1. Introduction

So far, there is only limited empirical evidence on assessment of capacity to consent in dementia research, and most research groups have only limited experience with the development of informed consent procedures specifically adapted to dementia research. However, this area is getting more and more important, as dementia research is quickly expanding and numerous Alzheimer trials are being carried out. At the same time, legislation on biomedical research is becoming more and more complex and precise. Patients, Alzheimer societies, politicians, regulatory bodies, ethical committees and ethicists will critically monitor research protocols, and especially the consent procedures in forthcoming dementia research, because quality standards are not always met in research practice [1,2].

The approval of a study by the responsible ethics committee should guarantee, amongst others, uniform quality control of consent procedures. Unfortunately, this uniformity does not exist in current research practice. Ethical review boards vary widely, both between and within countries, in the assessment of informed consent procedures [1]. Moreover, in research in older participants, the consent assessment procedures are typically scarcely described, and detailed specifications are found in only very few papers [3]. In our survey of the literature [3], the frequency with which information on informed consent procedures by ethics committees were published was unexpectedly low, though the general public, editors of scientific journals, granting research councils, and patient organisations emphasise the importance of this topic.
Researchers, ethical committees, patients and families will profit from careful guidance, education and training on informed consent issues, because this enables them to sail safely between the Scylla of avoiding research with these vulnerable, cognitively impaired patients, and the Charybdis of carrying out medical research without sufficiently taking care of the protection of participants with dementia. This dilemma is exactly the incentive for this paper, which aims at giving a narrative review of the domain of informed consent issues in dementia research. We will first focus on the legal and theoretical background, and subsequently on empirical findings. The aim of this paper is to discuss rather than summarize the available evidence.

2. Legislation

International rules, such as the Declaration of Helsinki (last revision, 1989), the Nuremberg Code (1947) and the International Convenant on Civil and Political Rights of the United Nations (1966), require free and informed consent of all research participants. In the context of European harmonisation, some major documents have been signed: the Council of Europe Convention on Biomedicine and Human Rights (ETS 164), its Additional Protocol on Biomedical Research (ETS 195), and Directive 2001/20/EC on Clinical Trials on Medicinal Products, which together form the European legal informed consent framework. The latest directive is the recently amended version of the Guidelines for Good Clinical Practice (GCP). These guidelines are now formally accepted as EU Directive, after having been approved by the European Committee in December 2000. From May 2004 onwards, all EU countries started to implement them.

These rules and regulations agree that mentally incompetent individuals should not be included in research, with the exception of research that is judged necessary to promote the health of the population represented and which cannot be performed on legally competent persons. Such research should be possible only if the physical and mental condition that prevents obtaining informed consent is inherent to the research population. This is a basic request for all dementia research, on which there is wide consensus in research practice.

While this widely accepted legislation should improve and harmonise quality standards in dementia research, there are specific barriers to reach this goal. Firstly, implementation of the guidelines differs greatly across the EU countries, because of interaction with national legislation, resulting in hybrid procedures that may seriously hinder international multi-centre studies. Second, although the GCP guideline describes some clear procedures and restrictions for research on individuals who are incompetent to consent, this directive also introduces various terms that may be interpreted and implemented in many different ways (e.g., research ‘directly related to a debilitating condition’, ‘life-threatening condition’ and ‘grounds for expecting benefit’), and are often ill-defined. This may even increase the heterogeneity, instead of diminishing the differences in interpretation of informed consent procedures across Europe, both from the point of view of the ethics committee as well as the (medical) professional. Third, international legislation requires that individuals must give truly informed and free consent before participating in medical research. However, none of the countries involved has quality indicators to assess to what extent the legal and ethical standards are reached, nor issues penalties for not reaching sufficient quality.

In conclusion, despite great similarities between national laws and internationally accepted ethical codes, research practice is still highly heterogeneous, which especially concerns dementia research with respect to the complex issue of decline of capacity to consent [1]. To reach a more uniform approach, ethical committees and journals for example might require specific details of the informed consent procedures applied in research projects that included patients with dementia.

3. Theory of informed consent

Informed consent procedures depend on whether an individual is judged competent or incompetent to consent. The assessment of competency is required by the legal and ethical framework in which the research has to take place. The diagnosis of dementia does not mean that a person is by definition incompetent to consent for participation in any research [4]. Therefore, it is important in dementia research to be able to judge the capacity to consent on an individual basis.

Classically, what is at least needed for competent judgement is summarized as:

1. ability to receive and understand information;
2. ability to process information;
3. ability to appreciate the situation and its consequences;
4. ability to weigh benefits, risk and alternatives;
5. ability to make and communicate a decision.

Several instruments are available for the evaluation of competency to consent based on the specific clinical or research question that motivated assessment of capacity to consent, such as the Aid to Capacity Evaluation (ACE) [5] and the MacArthur Competence Assessment Tool (MacCAT) [6,7]. Other instruments are based on vignettes providing a hypothetical description of a research situation (or treatment situation), which include elements that are considered crucial in decision-making in (dementia) research in general [8]. This also reflects the major distinction in theory on informed consent assessment: on the one hand, one can make a judgement on capacity tot consent in general, on the other hand, one can only judge the ability for a very specific situation. We present some basic characteristics of assessment instruments reflecting this dichotomy (Table 1). Validity often is tested against expert opinion, as a real gold standard is lacking. Most instruments use scoring systems per ability tested (understanding, reasoning, appreciation, evidencing a choice etc), though also statistical cut-offs are used (e.g. two standard deviations below the control group).

Helping the individual to understand research information as fully as possible and checking whether the individual indeed understood the information, are the first prerequisites for a valid assessment of informed consent. Important conditions to reach these goals are: sufficient time for the information process, and information, which is compatible with the cognitive, visual and hearing capacities of frail older patients.

Diminished understanding of informed consent information is associated with older age and fewer years of education [9]. Also, older age is associated with decreased participation in research. In general, elderly patients and patients with below-average levels of intelligence, impaired cognitive functions, and an external locus of control have poor information recall of the important issues related to the research [10]. To explain to dementia patients the highly sophisticated research techniques that are currently used in medical research is a formidable task. The omnipresence of cognitive impairments in this population, often accompanied by visual, auditory and language deficits, constrains acquiring understanding and adequately weighing the information provided by the researcher. So far, most authors have focussed on the application of various kinds of visual and hearing aids, such as pictures, vignettes, storybooks and audio- or videotapes. However, Tymchuk and Ouslander showed that these aids proved a distraction rather than an aid for older people [11]. Educational
Different forms of assessing decision-making capacity in dementia research.

<table>
<thead>
<tr>
<th>Type of Instrument</th>
<th>Abilities of competence tested</th>
<th>Scoring range</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessing the real situation</td>
<td>Understanding</td>
<td>Yes, unsure, no</td>
<td>No cut-off: expert opinion</td>
</tr>
<tr>
<td></td>
<td>Evidencing a choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appreciation</td>
<td>0–6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reasoning</td>
<td>0–8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidencing a choice</td>
<td>0–2</td>
<td></td>
</tr>
<tr>
<td>Assessing hypothetical vignettes</td>
<td>Evidencing a choice</td>
<td>0–7</td>
<td>&lt;95% of control group</td>
</tr>
<tr>
<td>1. Assessment according to Schmand et al. [28]</td>
<td>Understanding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manipulate info rationally</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appreciation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Willingness to participate, reasoning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Assessment according to Sachs et al. [29]</td>
<td>Qualitative evaluation</td>
<td></td>
<td>No cut-off: expert opinion</td>
</tr>
</tbody>
</table>

Only weighing and evaluating the results of the formal assessment of the capacity consent combined with evaluation of the person’s emotions and mood, can result in a valid answer to the question whether an individual is fully competent to consent in the legal sense of the word. For example, cognitively mildly impaired patients with frontal lobe dementia may not be capable to consent, because of disinhibition of behavioural responses to the invitation to participate in research. In addition, the invasiveness, risks, and burden of an intervention on the one hand, and the profits of the study on the other hand, should be weighed carefully, to determine the level of capacity to consent needed for a study. The more risky and burdensome, the higher the required standards of consent should be. The more likely patients have profits and the lower the burden for the participants of a study, the lower the standards of capacity to consent may be. This is called the principle of proportionality for capacity to consent assessment [15], which is a cornerstone of proper research ethics (Table 2). This principle, illustrated in Table 2, probably is the key-point of this paper. One may intuitively think that capacity to consent should be higher for therapeutic than for non-therapeutic research, because the risks seem to be more important, thinking for example of the dramatic study with the active vaccination essay in Alzheimer’s disease. However, when risks and burden are equal (second column of the table), the level of capacity to consent required is lower when there is a reasonable chance that patients may have some profit from taking part in the study. This is for example the case for non-pharmacological interventions, which rarely require any risky intervention or investigation. However, (looking in the table within the row of therapeutic research) when therapeutic research is accompanied by considerable risk (e.g. vaccination studies) or a high burden (e.g. lumbar punctures, which are often used in monitoring the effects of inhibition of amyloid aggregation in drug trials), the level of consent required should be substantially higher. Patients should be more aware of the risks and burden and their right to stop the trial.

In genetic research, advantages and disadvantages are less certain and the impact on the patients’ family and other personal issues (e.g. insurances) may be higher, requiring an even higher quality of consent when the study as such shows equal risk and burden compared to therapeutic or other non-therapeutic studies (therefore genetics research is positioned lowest within the columns of Table 2).

Combining all these elements will guide the researcher in the dilemma of whether or not an individual with cognitive decline is capable to consent for a specific study. The first challenge is how to involve patients with cognitive decline as much as possible in decision making, despite decline or even absence of formal competency to consent, and second how to carefully monitor whether the behaviour of a participant unable to consent formally also confirms willingness to participate and does not show any objections and disapproval.

Despite these widely shared notions on informed consent in dementia, there are no well-accepted standards for uniformly determining capacity to consent [4,14]. Much has been published on the informed consent issue with regard to geriatric research and on specific subtopics, such as decision-making capacity, voluntariness, disclosure, understanding, consent forms, authorization policies, and others [4,9]. However, the scope of the present paper is not on consent procedures in geriatric research as such, but on informed consent in patients fulfilling the criteria for dementia.
4. Empirical data on informed consent

As mentioned before, the diagnosis of dementia as such is not informative for capacity to consent [4]. This is the most firm and important conclusion from empirical studies on informed consent. In fact, capacity to consent depends both on the cognitive capacity of the individual and the design of the study. For example, in a longitudinal study of healthy aging (n = 165) and mild dementia (n = 250), 92% of participants with mild dementia provided a sufficient number of correct answers for the test of capacity to consent [16,17]. Individuals in the early stages of dementia understood informed consent information for this non-therapeutic study [16]. However, understanding notably declined in the moderate stage of dementia. Because of the rapid decline in capacity to consent in participants with dementia, there is a great need for valid, reliable and efficient instruments and procedures to assess capacity to consent, which we will address next.

4.1. Instruments for assessment of capacity to consent

In her research, Vellinga et al. showed that all well-validated instruments used to assess competency to consent aim at covering the aforementioned criteria, though only few actually succeed in doing so [6,7,8]. The best validated instrument currently available is the MacArthur Competency Assessment instrument, which is available both for research aims and for clinical practice [18]. The MacCAT-CR is the instrument for the assessment of decision-making capacities to participate in clinical research. It was developed by Appelbaum and Grisso, with support from the Research Network on Mental Health and the MacArthur Foundation [6,7,8]. The MacCAT instrument is based on asking critical questions to the participant whose competency should be judged. These questions address understanding of the research information, reasoning, appreciation of the choices, and finally making a choice. The MacCAT-Clinical Research Version (CRV) is used in dementia research, psychiatric research, and adapted versions are available both for research aims and for clinical practice [18]. The MacCAT instrument consists of asking structured questions crucial for competency to consent, which can be applied in most consent procedures rather easily.

4.2. Consent in new research areas

Dementia research covers different topics, and both clinical trials on symptomatic and disease modifying drugs, as well as basic research (genomics, proteomics, metabolomics, cognitive neuroscience) are now rapidly expanding. Because of the changing content of dementia research, we have conducted a study on the impact of current research aims and methods on research ethics [21,22]. With regard to traditional biomedical research, a panel of expert respondents mentioned communication difficulties as one of the major barriers that need improvement in the informed consent procedure [21]. For trials, the protection of the patient and the possibility of different levels of consent for invasive (e.g., vaccination studies, parenteral drug application) or non-invasive research (oral drugs) were mentioned.

In genetic research, there is concern about the privacy of obtained research material. It was suggested that a special consent procedure for routinely taken genetic materials (e.g., DNA) should be developed. Also, a higher level of competence may be necessary for genetic research. There were three arguments for this claim. First, genetic research is more complex to interpret than traditional research, which makes it more difficult for possible research participants to make an adequate judgement of the consequences. Second, genetic research is still non-therapeutic, and therefore patients will not have personal benefit options, as potentially available in clinical trials. Finally, it was mentioned that in genetic research the risk for possible discrimination (e.g., in relation to insurance companies) may be higher, which would also suggest the need of a higher level of competence.

Proxy consent was a topic of interest in both drug trials as well as in novel biomarker (e.g., genetic) research. In epidemiological research, the active involvement of relatives as part of the data collection is a clear reason for ‘double consent’: consent is acquired from both patient and caregiver. In therapeutic drug studies and in non-therapeutic studies, proxy consent may be added and enforce informed consent of the patient, if the ethical committee judged the study would include patients who are not capable to consent. For genetic research panelists mentioned specific problems for proxy consent [22]. Family members might be motivated to include the affected relative in a research study to help clarify the impact of their own genetic burden. Therefore, it was questioned to what extent children are still able to make a decision in the best interest of the parent, because they may profit from the results of genetic research. The option of ‘family consent’, in which a whole family gives consent for participation in such a genetic study, may be a solution for this.

Currently the number of Alzheimer dementia (AD)-biomarker studies is also rapidly increasing. This rather easily available material, which can even be sold to drug companies or other stakeholders has its own pitfalls and requirements in informed consent issues. In a recent survey 54 memory research centres from the European Alzheimer’s Disease Consortium (EADC) (http://eadc.alzheimer-europe.org/introduction.html) were asked about practical and ethical aspects of biomarker collection in dementia diagnostics [23]. Centres had been selected as EADC member because of their expertise in clinical and basic research on Alzheimer’s disease and related disorders and their best practice representation of most European countries (18 members states are part of the EADC).

The survey had a 63% response rate. Although all centres reported that they obtained informed consent before collecting cerebro spinal fluid (CSF) biomarkers, the extent of consent taking was variable: 44% of the centres obtained separate consent for each biomarker to be collected, whereas 85% obtained informed consent for all possible future research use. Furthermore, 65% of the centres retained the ability to relate biomarkers to patients and more than half of the centres (59%) reported sending materials abroad for diagnostic and/or scientific reasons, for which the consent for all future use should cover sufficient approval.

From this survey we learn that there is wide acceptance of obtaining informed consent for collecting CSF and other biomarkers across Europe. However, medical-ethical procedures with respect to handling of these materials, such as asking consent for future use, the shipment of materials, and anonymisation of samples varied between centres. Although the clinical application of biomarkers as part of diagnostic criteria is yet only limited [24], the potential role of biomarkers in dementia is rapidly growing and likely to expand substantially over the upcoming years. The successful maturation of this biomarker-dominated era in Europe would therefore be facilitated by the development of an ethical guideline for acquisition of biomarkers in dementia research [25].

5. Synthesis of theory and empirical data

A sufficient quality of informed consent is needed to stimulate rather than frustrate dementia research. This means that a joined task force is waiting for researchers, journal editors, ethical review boards, politicians, grant givers and Alzheimer’s disease societies.
Alzheimer Europe made a clear policy standard on the research ethics in dementia research, including informed consent issues (http://www.alzheimer-europe.org/Our-Research/Understanding-dementia-research/Participating-in-research/Ethical-issues). Here, the challenge that researchers have to meet is to ask informed consent from individuals with dementia in accordance with current legal and ethical standards. Researchers will not only have to deal with informed consent dilemmas in drug trials, but more and more also in basic non-therapeutic biomarker research. Thus, drug companies, grant-giving bodies and researchers themselves have to invest money, time and effort in the acquisition of proper informed consent, and also in a more formalised and witnessed assessment of people’s capacity to consent.

Currently, based on this review of literature researchers may be advised to adopt a step-wise procedure, which starts with sufficient time and effort for transfer of information on the study aimed for. If feasible, a try-out of the measurements might help to improve understanding of the study procedures in participants with mild stage dementia and their relatives and/or caregivers. This may be important, because sufficient understanding of research information is prerequisite for weighing and appreciating the risks and benefits of a study. Consequently, proper weighing and genuine consent may help preventing high attrition rates. The next step consists of asking whether the fundamental information needed for informed consent is understood by a potential research participant. The quality and level of understanding that is required is determined by the risk and burden of the study on the one hand, and the (potential) profits on the other. Informed consent can be judged irrespective of the diagnosis made, but cannot be judged without valuing the complexity, societal relevance, risks and burdens and scientific importance of the research project.

Special precautions are necessary if the individuals with cognitive decline are judged to be incapable to consent and have not signed an advance directive in which they state their preference for participation in dementia research. For an individual who is under legal guardianship, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. This should even be added to a positive advance directive.

In general, apart from basic biomarker research, we advocate a dual or double consent procedure for therapeutic dementia research as well, in which the researchers acquire informed consent of the patient, if capable to consent, or assent (i.e., agreement as far as the study is understood and weighed) of the patients who are judged not (fully) capable to consent, in addition to verbal assent by proxy. Carrying out research with dementia patients without support of the caregivers, will probably result in high attrition rates.

A lot of terms are used to describe the procedure in which a third party (most often a relative) consents for someone else in the literature, like: ‘substituted judgment’, ‘proxy consent’ and ‘surrogate consent’. Although there may be differences between literature, like: ‘substituted judgment’, ‘proxy consent’ and third party (most often a relative) consents for someone else in the study is understood and weighed) of the patients who are judged not (fully) capable to consent, in addition to verbal assent by proxy. Carrying out research with dementia patients without support of the caregivers, will probably result in high attrition rates.

A lot of terms are used to describe the procedure in which a third party (most often a relative) consents for someone else in the literature, like: ‘substituted judgment’, ‘proxy consent’ and ‘surrogate consent’. Although there may be differences between them, the main characteristics are:

1. (1) that a person consents (partly) for someone else; (2) that this method of soliciting consent is used to extend the individual’s autonomy.

Several arguments can be given in favour of third-party consent. Most importantly, third-party consent respects the autonomy of the patient as much as possible. Proxies who are close to the patient are generally most knowledgeable about what the patient would have wanted [26]. Kim et al. showed for instance that respondents are cautious in their attitude, when they are responsible for their loved ones. Additionally, this study showed that valuing consent by proxy as important additional information was widely accepted among older persons [27].

In sum, researchers have to meet the serious challenge of an adequate informed consent procedure, in case they want to carry out studies on vulnerable individuals with cognitive decline or dementia. Apart from the obligations expressed by research councils’ and journals’ guidelines, researchers should be fully aware of the societal and scientific responsibilities they bear in this type of research with fragile participants. It is highly essential that relevant details of the assessment of capacity to consent and of special measures applied in informing elderly individuals are published as well. A good consent procedure in dementia research (like double consent) should be regarded as important as the research design, and the selection of the intervention or the outcome measures. Ethical research committees and the patients’ and carers’ societies should be contacted to join forces and to help researchers meet the great challenge of relevant, but at the same time ethically sound, dementia research.

Conflict of interest

None declared.

References


