support and sustain personal autonomy [2-3]. Before the onset, patients suffering from neurodegenerative diseases have usually lived an autonomous life and developed individual preferences and values. This can include the wish to endorse scientific research and to help future patients suffering from the same disease [4, p. 662]. ARDs allow such patients to maintain their preferences and values even if they can no longer articulate them distinctly. At the same time, ARDs may take the pressure off patients’ proxies when it comes to deciding on their behalf. Finally, ARDs can help to facilitate important research for the benefit of vulnerable patients that would otherwise be ethically highly problematic.
Current Debates

In the US and in Canada, ARDs were discussed and partly implemented already decades ago [2-3, 5-6]. In contrast, the discussion of ARDs in Europe has intensified only rather recently ([7]; for previous discussion in Europe see e.g. [8-9]). One reason for this growing interest is that in some European countries, advance consent has been added to the existing legal regulations on research involving humans. In Switzerland, for example, the *Federal Act on Research Involving Human Beings [Humanforschungsgesetz – HFG]* as of 2011 includes such a provision (Art. 24). In Germany, a recent amendment to the *Medicinal Products Act [Arzneimittelgesetz – AMG]*, based on the EU Regulation No 536/2014, added a similar provision.¹ Despite the inclusion in European regulations on research involving humans, the implementation of *advance research directives* remains controversial (cf. pro ARDs [10-11]; moderately skeptical [12]; critical [13]). Among other things, the disclosure requirements for such directives raise difficult problems.

Scholten et al. distinguish between “type disclosure” and “token disclosure”. While the former demands that potential participants are informed about “the general aims, methods, risks and burdens of the types of nontherapeutic research studies that can be conducted in incompetent populations”, the latter requires that potential participants are informed about the details of “the specific trial” [14, p. 82]. The authors continue to argue that “token disclosure” would render nontherapeutic research in incompetent populations impossible because the details of a specific trial will not be available well in advance. On the other side, “type disclosure” significantly deviates from the established practice in research with competent adults. Such a deviation is certainly in need of justification. Even if it is true that “a

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¹ This amendment is not yet in force. In accordance with EU Regulation No 536/2014, it will become effective six month after the new EU portal and the EU database for managing clinical trials have achieved full functionality.
clear, properly construed advance directive provides the most accurate account of a person’s wishes that it is possible to reasonably obtain” [15, sec. 28.2.2], it could still be the case that, from an ethical point of view, it is ultimately an insufficient basis for nontherapeutic research.

**Methods**

While in some countries ARDs have already been part of the regulatory framework for a couple of years, their implementation is underway in others, and in yet others they are under consideration. Regardless of this heterogeneous situation, a number of empirical studies have been carried out in recent years in order to examine various aspects of ARDs, including their acceptance among researchers, potentially affected patients and proxies, but also possible implementation constrains. These studies provide a multifaceted picture and the findings need to be taken into account by any ethical analysis. A brief and selective review seems, therefore, in order.

**Empirical Findings**

Muthappan et al. [16] assessed all adults admitted as inpatients to the National Institutes of Health (NIH) clinical center (which are considered for participation in clinical research) between March 14 and September 13 2000. All of these patients received a document on “Advanced Directives at the NIH” which describes ARDs and their usage. The authors found that only 11% completed an ARD and of those who specified their preferences 13% were not willing to participate in future research. Muthappan et al. acknowledged that their study was limited to one institution only and therefore probably not generalizable. Nevertheless, they concluded that to allow cognitively impaired adults to participate in research only on the basis
of a formal ARD could impede important research. According to them, more flexible approaches should be considered.

Stocking et al. [17] conducted separated interviews with 149 dementia patients and family proxies about the future enrollment in different types of studies. Afterwards joint interviews were conducted with 69 pairs of patient and proxy to discuss their separate responses. The authors found that 82.9% of the patients were willing to cede future decisions about study participation to their proxies. The authors conclude that an ARD may be helpful for judging the types of research and associated risks dementia patients are willing to enroll in, acknowledging that a sizable minority of patients does not want to do so.

Bravo et al. [18] focused on the situation in Canada and investigated the frequency with which patients communicated their preferences about health care and research. They found that 69.1% reported oral expression of wishes and 46.7% written expressions of wishes. Among those, 91.2% had chosen a substitute decision maker. Notably, 80.9% had voiced health care preferences but only 19.5% had voiced preferences regarding research participation. The authors conclude that over the past two decades advance care planning has increased in Canada, but further efforts are needed.

Substantial research on ARDs has been conducted by Jongsma and van de Vathorst in the Netherlands. In a paper [19] they reported the results of a qualitative study exploring the opinions of dementia researchers. The authors were particularly interested in mapping the possibilities and constraints of ARDs. From the 13 interviews they carried out, they inferred that positive ARDs could be valuable to discuss research participation with proxies and negative ARDs should lead to exclusions from research. However, researchers argued that ARDs cannot replace the informed consent procedure and that in practice, proxy dissent will
overrule positive ARDs. Therefore, according to the interviewed researchers, the practical use of ARDs is limited.

Werner and Schicktanz [20] took a comparative stance and conducted focus group and in-depth interviews with German and Israeli professional stakeholders from various fields. While both countries have recognized the importance of ARDs, the authors found that Germany is in a more advanced stage because of the EU regulation process. Nevertheless, stakeholders in both countries expressed the need for a broader debate on ARDs. Only recently, Jongsma et al. [21] published the results of qualitative study which consisted of semi-structured in-depth interviews with 24 persons with cognitive impairment. This particular study was a sub-study of a larger project on dementia research in Germany. The majority of participants supported ARDs as a valuable tool for allowing them to make autonomous decisions. Interestingly, some participants explicitly argued that it is important to help others by participating in research and some added that it is more important to help others than to benefit from research themselves. However, several participants were sceptical regarding personal benefit and were, therefore, reluctant to participate in pharmaceutical research and more willing to take part in other types of research advancing the understanding of their cognitive decline’s aetiology. Finally, some participants expressed negative or ambivalent attitudes towards the use of ARDs. They either did not want to make anticipated decisions or felt unable to decide for about something they had not experienced before. In summary, empirical studies show an increasing interest in ARDs over the past decades. However, there are still considerable reservations about the use of ARDs among both researchers, patients, and proxies. Most importantly, a clear vision of the practical implementation of ARDs is still missing as is a shared opinion about their moral authority. Finally, issues of informed consent are still lurking.
Informed Consent in Biomedical Research

Informed consent is generally recognized as paramount for ethically acceptable research involving humans. The World Medical Association’s Declaration of Helsinki [22] is one of the most widely accepted policy frameworks in this context. Eight out of thirty-seven paragraphs of the Declaration are devoted to informed consent. Paragraph 25 states: “Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.” [22, Nr. 25] The following paragraph includes an extensive list of items that should be covered in the information process: “In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.” [22, Nr. 26] To be sure, the Declaration explicitly allows for special provisions in case of potential research subject who are incapable of giving informed consent [cf. 22, Nr. 28 and 29]. Nevertheless, the detailed provisions of Nr. 26 illustrate not only that informed consent is essential, but also that the range of issues that should be covered in the regular information process is considerable. This is in line with many other national laws and super-national frameworks for
research involving humans which are based on a rather rigid model of informed consent and which include an extensive disclosure standard. In their influential book *Principles of Biomedical Ethics*, Tom Beauchamp’s and James Childress’ discuss three different standards: the professional practice standard, the reasonable person standard, and the subjective standard [23, p. 126-127]. While the authors prefer the subjective standard, they recommend for practice the reasonable person standard, but acknowledge that many jurisdictions rely on the professional practice standard according to which “professional custom establishes the amount and type of information to be disclosed.” [23, p. 126] The rich list included in the *Declaration of Helsinki* provides an illustrative example of such a professional practice standard.

According to the prevailing view, the quality, if not validity, of consent is directly correlated with the degree of the patient’s understanding. On this view, “type disclosure”, i.e. disclosure of general features of a study type rather than full disclosure of specific features of a concrete study, is necessarily deficient for it can, by definition, not include all details about a future study. As a consequence, ARDs by default suffer from a lack of moral authority. They simply cannot meet the regular disclosure standard. This, in turn, sets strong limitations for all types of research involving incapacitated subjects. Proponents of ARDs are, therefore, (implicitly or explicitly) at pains to show why a mitigated version of consent is still sufficient in some contexts. By doing so, they are inevitably introducing a double standard which is hardly convincing.

**A Revised Understanding of Informed Consent**

An alternative route for dealing with the problem of limited disclosure is to uncouple the validity of consent and the degree of patient’s understanding in the first place. This is in line
with recent criticism raised against the prevailing model of informed consent. In the past couple of years, some authors have maintained that the traditional concept of informed consent is theoretically flawed [24-25], not least because of its context-insensitive character. According to such an approach, consent is not a solitary act of a maximally informed agent, but rather located in “communicative transactions between agents” [24, p. 69]. Consequently, the standards for disclosure depend on various factors, including, of course, the study in question, its risks and burdens, but also the relationship between patient and physician or research subject and researcher respectively. Most important in the present context, such a revised understanding of informed consent allows for different disclosure standards, which may, in turn, help opening up the way for “token disclosure” in advance research directives. While on the traditional view maximal disclosure is the standard and any deviation from this standard negatively affects the moral authority of informed consent, the revised understanding proceeds from a different point: There is no fixed list of items that needs to be covered in the information process, but rather the provision to determine a standard of disclosure which is adequate for the concrete situation. Limited disclosure can be as appropriate as full disclosure and both standards can also be improper. What is crucial for the present purpose is that since there is no general standard, there can also be no double standard.

ARD in Practice

Despite concerns, ARDs have already become a tool in some ethical and legal frameworks for research involving humans. However, given the prevailing model of informed consent, their moral validity is questionable as they inevitably introduce a problematic double standard. Only if the context-insensitive fixation on disclosure standards is discarded can ARDs gain full
moral authority. This, in turn, asks for a cautious implementation that allows for robust safeguards against misuse.

ARDs should originate in well-established physician-patient relationships and may additionally include relatives or other trusted persons. The decision for participating in a future study should be embedded in a more comprehensive approach and should not be regarded as an isolated act. If the decision to participate in a future research project is part of an established and well documented relationship, “type disclosure” can be sufficient from an ethical point of view, not because a lower standard of informed consent is applicable, but rather because it is the appropriate standard in this particular context.

In practice, this means that physicians and their patients should discuss a potential participation in research at an early stage. It is easily conceivable that the topic is regularly raised by general practitioners during ordinary medical check-ups, in view of dementia research possibly starting from a certain age on. During such an iterated process individual attitudes and preferences can be gradually determined and documented. If a patient shows general interest, a physician may provide information on ongoing studies. By reference to such concrete examples, an ARD could be specified. Such an ARD would be based on “type disclosure” since the specific study design of future research projects would be unknown at the time of drawing up. However, the communicative process that led to the ARD would provide a sufficiently detailed picture of the preferences of a patient and back up the moral authority of the consent.

Even if this revised understanding of informed consent is accepted, there remains one serious problem. According to this approach, consent is always granted to a specific person or group of persons [25, pp. 41-42]. By definition, “to consent” means that a person A (temporarily) grants another person (or group of persons) B the right to perform some action \( \varphi \) that touches
on a right that A is acknowledged to have [25, p. 37]. To think of “B” as a placeholder which can be left unspecified is mistaken. For it is easy to imagine that A would agree to B to φ, but not someone else, say C. Especially when “to consent” is understood as a communicative act, the relationship between A and B is crucial. Then, the designation of a researcher (B) is not just a piece of information that may or may not be covered during the information process. Rather, it is the patient (A) and the researcher (B) together who constitute the communicative community in which the communicative act (of which the information about φ is a part) takes place.

However, if it is the general practitioner who arranges the process which leads to an ARD, it is typically not quite the person who will carry out the research. Technically speaking, the general practitioner is not the person B who wants to φ on A. Yet, this would be necessary to validate the consent as communicative act between the patient (A) and the physician (B). Ultimately, the physician is in a danger of becoming just an ordinary proxy for facilitating the patient’s future wishes. Then, ARDs might still not be entirely useless, but their usefulness would be considerably lower. What is more, their ethical way of functioning would change: they would serve as a basis for proxy consent and not count as instances of first-person consent.

The only way to solve this problem is to involve researchers in the process of drawing up an ARD. This does not necessarily mean that an individual researcher or group of researchers is being designated in the ARD – which would hardly be possible. Rather, a patient needs to get in direct contact with a representative of a future research project. This could, for example, be organized via patient organizations or designated representatives of research institutions. What is important is that a patient has some idea who will be involved in a future study and accepts this. It might, for example, be that a patient has an affinity for a particular research
institution, but an aversion to another. Accordingly, he might be willing to consent to participate in a research project of the former, but not of the latter. Under the terms of the revised model of informed consent, it is not sufficient that such affinities and aversions are included in the ARD. Eventually, such delegates must be the communicative partner of patients who jointly agree on an ARD while the general practitioner takes the important role of a facilitator.

Discussion
To be sure, such an approach raises objections, two of which are especially important: First, the model described runs the risk of being abused. It could be taken as an invitation to lower disclosure standards allowing for easier recruitment of incapacitated research participants. Second, it could appear to be a somewhat naive approach that does not consider aspects of verifiability in cases of conflict. Both objections are serious, but not sufficient to justify a rejection of the approach.

The possibility to decrease the disclosure standard in some contexts goes hand in hand with an increased responsibility of all parties involved. It is, therefore, by no means an easy route to get research participants involved. In contrast, ARDs including “type disclosure” will only be possible in the context of well-established physician-patient(-relative) relationships and with the involvement of research institutions. Note that such relationships are verifiable, at least to some extent. Medical consultations are typically documented. Such documentation should include notes on talks about research and personal involvement. In cases of uncertainty, a documentation that spans over a period of time is certainly more informative and reliable than an unconnected signature on an informed consent form can ever be. In short, a context-sensitive understanding of informed consent is not naive. It is well-equipped
to protect both research participants against undue influence and researchers against false accusations.

Secondly, ARDs are not incontestable. In cases of doubt revisions are always possible. Imagine the case of a patient now suffering from late-stage Alzheimer’s who has declared his willingness to participate in research and signed an ARD before. Imagine further that the study in question fits the “type disclosure” provided initially so that the patient is being included in the study. Imagine, finally, that during the study the patient shows severe discomfort or disaffirmation. Such reactions should, of course, be taken as withdrawal of consent which is possible at any time. In order to minimize the danger of exploitation, an independent trustee could be appointed as an additional safeguard for patients unable to consent.

In sum, a context-sensitive approach to informed consent that allows for a flexible disclosure standard does not at all imply more limited protection of research participants. To the contrary, it installs strong safeguards at the right place.

Finally, it might be objected that the approach described is excessively complex and not suitable for practice. It does, in fact, put some burden on general practitioners, namely repeatedly discussing the question of future research participation with potential patients, and additionally foresees a continued commitment of research institutions and/or patient organizations. This could complicate the recruitment process for research studies and increase their costs. On the other side, the additional expenses would probably not be huge. The integration of the recruitment process in the general medical service and the involvement of research institutions and patient organizations could even increase acceptance and the willingness of patients to participate in research, although the empirical findings cited above are not clear in this regard.
Conclusion

Advance research directives have been suggested as a suitable amendment to the principle of informed consent in order to allow for research with participants suffering from neurodegenerative diseases, in particular dementia. However, ARDs raise doubts about introducing different disclosure standards. In particular, informing potential participants in advance will often, if not always, only be possible if “type disclosure” rather than “token disclosure” is considered sufficient. Yet, according to the established model of informed consent, the quality of consent is directly correlated with the degree of the patient’s understanding and, hence, full disclosure is deemed to be essential. Against this background, “type disclosure” appears to be second-rate and its introduction for a vulnerable population is ethically highly problematic. According to an alternative understanding, informed consent should be seen as a communicative act. Such a view renders it possible to apply a more context-sensitive disclosure standard. As a consequence, “type disclosure” can be acceptable under suitable circumstances for various kinds of research projects. Such an approach avoids introducing a double standard for particular types of research such as dementia research and is, therefore, more convincing from an ethical point of view. Against the background of such an approach, an ethically compelling and practically feasible implementation of ARDs becomes apparent.

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Abbreviations

ARD: Advance Research Directive

WMA: World Medical Association

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