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# Integrating Advance Research Directives into the European Legal Framework

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## Abstract

The possibility of using advance directives to prospectively consent to research participation in the event of dementia remains largely unexplored in Europe. Moreover, the legal status of advance directives for research is unclear in the European regulations governing biomedical research. The article explores the place that advance research directives have in the current European legal framework, and considers the possibility of integrating them more explicitly into the existing regulations. Special focus is placed on issues regarding informed consent, the role of proxies, and the level of acceptable risks and burdens.

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## 1 Introduction

Over the past decade, significant efforts have been made in Europe to promote patients' self-determination. An important step in this direction was the explicit support given by the Council of Europe and several European countries to the use of advance directives to specify healthcare preferences in case of future incapacity<sup>1</sup>. In contrast, the possibility of using advance directives to prospectively consent to research participation remains largely unexplored in Europe. Moreover, legal instruments in the area are virtually silent. However, despite the current regulatory vacuum, the use of advance research directives (ARDs) is gradually drawing interest

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<sup>1</sup> Andorno R., Biller-Andorno N. & Brauer S., "Advance Health Care Directives. Towards a Coordinated European Policy?", *European Journal of Health Law*, Vol. 16, n°3, 2009, pp. 207-227; Negri S. (ed.), *Self-Determination, Dignity, and End-of-Life Care. Regulating Advance Directives in National and International Law*, Leiden: Brill Academic Publishers, 2012; Goffin T., "Advance Directives as an Instrument in an Ageing Europe", *European Journal of Health Law*, Vol. 19, n°2, 2012, pp. 121-140; Veshi D. & Neitzke G., "Advance Directives in Some Western European Countries: A Legal and Ethical Comparison between Spain, France, England, and Germany", *European Journal of Health Law*, Vol. 22, n°4, 2015, pp. 321-345.

among scholars<sup>2</sup>. In addition, non-governmental organisations promoting the care of patients suffering from dementia have, in recent years, given their explicit support to the use of ARDs, provided that certain safeguards are in place<sup>3</sup>.

ARDs can serve as a useful tool for patients in the early stage of dementia who are still capable of consenting to research participation. These documents allow them to express their preferences about their participation in future or ongoing clinical trials should they lose decision-making capacity. Without such directives, family members are placed in the difficult role of having to make a decision based on the presumed wishes of the patient or on the assessment of his or her best interests, which are not obvious when no direct benefit is expected. Several studies show that proxies cannot reliably guess patients' preferences: they are either too reluctant to authorise their enrolment in clinical trials, or consent to studies that do not really correspond to the preferences and values of the persons they represent<sup>4</sup>.

The current situation is challenging since there is a crucial need to conduct research involving dementia patients to better understand the conditions that cause dementia (in particular Alzheimer's disease), and to develop more effective therapeutic or preventive measures. Dementia is at present one of the greatest global health challenges as the number of people suffering from this condition worldwide is estimated at 44 million and is set to almost double by 2030<sup>5</sup>. Rates increase significantly with age, as dementia affects 5 per cent of the population older than 65 and 25-50 per cent of those older than 85<sup>6</sup>.

The moral advantage of ARDs, if compared to the current practice of proxy consent, is that participants themselves, while still competent, provide their consent to research participation. This possibility can be regarded as a mechanism of empowerment<sup>7</sup>. Like advance directives for healthcare, advance directives for research can be justified on the grounds that they offer a tool for prospective self-determination to those individuals who anticipate incapacity: if autonomous choices regarding one's own healthcare can be applied beyond one's competence, why should it be different for participation in clinical trials? From a more practical perspective, ARDs have the advantage of helping to solve the problem posed by the lack of information about the willingness of dementia patients to be enrolled in clinical trials. ARDs can facilitate the task of proxies in making decisions, while ensuring a greater respect for the personal preferences and values of participants<sup>8</sup>. These documents also have the potential to increase the participation of dementia patients in clinical trials and consequently, contribute to the development of specific treatments for this group of people.

It should be noted that it is beyond the scope of this article to address the philosophical objection, sometimes levelled against advance directives, that there is no continuity of identity before and

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<sup>2</sup> Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *European Journal of Health Law*, Vol. 13, n°3, 2006, pp. 235-261; Helmchen H., "Ethics of clinical research with mentally ill persons", *European Archives of Psychiatry and Clinical Neuroscience*, Vol. 262, 2012, pp. 441-452; Jongsma K. and van de Vathorst S., "Advance directives in dementia research: The opinions and arguments of clinical researchers – an empirical study", *Research Ethics*, 2014, published online 8 August 2014: doi: 10.1177/1747016114523422.

<sup>3</sup> Alzheimer Europe, Position paper on the use of advance directives, 2009, §31.

<sup>4</sup> Stocking C.B. *et al.*, "Speaking of research advance directives: planning for future research participation", *Neurology*, Vol. 66, n°9, 2006, pp. 1361-1366.

<sup>5</sup> Alzheimer's Disease International, World Alzheimer Report 2014, Dementia and Risk Reduction: An Analysis of Protective and Modifiable Factors, [www.alz.co.uk/research/world-report-2014](http://www.alz.co.uk/research/world-report-2014) [14 July 2015].

<sup>6</sup> Yudofsky S. and Hales R. (eds.), *The American Psychiatric Publishing Textbook of Neuropsychiatry and Behavioral Neurosciences*, Washington, DC, Psychiatric Publishing, 2008, p. 452.

<sup>7</sup> Pierce R., "A changing landscape for advance directives in dementia research", *Social Sciences and Medicine*, Vol. 70, 2010, p. 624.

<sup>8</sup> Abdoler E. and Wendler D., "Using data to improve surrogate consent for clinical research with incapacitated adults", *Journal of Empirical Research on Human Research Ethics*, Vol. 7, n°2, 2012, pp. 37-50.

after the onset of dementia<sup>9</sup>. We assume, as legal norms do, that people affected by dementia should still be regarded as the same persons they were before the onset of the cognitive impairment, no matter how serious their loss of memory or cognitive capacities. This is to say that advance directives should not be automatically disqualified as legally invalid on the ground that they were made by a different person to the one who is now suffering from dementia.

The article begins by exploring the place that ARDs have in the European legal framework governing biomedical research. The discussion then proceeds to consider the possibility of integrating them more explicitly into the existing European norms. The central questions addressed in the article are: What is the legal status of ARDs in Europe? What possibilities does the European legal framework offer for using ARDs? In addressing these questions, special focus is placed on issues regarding informed consent, the role of proxies, and the level of acceptable risks and burdens.

## 2 European Legal Framework for ARDs

The concept of advance directives for research has been discussed in the US since the end of the 1980s<sup>10</sup>. Some American scholars have emphasized the potential utility of these documents to facilitate research involving people with mental disorders<sup>11</sup>. As a result of these discussions, several proposals for the regulation of ARDs have been made in the US<sup>12</sup>. In Canada, the regulations governing research involving human subjects make explicit mention of advance directives for research<sup>13</sup>. In contrast, no proposals for guidelines or legislation in this area have been brought forward in Europe, and the European literature on ARDs is almost non-existent. The legal frameworks on biomedical research adopted by European bodies, namely the Council of Europe and the European Union, are ambiguous in this respect<sup>14</sup>. Similarly, European domestic laws are virtually silent about the possibility of consenting to research participation in the event of future mental incapacity.

It is important to stress that research involving persons unable to consent is not per se prohibited in Europe, but subject to additional safeguards, such as the requirement that the research poses no more than minimal risk and minimal burden to participants in circumstances where no direct benefit to them is expected, that the legally authorised representatives give their consent, and that the research protocol is approved by an independent ethics committee. The legal basis for such safeguards can be found in the 1997 European Convention on Human Rights and

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<sup>9</sup> See for instance Dresser R., "Dworkin on Dementia: Elegant Theory, Questionable Policy", *Hastings Center Report*, Vol. 25, n°6, 1995, pp. 32-38.

<sup>10</sup> Levine R., *Ethics and Regulation of Clinical Research*, Baltimore, MD: Urban and Schwarzenberg, 1986, pp. 270-274; National Institutes of Health, *Consent Process in Research Involving Impaired Human Subjects*, 1987, *Clinical Center Policy and Communications Bulletin*, n87-4; National Bioethics Advisory Commission (NBAC), *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*, Report and Recommendations, vol. I, Washington, DC: US Government Printing Office, 1998, chapter 3.

<sup>11</sup> Moorehouse A. and Weisstub D., "Advance directives for research: ethical problems and responses", *International Journal of Law and Psychiatry*, Vol. 19, n°2, 1996, p.107; Backlar P., "Anticipatory planning for research participants with psychotic disorders like Schizophrenia", *Psychology, Public Policy, and Law*, Vol. 4, n°3, 1998, pp. 829-853.

<sup>12</sup> Pierce R., "A changing landscape for advance directives in dementia research", *op. cit.*, p. 624.

<sup>13</sup> Canadian Institutes of Health Research, National Science and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, December 2014, Articles 3.10 and 3.11, [www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS\\_2\\_FINAL\\_Web.pdf](http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf) [14 July 2015].

<sup>14</sup> Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *op. cit.*

Biomedicine<sup>15</sup>, and in the 2014 EU Regulation on Clinical Trials<sup>16</sup>, which will replace the currently applicable 2001 EU Clinical Trials Directive<sup>17</sup> in 2016.

## 2.1. Council of Europe

The Council of Europe's Convention on Human Rights and Biomedicine 1997 (hereinafter Biomedicine Convention) includes only one provision relating to advance directives, which stipulates that "[t]he previously expressed wishes relating to a medical intervention by a patient who is not, at the time of the intervention, in a state to express his or her wishes shall be taken into account"<sup>18</sup>. It is important to point out that this provision was exclusively developed in relation to advance directives for healthcare. The Convention's drafters did not have in mind the use of these documents for research purposes. This is clear not only from the Explanatory Report to the Convention, which in its commentary on Article 9 refers to the "patient" and the "practitioner"<sup>19</sup>, but also from the fact that Section V of the Convention, which specifically deals with biomedical research, does not mention the possibility of making advance directives in this context. Interestingly, the Convention does not say anything about positive advance directives for research. But it can be argued that refusals to participate in research, made either before or after the onset of the mental incapacity, would be binding. This can be inferred from Article 17.1(v), which enumerates, among the conditions for conducting research involving persons unable to consent, that "the person concerned does not object"<sup>20</sup>.

In comparison to the Biomedicine Convention, the Convention's Additional Protocol on Biomedical Research 2005 takes a step towards the recognition of ARDs. Article 15, 1.iv indirectly refers to ARDs stipulating that the consent of the legal representative must be given "taking into account the person's previously expressed wishes or objections". This means that although prior wishes -including written wishes and objections- are regarded by the Protocol as relevant, they are not accepted as a stand-alone requirement. Instead, a kind of double safeguard mechanism for the protection of incapacitated research subjects is suggested. Therefore, the previously expressed wishes have to be assessed by the proxy decision-maker, who can eventually overrule them (as they need only to be "taken into account", and not strictly followed). Indeed, these instructions seem to be considered as an element that might complete the consent given by the legal representative of the incapable person, as opposed to an independent basis for the decision, and not as instructions documents that can operate independently. When such documents exist, the decision of the legal representative cannot be exclusively based on his or her own personal opinion, but should be *guided* by the preferences expressed by the individual before the onset of the incapacity.

## 2.2. European Union

At the level of the European Union, the 2001 Clinical Trials Directive refers only indirectly to ARDs. Article 5 reads: "In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving consent shall apply. In addition to

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<sup>15</sup> Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo, 4. IV. 1997, ETS 164 (hereinafter "Oviedo Convention"), Article 17.

<sup>16</sup> Council Regulation 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, 2014 OJ (L 158) 1 (hereinafter "Regulation 536/2014"), Article 31.

<sup>17</sup> Council Directive 2001/20 on the Approximation of the Law, Regulations and Administrative Provisions of the Member States relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, OJ L 121/34 (2001) (hereinafter "Directive 2001/20/EC").

<sup>18</sup> Oviedo Convention, Article 9.

<sup>19</sup> Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research, Strasbourg, 25 I. 2005, ETS 195 [hereinafter Explanatory Report to the Additional Protocol], §62.

<sup>20</sup> Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *op. cit.*, p. 243.

these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if..." [the list of additional requirements follows]. Since advance consent to participation in research is only mentioned in passing as a negative condition for the application of the general rules for conducting research involving incapacitated persons, it is hard to draw from this norm any positive conclusion about the general conditions for making ARDs and about their efficacy. Therefore, it seems excessive to deduce from this provision that "the effect of a valid previously given informed consent or refusal is that the potential research participant is legally treated as a competent research subject and therefore, the additional safeguards listed in the latter part of Article 5 (including consent given by a legal representative) need not be applied"<sup>21</sup>.

In April 2014, a new Regulation on Clinical Trials was adopted by the EU to replace the 2001 Clinical Trials Directive. The Regulation, which will become directly applicable to Member States no earlier than on May 2016, uses almost the same wording as the 2001 Directive to refer - indirectly- to ARDs in Article 31. The only novelty of the new Regulation in this regard concerns research in emergency situations and the need for the researcher to ensure that the potential participant has not previously expressed objections to participate in the clinical trial (Article 35, d). However, advance directives as envisaged by the Regulation, expressing a wish not to be involved in specific emergency trials, seems very unlikely. Therefore, it is difficult to draw from this provision any conclusions that could be applicable to advance consent to clinical trials in the event of mental incapacity.

In short, the current European legal framework neither explicitly mentions the possibility of using ARDs nor forbids them. Concerning domestic regulations, the Swiss Law on Research Involving Human Beings 2011 is, to our knowledge, the only legal instrument in Europe that explicitly refers to the possibility of using advance directives to prospectively consent to medical research<sup>22</sup>. The UK Mental Capacity Act 2005, covering England and Wales, mentions ARDs only as a means for objection to involvement in research, as it stipulates that research on incapacitated persons cannot be performed if, among other things, it is contrary to "an advance decision of his which has effect"<sup>23</sup>. The following section will discuss the conditions for integrating advance research directives into the European legal framework governing biomedical research.

### 3 Challenges for Integrating ARDs into the European Legal Framework

On the one hand, the need for some common European requirements for the validity of consent to research participation (including dementia research) is undeniable. Although only 24 per cent of all clinical trials applied for in the EU are conducted in more than one Member State, they involve approximately 67 per cent of all subjects enrolled in clinical trials. This is to say that in Europe the majority of trials involving a large number of research subjects (40 or more) are

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<sup>21</sup> Lötjönen S., "Medical research on patients with dementia: the role of advance directives in European legal instruments", *op. cit.*, p. 246.

<sup>22</sup> Article 24, §1 stipulates that "[r]esearch projects involving persons unable to consent which offers prospects of direct benefit to participants can be conducted if the following conditions are met: 1. the subjects have given their consent when they were still competent and the consent is evidenced by a document; 2. in the absence of a document evidencing the consent, the legal representative, a trustworthy person or their relatives gave a written informed consent; 3. the subjects do not express in an identifiable manner, verbally or by a particular behavior, their refusal to participate in the research project". Article 24, §2 provides that in the case of research not offering prospect of direct benefit to participants, two additional conditions must be met: "the risks and burden associated with the project are minimal" and "the project is expected to offer long-term benefit to people suffering from the same disease, or having a comparable health condition" (Article 24, §2).

<sup>23</sup> Mental Capacity Act 2005, s 33(2).

multinational<sup>24</sup>. On the other hand, when aiming at a regional consensus on the use of ARDs it should be acknowledged that these documents raise a variety of ethical and legal questions, especially regarding informed consent, the role of proxies, and the level of acceptable risks and burdens. These three topics are discussed in this section.

### 3.1 Informed Consent

In general, participation in clinical trials is subject to stringent conditions and additional safeguards that do not apply to healthcare. These specific requirements are understandable because clinical trials do not generally aim to improve the health of research participants, but are primarily conducted to gain scientific knowledge that can potentially benefit future patients. In giving their consent, it is important that potential research subjects understand the *altruistic* nature of their involvement. Obviously, this must also be understood by those who give consent in the form of an ARD. In this regard, it has been argued that, in such a context, the individual must, at least, be able to understand the distinction between being a "patient" and a "research subject"<sup>25</sup>.

Rebecca Dresser has pointed out how demanding it is to ask people at risk of dementia to imagine how it would be to participate in research after the onset of cognitive impairment. She even notes that "it may be a rare person who can genuinely achieve this level of understanding"<sup>26</sup>. In addition, although therapeutic misconception is not the prerogative of only dementia patients, Dresser reports empirical results demonstrating how frequently potential dementia research participants misunderstand the proposed study, notably the fact that it is not another treatment option, but principally aims to produce generalizable knowledge<sup>27</sup>. This "therapeutic misconception" can be even greater if the same advance directives combine treatment and research purposes<sup>28</sup>. This kind of misunderstanding is more likely to happen if the research subjects are already mildly affected by dementia. The assessment of the decision-making capacity of such individuals poses a significant ethical and legal challenge<sup>29</sup>, and should be exercised with caution, in order to prevent any misuse or deception of potential research subjects.

It is generally accepted that participants in medical research "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 (...)"<sup>30</sup>. There are in principle no reasons for departing from these requirements in the case of prospective consent to dementia research. This is certainly the case for ongoing clinical trials, providing that there are no changes in the protocol. However, it should be noted that it may be more difficult when dealing with future clinical trials, the design of which are not finalized. In any case, it is crucial that ARDs are very specific about the procedures to which participants will be exposed (for

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<sup>24</sup> European Commission, Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicine Products for Human Use, and Repealing Directive 2001/20/EC, Brussels, 17 July 2012, p. 2, [http://ec.europa.eu/health/files/clinicaltrials/2012\\_07/proposal/2012\\_07\\_proposal\\_en.pdf](http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf), [14 July 2015].

<sup>25</sup> Backlar P., "Anticipatory planning for research participants with psychotic disorders like Schizophrenia", *op. cit.*, p. 842; Alzheimer Europe, "The Ethics of [Dementia](#) Research", 2011, chapter 4, [www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/Ethics-of-dementia-research](http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/Ethics-of-dementia-research) [14 July 2015].

<sup>26</sup> Dresser R., "Advance directives in dementia research. Promoting Autonomy and Protecting Subjects", *IRB. Ethics & Human Research*, Vol. 23, n°1, 2001, p. 4.

<sup>27</sup> *Ibid.*

<sup>28</sup> Pierce R., "A changing landscape for advance directives in dementia research", *op. cit.*, p. 624.

<sup>29</sup> Trachsel M., Hermann H., and Biller-Andorno N., "Cognitive Fluctuations as a Challenge for the Assessment of Decision-Making Capacity in Patients with Dementia", *American Journal of Alzheimer's Disease and Other Dementias*, Vol. 30, n°4, 2015, pp. 360-363.

<sup>30</sup> World Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 2013, §26.

instance, taking blood samples, monitoring blood pressure, testing new drugs, etc.), as well as about the risks and burdens associated with these procedures<sup>31</sup>.

Even though ARDs are defensible as an initial authorisation for research participation, and are a valuable means to promote patients' autonomous decisions, other safeguards remain necessary to ensure the well-being of cognitively impaired participants. It has been pointed out that in practice, at any sign of distress, dissent or discomfort, incompetent participants are excluded from clinical trials<sup>32</sup>. Nevertheless, the protection of incapacitated subjects cannot merely depend on the good will of researchers but should be ensured by legal mechanisms. It is important to guarantee that the well-being of participants is constantly monitored from both the researchers' side and also from the participant's side (*i.e.* the proxy). Physicians, researchers and ethics committees, due to the regular assessment of any changes in the protocol and in the balance benefit/risk, have to make sure that the participation of incapacitated subjects is in conformity with the prior consent and with the legal requirements. Such consent should therefore not be understood as a simple authorisation at the start of the study, but as a continuous process throughout the trial<sup>33</sup>. This is why the involvement of a legal representative is crucial in terms of monitoring and accountability. The proxy, who is someone close to the participant and has no personal interest in the research, is in a good position to assess the burdens that may result from research participation, and evaluate the subject's willingness to continue participation in the trial.

Concerning the possibility of withdrawal from research trials by participants after the onset of their incapacity, it has been argued that ARDs can be revoked at any time, even when the individual has already lost his or her decision-making capacity<sup>34</sup>. This means that "the threshold for the capacity to revoke or refuse to participate should be lower than the capacity to consent"<sup>35</sup>. Similarly, Alzheimer Europe lists among the conditions for the implementation of ARDs that the person "does not show any sign of unwillingness to participate at the start of the research, e.g. refusing to take medication when offered, obvious distress when interviewed, etc., and that the participant does not display signs of unwillingness to continue participating and/or experience distress as a result of the research"<sup>36</sup>. These conditions are in conformity with the European Biomedicine Convention, which requires that the incompetent individual "does not object"<sup>37</sup>. Similarly, the 2014 EU Regulation on Clinical Trials expressly gives incapacitated persons the right to withdraw from trials, independently from the opinion of their legal representatives<sup>38</sup>. However, this right to withdraw is rather demanding in the Regulation, as the patient has to express an "explicit wish" and must be "capable of forming an opinion and assessing the information"<sup>39</sup>.

The right to withdraw from research can be compared to the way in which advance treatment refusals operate. Incapacitated patients who ask for life-saving treatments, which they have refused in an advance directive, would probably be treated, even if they have already lost their

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<sup>31</sup> Regarding the importance of the specificity of the consent, see Gevers S., "Dementia and the Law", *European Journal of Health Law*, Vol. 13, n°3, 2006, p. 217.

<sup>32</sup> Jongsma K. and van de Vathorst S., "Dementia research and advance consent: it is not about critical interest", *Journal of Medical Ethics*, 2014, published online 19 September 2014; doi:10.1136/medethics-2014-102445.

<sup>33</sup> See Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 25.I. 2005 (hereinafter "Additional Protocol"), Article 24.2.

<sup>34</sup> Backlar P., "Anticipatory planning for research participants with psychotic disorders like Schizophrenia", *op. cit.*, p. 842.

<sup>35</sup> Moorehouse A. and Weisstub D., "Advance directives for research: ethical problems and responses", *op. cit.*, p. 133.

<sup>36</sup> Alzheimer Europe, Position paper on the use of advance directives, *op. cit.*, §32.

<sup>37</sup> Oviedo Convention Article 17.1.v; Additional Protocol, Article 15 1.v.

<sup>38</sup> Regulation 536/2014, Article 31.

<sup>39</sup> Regulation 536/2014, Article 31.1.c.



decision-making capacity<sup>40</sup>. This is because priority is given to the least harmful alternative, which is non-refusal of life-saving treatments, and in the case of ARDs, non-participation in research, even when the risks and burdens are very low. In other words, the initial consent given by means of ARDs is not sufficient to continue research procedures when participants show clear signs of unwillingness to continue participating in the trial.

### 3.2 The Role of Proxies

Legal instruments in Europe state explicitly that the consent of the legally authorised representatives or proxies is absolutely required to enrol incapacitated adults in research trials<sup>41</sup>. However, from a theoretical perspective one may wonder whether such consent is necessary when the patient had consented in advance to research participation at a time when he or she was still competent. In this regard, Pierce suggests that ARDs can operate without the involvement of a proxy<sup>42</sup>. She argues that there are individuals who do not wish to defer the decisions concerning their participation in research to a surrogate decision-maker<sup>43</sup>. Therefore, she claims that, for reasons of equality, ARDs should be available to all competent individuals who wish to prospectively consent to research, regardless of whether they appoint a proxy<sup>44</sup>.

This proposal is problematic, at least for practical reasons. It is difficult to imagine how a cognitively impaired individual could participate in clinical trials without the assistance of a trusted, independent caretaker. It must be noted that the proxy does not necessarily have to be a family member but could be any trusted person, including the treating physician, insofar he or she does not have any direct interest in the clinical trial. Proxies are in a better position than researchers to detect any discomfort or adverse reaction that the demented person may experience as result of his or her participation in the trial. Furthermore, proxies can be consulted by researchers about the interpretation of the directives and about any possible change in the original protocol that may imply additional risks or burdens for participants.

A related question is whether the proxy should be allowed to override the advance consent of the participant. As Pierce has pointed out, there could be situations in which this would be acceptable, for instance, a change in protocol that results in an alteration in the research experience, a change in patient behaviour with assessment by an independent behavioural psychologist, or a change in risk exposure, either as a result of a change in protocol or in the participant's health condition<sup>45</sup>. Certainly, those changes have to be relevant enough to justify overriding the consent of the participant. This can be the case, for instance, if the changes in the protocol or in the health condition of participants create unanticipated burdens and risks for them, or if the subjects show clear signs of distress, fear or pain as a result of their participation in the trial. These situations show how important the involvement of an independent, trusted person to ensure the well-being of the incapacitated subject.

### 3.3. Level of Acceptable Risks and Burdens

It has been pointed out that "perhaps one of the most complex issues in the use of ARDs is whether it should be acceptable to prospectively consent to the full spectrum of risk, including risky research"<sup>46</sup>. Some scholars claim that it is permissible to consent to more than minimal risk and minimal burden on the grounds that the advance directive reflects the autonomous decision

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<sup>40</sup> Lemmens T., "End-of-life decisions and demented patients. What to do if patient's current and past wishes are in conflict with each other?", *European Journal of Health Law*, Vol. 19, n°2, 2012, pp. 177-186.

<sup>41</sup> Oviedo Convention, Articles 6.3 and 17.iv; Regulation 536/2014, Article 31.1.a.

<sup>42</sup> Pierce R., "A changing landscape for advance directives in dementia research", *op. cit.*, p. 627.

<sup>43</sup> Pierce R., "A changing landscape for advance directives in dementia research", *op. cit.*, p. 627.

<sup>44</sup> *Ibid.*

<sup>45</sup> *Ibid.*

<sup>46</sup> *Ibid.*

of the individual at a time when he or she was still competent<sup>47</sup>. But it can also be legitimately argued that ARDs are subject to the general limit of minimal risk and minimal burden that applies to all research studies involving incapacitated subjects. The reason for this is that the participant is especially vulnerable when the research is conducted and therefore deserves special protection at the time of the trial, it being irrelevant whether he or she was competent when the advance directive was made.

The current European legal framework on biomedical research clearly follows this second position: incapacitated subjects can be enrolled in research that does not offer the prospect of direct benefit only when it poses minimal risk and minimal burden<sup>48</sup>. There is no exception to this rule based on the circumstance that the individual had previously made an advance directive and accepted levels of risk and burden higher than minimal. In the European regulations, the "minimal risk and minimal burden" limit seems to have the status of an *ordre public* rule, which means that it cannot be the subject of renunciation. In this respect, it must be mentioned that the Biomedicine Convention prescribes that some of the protective provisions it contains cannot be set aside by the states' domestic laws<sup>49</sup>. Interestingly, Article 17, which sets the "minimal risk and minimal burden" limit, is explicitly mentioned as one of those non-negotiable provisions<sup>50</sup>.

In the past, several American experts have favoured the first position mentioned above. They have argued that an advance consent would be an acceptable basis for allowing the incompetent individual to be involved in research with higher risk than the one permitted for other incompetent subjects<sup>51</sup>. More recently, Buller claims that advance directives for research and for treatment are similar and therefore, the level of acceptable risks should be similar as well<sup>52</sup>. Based on the comparison with advance refusals of life-sustaining treatments, he argues that a person has the right to expose herself to high risks, including the risk of death. Therefore a person should equally be able to decide in advance to expose oneself to risky research, and not be limited to research involving minimal risk.

However, leaving aside the current legal obstacles to the use of ARDs for research involving risks higher than minimal, there are reasons to remain sceptical about this possibility. The analogy with advance directives for healthcare is not satisfactory. There is a crucial difference between prospectively consenting to treatment and to participation in research. Preferences regarding healthcare, including the refusal of treatments that the patient considers to be too burdensome or useless, are directly related to the well-being of that same patient who made the advance directive. On the contrary, research studies are normally not designed to benefit participants themselves, but to gain scientific knowledge that may eventually help future patients. The altruistic nature of research participation explains why research involving human beings is subject to conditions that do not apply to treatment, not even to treatment refusals. These additional safeguards concerning research need to be taken particularly seriously when participants are cognitively impaired at the time the research is carried out.

Moreover, from a practical point of view, there are reasons to believe that most individuals consenting to research participation by means of advance directives would prefer not to be exposed to risks higher than minimal. In this regard, it is interesting to note an empirical study in

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<sup>47</sup> See Buller T., "Advance consent, critical interests and dementia research", *Journal of Medical Ethics*, 2014, published online 12 August 2014, doi: 10.1136/medethics-2014-102024; Pierce R., "A changing landscape for advance directives in dementia research", *op. cit.*, p. 628.

<sup>48</sup> Oviedo Convention, Article 17; Additional Protocol, Article 15; Regulation 536/2014, Article 31.

<sup>49</sup> Oviedo Convention, Article 26.

<sup>50</sup> Oviedo Convention, Article 26.2.

<sup>51</sup> American College of Physicians (ACP), 'Cognitively Impaired Subjects. Position Paper', *Annals of Internal Medicine*, Vol. 111, n°10, 1989, p. 843; National Bioethics Advisory Commission (NBAC), *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity, Report and Recommendations*, *op. cit.*, chapter 3.

<sup>52</sup> Buller T., "Advance consent, critical interests and dementia research", *op. cit.*, p. 6.

which patients were asked to complete a research advance directive and to express their preferences regarding participation in clinical trials<sup>53</sup>. Only 11 per cent of patients accepted to complete a research advance directive. The great majority of them (76 per cent) were not willing to be exposed to more than minimal risk, while 49 per cent were also willing to take part in research without direct benefit, but which only posed minimal risk. Only 9 per cent of those who were in favour of making an ARD (that is, 1 per cent of the total of patients who were initially invited to complete an ARD) would accept to participate in research that would not help them and posed greater than minimal risk.

#### 4 Conclusion

This article has sought to draw attention to the fact that the European legal framework for biomedical research, as well as most European domestic laws, are virtually silent about the use of advance directives for research purposes. At the same time, it has shown that these same norms do not explicitly exclude the possibility of prospective consent to research participation. Considering that ARDs are perfectly in line with the commitment of European institutions to support patients' self-determination, we think that these tools could be integrated into the existing European norms relating to biomedical research. However, essential questions remain to be explored in greater depth. These include questions around how detailed the trial information which is given to potential participants must be, the role of the proxy before and during the trial, and the level of acceptable risk and burden which should be permitted in the context of ARDs.

As mentioned above, the use of ARDs can be justified in moral terms on the grounds that they contribute to patients' self-determination. Besides, ARDs could help to increase the amount of clinical trials with dementia patients and facilitate the development of specific drugs for this population. On the one hand, ARDs could do more justice to the patient's prior wishes than proxy consent does. On the other hand, it is unlikely that ARDs without the appointment of a proxy can offer a stand-alone solution to the requirement of informed consent. The involvement of a proxy seems indispensable to implement the advance directives in the light of the complete information at the time the research is conducted. In addition, other safeguards are necessary to ensure the well-being of incompetent participants, for example the right to withdraw or to be withdrawn from the trial at any time. Another question concerns the level of risks that can be accepted by means of ARDs. From the legal point of view, current regulations clearly forbid exposing incompetent participants to more than minimal risk and minimal burden, regardless of whether they have consented to them in advance or not. But from an ethical point of view, the question remains open for discussion.

In conclusion, it is desirable to clarify the legal status of ARDs and the conditions for their use in Europe. This would not only help to satisfy the wish of potential participants in dementia research, but also benefit future dementia patients by developing more effective therapeutic or preventive measures. This clarification would also facilitate the task of researchers and ethics committees. In this regard, it would be appropriate for the Council of Europe, for instance, to address the use of ARDs, at least in their Guide for Research Ethics Committees<sup>54</sup>. Similarly, the European Commission could include guidance on ARDs while revising and updating the current guidelines

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<sup>53</sup> Muthappan P., Foster H., and Wendler D., "Research advance directives: protection or obstacle?", *American Journal of Psychiatry*, Vol. 162, n°12, 2005, pp. 2389-2391.

<sup>54</sup> See Council of Europe's Steering Committee on Bioethics, *Guide for Research Ethics Committee Members*, Strasbourg: Council of Europe, 2012, [www.coe.int/t/dg3/healthbioethic/activities/02\\_biomedical\\_research\\_en/guide/Guide\\_EN.pdf](http://www.coe.int/t/dg3/healthbioethic/activities/02_biomedical_research_en/guide/Guide_EN.pdf) [14 July 2015].

ANDORNO R., GENNET É., JONGSMA K. & ELGER B. S., "Integrating Advance Research Directives into the European Legal Framework", *European Journal of Health Law*, Vol. 23, n°2, 2016, pp. 158-173.

and recommendations on clinical trials in the light of the new Clinical Trials Regulation<sup>55</sup>. In the context of an increasingly ageing population, the incidence of dementia is expected to grow in the coming years. Therefore, the need for research with incapacitated elderly patients will become more and more pressing. In this scenario, ARDs could turn out to be a useful tool to both empower potential research participants and contribute to the development of more effective treatments for dementia.

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<sup>55</sup> See European Commission, *Clinical Trials. General Information*, [http://ec.europa.eu/health/human-use/clinical-trials/information/index\\_en.htm#ct4](http://ec.europa.eu/health/human-use/clinical-trials/information/index_en.htm#ct4) [14 July 2015].