Alzheimer Europe Report



The ethics of dementia research



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Preface

This report entitled "The Ethics of Dementia Research" provides a detailed discussion of some of the main ethical issues linked to carrying out dementia research in an ethical manner. It covers all kinds of research in the medical and social science domains. The recommendations at the end of each chapter are aimed at encouraging researchers to consider various ethical issues, some of which are not always immediately apparent.

The report is the result of a year's work carried out by a very active working group not only with experience in carrying out or participating in dementia research but also with professional expertise in the field of bioethics, the development of medical drugs, old age psychiatry, psychology, acute geriatry, neurology, social studies and end-of-life care. In addition, the working group benefited from the practical experience and valuable insight into dementia of a person with dementia, two carers (one of whom was also a lay member of a research ethics committee) and two representatives from national Alzheimer Associations in the Czech Republic and Germany. I would therefore like to offer my sincere thanks to the members of the working group who were (in alphabetical order): Peter Annas, Angela Clayton Turner, Julie Fraser, Thomas Frühwald, Dianne Gove (Chair), Fabrice Gzil, Iva Holmerová, Sabine Jansen, James and Maureen McKillop, Carlo Petrini, Rasa Ruseckiene, Sandro Sorbi and Lieve Van den Block.

We hope that this report will be of interest to researchers, people taking part in research and anyone with an interest in ensuring that dementia research is carried out in an ethical manner (e.g. those commissioning or funding research, ethics committees and Alzheimer associations). Many of the issues addressed are fairly complex. Although we have tried to present a balanced portrayal of current debates, we accept that people may have different views and that what is considered ethical today might not be considered as such in years to come.

We hope that this report contributes in some way towards the ethical conduct of dementia research but also serves as a basis for further discussion and debate on the very important issues that have been raised. I hope that you find this report interesting and thought provoking, and would welcome your thoughts and reactions to any of the topics covered.

Heike von Lützau-Hohlbein Chair Alzheimer Europe



The dementia ethics research project

1 The dementia ethics research project

1.1 Background to the project on the ethics of dementia research

This document is the second report produced by Alzheimer Europe in collaboration with a team of experts in the framework of the European Dementia Ethics Network (EDEN), which was set up in 2009. The aim of EDEN is to discuss ethical issues of relevance to people with dementia within a multidisciplinary group of experts including people with dementia and carers in order to present the ethical issues related to specific topics for further reflection, along with a set of recommendations reflecting the position of Alzheimer Europe. Each year, Alzheimer Europe will address a different topic. In 2010, recommendations were produced on the ethical issues linked to the use of assistive technology for and by people with dementia. The topic of this year's report is the ethical issues linked to dementia research.

1.2 Goals and objectives

The overall goal of the working group was to produce recommendations and a position on ethical dementia research through a process of reflection and group discussion. The group had three specific objectives:

- To provide an overview of past and current ethical debates about issues linked to various aspects of dementia research,
- To explain its position,
- To provide recommendations, where possible, on a range of issues linked to dementia research.

It is clear that such recommendations need to be applied to particular situations involving particular people because situations and people develop and change over time. For example, the ethical issues linked to the use of advance directives for research have only come into being in recent years as before that, such directives did not, and in many countries within Europe still do not, exist. Attitudes also change and thanks to the progress of both the dementia and the disability movement, people with dementia are no longer considered as passive recipients of care and treatment but rather as active participants with the same rights as other members of society. Such rights include the right to be treated with respect, the right to privacy and protection and also the right to participate in research.

These recommendations were developed within a particular cultural context and historical period. Such debates do not occur once and for all, resulting in clear instructions on how to behave thereafter. Hopefully, the paper will promote further discussion and encourage people to approach dementia research in a thoughtful and morally responsible way, based on an understanding of the main ethical issues involved, even or especially in the absence of clear legal obligations.

1.3 Acknowledgements

The members of the working group to whom Alzheimer Europe is immensely grateful for developing these recommendations and contributing towards the position of Alzheimer Europe are (in alphabetical order):

<u>Dr Peter Annas</u>, Senior Research Scientist, PhD. and AstraZeneca's representative in the PharmaCog project (and co-leader of the Ethics work package in the same project).

<u>Ms Angela Clayton-Turner</u>, volunteer, carer and involved in selecting, monitoring and disseminating research for the Alzheimer's Society and in ethical procedures for brain donations for research. She is also a lay member of her local Research Ethics Committee.

Ms Julie Fraser, Editor, Dementia in Europe Magazine.

<u>Dr Thomas Frühwald</u>, Senior physician of the Department of Acute Geriatry of the Hietzing Hospital in Vienna, Austria. Committee member of the Geriatric Medicine Section of the European Union of Medical Specialists. Board member (Vice President) of the Austrian Society of Geriatrics and Gerontology.

Ms Dianne Gove, Information Officer at Alzheimer Europe, Luxembourg.

<u>Dr Fabrice Gzil</u>, Head of Social Studies Department, Fondation Médéric Alzheimer in Paris, France. He recently produced ethical guidelines for researchers interested in obtaining funding for social sciences research.

<u>Associate Professor Iva Holmerová</u>, Charles University, Centre of Gerontology in Prague, Czech Republic.

Ms Sabine Jansen, Executive Director of the Deutsche Alzheimer Gesellschaft e.V. (the German Alzheimer Society).

Mr James McKillop (MBE) and Mrs Maureen McKillop. James has taken part in several research studies and has been a member of several working groups within Alzheimer Europe (including the last ethics project). He is a founding member of the Scottish Dementia Working Group. James has dementia and Maureen is his wife and carer.

<u>Dr Carlo Petrini</u>, Head of the Bioethics Unit of the National Institute of Health in Rome, Italy.

<u>Dr Rasa Ruseckiene</u>, Consultant in adult and old age psychiatry, therapist, work experience in UK psychiatric hospitals, involved in project to promote psychiatric services in Lithuania.

<u>Prof. Sandro Sorbi</u>, Professor of Neurology, Department of Neurological Science and Psychiatry at the University of Florence, Italy. He is responsible for coordinating the new EFNS guidelines on dementia with a section on the ethics of research.

<u>Prof. Dr Lieve Van den Block</u>, senior founding member of the End-of-life care Research Group of Ghent University and the Vrije Universiteit Brussel and Professor of Communication and Education in Family Medicine at the Vrije Universiteit Brussel, Belgium.

Alzheimer Europe would also like to thank Prof. Mary Marshall (Emeritus Professor at the University of Stirling, Scotland) for commenting on the draft texts.

1.4 Structure of the report

The aim of the next chapter is to set the scene by providing a brief overview of some of the important concepts linked to the topic of ethical dementia research. We explain, for example what we mean by research, what kinds of research are carried out, what we mean by dementia research and ethical dementia research and how ethical principles and models can be applied to specific issues like dementia research.

The remainder of the report is structured firstly, around key relevant issues and secondly, around a few specific types of research. Each of these chapters has three sections: 1. a brief introduction about the issue or area of research, 2. a discussion/presentation of the main ethical issues identified and 3. a list of recommendations.

The structure is designed to help the reader find his/her way through the text, maybe jumping to some sections of particular interest and then back to others, rather than reading the report from start to finish as one might read a novel. Many of the issues discussed are relevant to more than one section of the report. To avoid too much repetition, they have been largely confined to one topic area but this is admittedly an artificial separation of related issues.

The report is targeted at a wide audience covering everyone who might be directly or indirectly involved in research. Although these issues may be of interest to people with dementia themselves, this particular format and style of presentation may not be ideally suited to people with dementia who might have some difficulties with language, concentration and memory. For this reason, a summary of the main recommendations of relevance to their possible participation in research will be summarised and put on the Alzheimer Europe website.



Background, definitions and scope

2 Background, definitions and scope

2.1 What is research?

Research is a general term which covers all kinds of studies designed to find responses to questions by means of a systematic and scientific approach. It generally involves the use of predefined methods or procedures which are clearly documented, thereby making it possible for other people to understand exactly what the researchers did to arrive at their conclusions. In this way, the results and conclusions can be assessed and analysed in terms of relevance and accuracy, bearing in mind any limitations or factors which the researchers may have highlighted.

Simply asking for somebody's opinion about a particular issue or asking them to indicate their preferences is not research as it lacks the systematic and scientific approach described above. Also, as will described later in the report, people who participate in research must have been provided with detailed information about the study and, on the basis of that information, have consented to taking part (please see section 4 on informed consent).

2.1.1 Different types of research

method development

There are numerous types of research but a distinction is often made between medical research and social science research (particularly psycho-social research). Examples of medical research might, for example, include animal experimentation, genetic research and clinical trials of new medicinal products. Such research tends to draw mainly on the "natural sciences" such as biochemistry, physics and biology. Figure 1 below provides an example of different types of medical research.

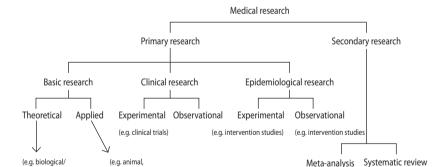
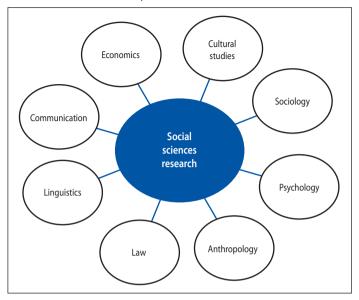


Figure 1: Different types of medical research (main source: Röhrig et al., 2009)

cell and genetic studies

Social science research, on the other hand, covers studies which focus on some aspect of society. It generally involves exploring, verifying or conceptualizing a particular social phenomenon or aspect of human life or behaviour. It has its roots in several fields of scholarship outside of the natural sciences. Figure 2 shows some of the main social science disciplines.

Figure 2: The main social science disciplines



Whilst some studies are clearly medical or social science research, the distinctions are sometimes blurred as researchers increasingly recognise the benefits of multi-disciplinary research. For example, medical researchers may want to explore psychological responses to various treatments and therefore adopt methods more typically associated with social science research (more information about different methods can be found in sub-section 2.1.3). It is therefore important to realise that there are, broadly speaking, two types of research but that there may be some overlap. Also, as researchers come from very different scholarly fields, they may approach research from different angles and have different perspectives of research.

2.1.2 World views guiding research

Researchers have different world views or belief systems which guide them in their research, influencing the decisions they make about how to conduct their studies, what counts as valid knowledge, what is the right way to obtain that knowledge, how it should be analysed (e.g. using quantitative or qualitative-based methods), and what their own role is in the process (Ritchie and Lewis, 2003; Tashakkori and Teddlie, 1998).

The various approaches to research are sometimes called research paradigms. The most common are perhaps positivism and interpretivism, which are generally associated with quantitative or qualitative methods of data collection and analysis, respectively (Snape and Spencer, 2003). In the past, there was considerable debate about which approach was "right" and some people argued that the two approaches were incompatible. For many years, the positivist paradigm was dominant and there was a tendency to judge the quality of research on the basis of whether it respected criteria applicable to the posi-

tivist tradition such as the researcher not having any influence on the data collected and whether the findings could be reproduced if the exact same procedure was carried out.

Nowadays, it is generally accepted that both approaches are valid and have their advantages and disadvantages. Principles of scientific integrity and procedure apply to research guided by both paradigms and include issues such as honesty, transparency about the procedure and a systematic approach to data collection and analysis, as well as avoiding misconduct such as the falsification or misrepresentation of findings, plagiarism and undeclared possible conflicts of interests (Aita and Richer, 2005).

Consequently, there is a third paradigm, that of pragmatism, in which the method used is that which appears to be suited to the research problem without getting caught up in philosophical debates about which is the best approach (Patton, 1990). Pragmatic researchers grant themselves the freedom to use any of the methods, techniques and procedures typically associated with quantitative or qualitative research. They recognise that every method has its limitations and that the different approaches can be complementary. Other researchers may adhere rather rigidly to methods associated with a specific research paradigm.

2.1.3 Qualitative and quantitative research methods

Qualitative studies concentrate mainly on words and meanings and aim to capture the richness and complexity of human experience, whereas quantitative studies involve recording or converting information obtained from participants in numerical form so as to enable statistical analysis of the findings and the generalisation of those findings to the wider population.

In quantitative studies, particularly those involving the development of medication or the use of experiments or large-scale surveys, one of the aims is to be able to generalize the findings (i.e. to infer that the findings can, to a high degree of probability, be considered as applying to a much wider group of people than those involved in the actual study). In other words, conclusions may be drawn about preferences, attitudes or the effects of a particular drug on people with dementia based on the information obtained from the group of people who participated in the study. This might range from a couple of hundred to over a thousand people depending on the type of study. Hypotheses are formulated (i.e. precise, carefully worded questions, which state a predicted outcome as well as the possibility that the outcome might not occur). By means of statistical analysis of the findings, the researchers determine with what degree of certainty they can claim that the findings could not be due to chance. Such studies are often referred to as quantitative studies.

Qualitative studies, on the other hand, generally involve recording, analysing and attempting to uncover the deeper meaning and significance of human behaviour and experience, including contradictory beliefs, ambiguities, behaviours and emotions. Researchers carrying out such studies are interested in gaining an in-depth understanding of people's experience and not in obtaining information which can be generalized

to other larger groups. They usually clearly identify a problem or topic that they want to explore, may be guided by a theoretical lens (a kind of overarching theory which provides a framework for their investigation) and formulate research questions. The approach to data collection and analysis is methodical but allows for greater flexibility than in quantitative research. Data is collected in textual form on the basis of observation and interaction with the participants, e.g. through participant observation, in-depth interviews and focus groups. It is not converted into numerical form and is not statistically analysed.

2.2 Dementia and dementia research

Dementia is an umbrella term used to describe conditions which cause brain cells to die and lead to the gradual and progressive deterioration of memory as well as to changes in mood and personality. The gradual and progressive deterioration of cognitive functions, which is characteristic of dementia, such as memory, reasoning and planning, affects people's capacity to carry out various activities such as getting washed and dressed, finding their way around, preparing meals and handling money etc. (Graham and Warner, 2009; Alzheimer Europe, 2011). The most common type of dementia is Alzheimer's but there are numerous other types. Vascular dementia and dementia with Lewy bodies, for example, are also quite common and some people may have a combination of different types of dementia.

It is important to note that a person who has been diagnosed with Alzheimer's disease (AD) also has dementia (because AD is a type of dementia). On the other hand, a person who has been diagnosed with dementia does not necessarily have AD because they may have a different type of dementia. However, the whole issue of the medical labels applied to people with dementia is likely to change soon as there have been proposals to replace the term "dementia" with the term "major neurocognitive disorder" in the forthcoming DSM-V (the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association). It is further proposed to label different types of dementia as being conditions associated with neurocognitive disorder (e.g. major neurocognitive disorder associated with Alzheimer's disease) (American Psychiatric Association 2010).

Not all difficulties experienced by people with dementia can be attributed to the death of brain cells. According to the disability model, many of the problems faced by people with disabilities (including people with dementia) are due to the rather rigid and inflexible way that society is organised, which creates "excess disability". Excess disability is defined by Brody et al. (1971) as "The discrepancy which exists when the individual's functional incapacity is greater than that warranted by the actual impairment. In short, it denotes a gap between actual function and judged potential function" (pp. 125-126, in Werezak). Similarly, Kitwood (1993), whilst not denying the medical aspects of dementia, drew attention to a range of factors which might affect the progression of dementia including psycho-social factors.

Dementia research could be defined as any kind of research aimed at increasing the understanding of the disease biology and of disease prevention or improving the treatment, care, wellbeing and quality of life of people with dementia either directly or indirectly. This might include research into the condition itself, into the experience of having dementia or into care and treatment. People participating in dementia research (hereafter referred to as "participants") are usually people with dementia, informal carers or professional carers but in some cases could be people without dementia and other specific groups. For example, researchers might be interested in learning about the attitudes, knowledge or fears about dementia of the general public or student nurses.

2.3 Ethical dementia research

2.3.1 Determining what is ethical

Research should have scientific validity in the sense that it should be methodologically rigorous. It should have value in that it should be expected to result in health or knowledge advancement and it should involve minimum risk and have been independently reviewed (Emanuel et al., 2000). These are ethical concerns which apply to the whole research process from the initial choice of a research topic right up to the publication of results and the provision of feedback to participants, and will be addressed in more detail in various sections of this report. Ethical research must be based on morally sound principles and not on expediency (i.e. what is best for the researcher, sponsors or the government). The main focus of this document is on ethical issues in dementia research. By this, we do not mean dementia research carried out by ethicists but rather all kinds of research into dementia (e.g. medical, psychosocial, the development of assistive technology etc.), which is carried out in an ethically acceptable manner.

2.3.2 Different ethical models

There are different ways of determining whether a particular act is ethical (i.e. if it is morally acceptable to do it). This involves reflection about which actions are morally "right" and "wrong", bearing in mind that good motivations may lead to wrong actions and that bad motivations do not rule out actions which are considered right. Dilemmas may occur whereby it is necessary to decide on a particular course of action rather than another and in so doing to give greater weight to certain moral concerns at the expense of others.

Some approaches to ethics focus on the outcome. This might involve judging whether the consequences of the act are good or bad (Noble-Adams, 1999) or what the best outcome would be for the greatest number of people (Peach, 1995 in Aita and Richer, 2005). In the <u>utilitarian approach</u>, for example, which was formulated by Bentham and Mill in the 19th century, actions are considered as right if they are likely to promote the greatest happiness for the greatest number of people. Actions likely to result in the opposite would be considered as "wrong". Evaluations of the various outcomes tend to focus on pain and pleasure. However, as pointed out by Petrini (2011), this approach only considers the amount of good and not the way in which it is distributed.

Furthermore, there may be more than one issue at stake and it would be difficult to measure maximum happiness. Maximising happiness may even conflict with other values such as justice, fairness, solidarity and honesty. In addition, there are a lot of different actors ¹ directly or indirectly involved in or affected by research such as health and social care providers, pharmaceutical companies, shareholders, people in search of a cure or better treatment, researchers and academics, insurance companies and future generations. This means that there are a lot of different interpretations as to the value of different outcomes as well as different motivations driving action and different opinions about the importance of particular ethical principles.

Other theorists consider whether the nature of an act is right or wrong irrespective of the consequences because something is believed to be good if it is consistent with moral rules and principles. This is often described as a <u>deontological theory</u> and a classic example is Kant's theory. He stated that as man² is a moral agent, he is responsible for his actions. They are intrinsically right or wrong. Critics argue that the consequences of actions should not be ignored (Petrini, 2011).

Some people believe that ethical principles are universal (ethical universalism) whereas others take the view that such principles are related to a specific culture or individual choice (ethical relativism) and hence not generalizable to people with different cultural beliefs (Pojman, 2002). The latter has also been referred to as communitarian ethics which maintains that moral thinking has its origins in the historical traditions of particular communities and that consequently, it is a cultural rather than abstract concept in that communities share values, customs, institutions and interests (Petrini, 2011). Aita and Richer (2005) suggest that this approach is particularly important in the case of multi-site studies and healthcare research involving multidisciplinary collaboration. However, even research at a single site may involve people from different cultural backgrounds and both researchers and participants with diverse ethical perspectives. On the other hand, an over-emphasis on communitarian ethics might result in a "tyranny of the majority" in which the majority defines what is beneficial, morally right or "a good life", which may result in an unfair outcome for some groups of people (Petrini, 2011).

Contrary to approaches which focus on the majority or the community, "personalism" strives to achieve common good by promoting and enhancing the good of the individual guided by values such as respect for life, sociality and solidarity, and responsibility (Petrini, 2011).

2.3.3 Applying various ethical models to specific issues

In our previous work on the ethical issues linked to the use of assistive technology (AT) by and for people with dementia, Alzheimer Europe decided against developing a hierarchy of ethical principles or basing decisions solely on outcomes or motives. We opted for an approach to making decisions about the ethical use of AT based on a careful consideration of specific aspects of each decision needing to be made (set in a particular moment in time and place, involving a range of actors and relationships, and people with different needs, wishes and interests) but with an emphasis on the wellbeing of the person with

22

¹ Definition of actor = one who does something or who takes part in any affair.

^{2 &}quot;man" should be understood as meaning human beings (i.e. men and women). The term is used here simply to reflect the language usage at the time the statement was made.

dementia. This inevitably involves a consideration of principles, motives and outcomes and ensuring that we do not lose sight of individuals with dementia.

In the case of the ethics of research, there are different issues at stake. There is a need to reflect simultaneously on the wellbeing and happiness of the individual research participant as well as on that of the wider social group and future generations who stand to benefit from the research. The fact that many people participate in research with the aim of helping others does not lessen the need to protect their wellbeing and promote their happiness.

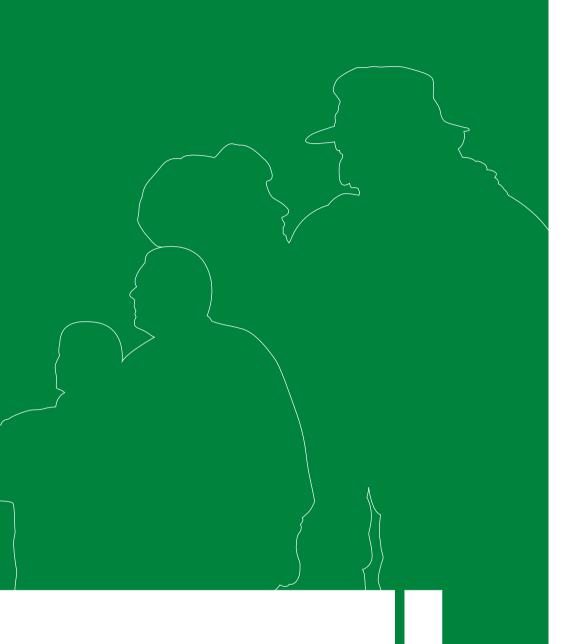
Some of the ethical models mentioned above might seem fairly contradictory and one might wonder how a working group made up of people from different professional and personal backgrounds and with different perspectives about dementia, research and ethics could come to any kind of consensus. However, a pragmatic approach to the topic of dementia research and a common concern about the wellbeing of participants in such research makes this possible.

According to Petrini (2011), pragmatic and utilitarian approaches are quite common nowadays. However, when faced with practical problems, it is possible to adopt a case-by-case approach, find common ground and reach a consensus. The core value is the individual and personalism (described in the previous sub-section) is the best approach to face ethical problems.

2.4 Researchers and the ethical conduct of research

In the case of research, we also need to consider the researchers themselves. Researchers come from a wide range of backgrounds and despite their common interest in research have a wide range of personalities and characters. They are not ethical or unethical *per se* but may conduct research ethically or unethically. Certain personality traits, such as integrity, trustworthiness and honesty, may increase the likelihood of researchers conducting ethical research but sometimes unethical conduct may be linked to lack of knowledge or awareness.

Beauchamp and Childress (2001) considered the relevance and desirability of five virtues for health professionals. These included compassion, discernment, trustworthiness, integrity and conscientiousness. They also considered the ethics of care which focuses on relationships involving care, responsibility, trust, fidelity and sensitivity with particular reference to the doctor-patient relationship. In some forms of research, researchers strive to maintain a certain distance from participants in order to minimise the possibility of influencing the kind of data collected whereas others approach data collection more from the perspective of a collaborative act involving the social (re)construction of meaning. Either way and even in the absence of a relationship based on the provision of care, researchers have responsibilities towards participants and should be trustworthy and sensitive to their needs.



Involving people with dementia

3 Involving people with dementia

3.1 Background information about involving people with dementia

Involving people with dementia in all aspects of research is increasingly recognised as being essential to good dementia research. Their involvement as research participants is of paramount importance and recognised as a significant contribution to society. This also reflects their value within society and their equal right to participate in research.

However, research is no longer simply carried out "on" people with dementia but also "with" them. They have a valuable contribution to make to the selection of research topics, the design of studies, issues related to recruitment and those linked to the interpretations and dissemination of the results. This involvement again reflects their value and is recognition that having dementia means possessing certain knowledge and experience that researchers are interested in learning about. It also reflects changing perceptions within society about people with dementia and the practice of social inclusion.

As people with dementia are equal members of society, they have views to share about a wide range of issues, in the same way as do people with diabetes, cancer or no health problems at all. People with dementia, as the term implies, "have dementia" but each person is different (e.g. might be a public transport user, go shopping, be an ecologist, enjoy skiing etc.) and has something to contribute towards society. The topic of this report is dementia research but clearly, people with dementia should not be excluded from taking part in research about other topics of interest to them just on the basis of their diagnosis.

It is also important to understand that people with dementia are not a homogenous group. Whilst they all have dementia, they are of various ages (but mainly older people), from different cultural groups and social classes and with different levels of education etc.

The term "older people" requires some explanation. Old age is often associated with retirement age but this may be misleading. Retirement, which was initially introduced in Germany by Otto von Bismark in the 1880s, was fixed at 65 as in those days life expectancy at birth was extremely low (Schulz, 1988). Most people therefore worked until they died and very few actually received a pension. With the exception of a few countries (i.e. Norway and Germany), this is still the retirement age in most countries in Europe even though life expectancy is now considerably higher. The term "old-old" is sometimes used to refer to people who are extremely advanced in age. On the other hand, with the cultural emphasis on youth in modern Western society, the term "senior" has been introduced which is usually understood as denoting a person over the age of 50 (and presumably under 65). In the ICH guidelines produced by the European Medicines Agency (EMA³) (1994), the geriatric population is defined as being comprised of people over the age of 65 with further reference being made to an even older population comprised of people over the age of 75. Nevertheless, the mean age in geriatric wards is now 80 to 83 years (European Forum for Good Clinical Practice, 2012).

Consequently, when discussing the involvement of older people in research, it is important to bear in mind that we are covering a very wide range of people aged from the albeit arbitrarily defined age of 65 onwards right up to centenarians. Most people who have dementia are over the age of 65. Both prevalence rates and the incidence of Alzheimer's disease increase dramatically with age, particularly in the 75+ age group.

On the other hand, there are many people with dementia under the age of 65. This number may increase in line with an increase in early diagnosis but also due to the ageing of groups with a relatively high risk of dementia such as those with intellectual difficulties (especially Down's syndrome) and those with head injuries. There are groups of people represented in the population of people with dementia such as people from ethnic groups, those with intellectual disabilities and lesbian, gay, bisexual and transsexual (LGBT) people etc. People with dementia from all walks of life have the right to be involved in research.

3.2 Ethical issues linked to involving people with dementia

3.2.1 Letting people with dementia speak for themselves

Barriers based on communication and understanding the nature of dementia Even a decade ago, relatively few people with dementia were involved in dementia research (other than clinical trials). Early diagnosis was less common and people were often not informed of the diagnosis. The views and experience of people with dementia were mainly obtained via proxies, mainly carers. This may have been due to negative perceptions of older people, the presumption that they were incapable of communicating their thoughts and feelings and an over-medicalized understanding of the experience of dementia (Hubbard, Downs and Tester, 2003).

The assumption that people with dementia are not capable of communicating their views, feelings and opinions has since been challenged by researchers (Barnett, 2000; Keady, Noland and Gilliard, 1995; Goldsmith, 2002; Wilkinson, 2002). It has also been challenged by people with dementia themselves who have taken part in research, published articles and books, and made speeches at high level European and international conferences (Davis, 1989; McGowin, 1993; McKillop, 2010, 2011). Whilst people with dementia may experience certain difficulties, there may be a tendency to overemphasize "problems" and underestimate the remaining capacities that people have. Talking about her first experience of interviewing older people with dementia, Elisabeth Barnett commented:

"It was quite a shock to discover just how "unproblematic, they actually were. Having arrived freshly armed with new techniques for interviewing confused elderly people, I was confused myself to find that the clients appeared not to be so! (..../....) I became decidedly uncomfortable and wondered if, in fact, their diagnoses were correct, or if everything I thought I knew about dementia was incorrect. In fact, I had

merely discovered the enormous range of variation in ability/disability that "dementia" covers" (Barnett, 2000, p. 49).

Unfortunately, not all researchers have sufficient knowledge of dementia or the openness and self-reflection needed to look beyond stereotypes and misconceptions about complete and global incapacity.

Others may be keen to involve people with dementia but lack the knowledge and necessary skills to involve people with moderate or more advanced dementia. This may result in a disproportionate number of people with early dementia in studies and a lack of research on issues of relevance to people in the more advanced stages of dementia. The increased difficulty in involving the latter results in a lack of equity and a failure to address issues of particular importance for people at different stages of dementia.

Overprotection – balancing risk and benefit in relation to inclusion

One of the reasons for involving proxies instead of people with dementia themselves is that the person with dementia might find the research process disturbing. This may sometimes occur but the solution is not necessarily to exclude people with dementia from research or replace them with carers, but rather to look for ways to reduce the likelihood or consequences of harm (e.g. by having a counsellor available). Methodological issues must be considered in order to make this possible.

An overemphasis on possible harm may lead to the possible benefits of participation being overlooked. Commenting on his own experience of participating in research, McKillop (2011) draws attention to the feeling of empowerment that can result from participating in research and the long-term benefits to other people with dementia. Hellström et al. (2007) conclude that there are serious consequences to not including people with dementia in research and suggests that the question should be not so much whether people with dementia should be included in research, but rather how can we best achieve this and how can we afford not to.

3.2.2 Involving older people in research

The need to involve older people in research

The need to avoid excluding people from clinical research solely on the grounds of age was recognised over 20 years ago, first by the American Food and Drugs Administration (FDA, 1989) and a little later by the European Medicines Agency (EMA):

There is no good basis for the exclusion of patients on the basis of advanced age alone, or because to the presence of any concomitant illness or medication, unless there is reason to believe that the concomitant illness or medication will endanger the patients or lead to confusion in interpreting the results of the study. (FDA, 1989)

Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug. (EMA, 1994)

Clearly, this practice is not yet widespread as highlighted in a paper produced by the European Forum for Good Clinical Practice (EFGCP) entitled "Medical research for and with older people in Europe: proposed guidance for ethical aspects" (EFGCP, 2012)⁴.

Are older people involved in research?

There is evidence that older people are notably absent from research, particularly clinical trials and pharmacotherapy research (Orwig et a., 2011; Van Spall et al., 2007)). For example, a search of two well-known research databases (PubMed and CINAHL) revealed that only 3 to 6% of clinical trials were based on older populations only (National Center for Biotechnology Information, 2010; EBSCO Publishing/Orwig et al., 2011). Consequently, clinical trials sometimes involve participants who are not representative of those for whom the medication is most likely to be used (Heait et al., 2002).

A comparison by Beswick et al. (2010) of the mean age of participants in 14 randomised control trials of cholinesterase inhibitors, as reported by Birks (2006) in a Cochrane review, revealed that only in three was the average age over 75 (and over 86 in one) and in six, the average age was 73. According to Beswick et al. (2010), the literature on the age of older people in clinical trials for Alzheimer's disease is limited but for clinical trials to be truly representative, they should include a large percentage of people between the age of 75 and 90. In another review of 109 clinical trials of therapeutic interventions in adults, assessing morbidity or mortality, it was revealed that 20% of studies automatically excluded patients above a certain age (Zulman et al., 2011).

On the other hand, there have been a number of initiatives involving older people such as the many longitudinal and retrospective studies in which their participation has been valuable. An example of an on-going study involving older people is that of the Alzheimer's Disease Neuroimaging Initiative (ADNI) whose aim is to explore changes of cognition, function, brain structure and function, and biomarkers in older controls, in subjects with mild cognitive impairment, and in subjects with AD (Weiner, 2011). The "nun study" is a good example of the inclusion of older people in research. This was a longitudinal study into healthy ageing and dementia involving 678 Catholic sisters aged between 75 and 107 (Snowdon, 2003). It involved examination of archives, annual examinations and a post mortem analysis of the brain.

In psychosocial studies too, researchers are increasingly aware of the need to involve older people and to avoid discriminating on the basis of age. Hubbard et al. (2003) draw attention to the importance of both verbal and non-verbal communication when trying to involve older people with dementia in research. Sometimes age is associated with a more advanced stage of dementia. They caution against categorising people into different stages, suggesting rather the need to focus on specific impairments and to use methods suited to the individual, irrespective of the duration or severity of dementia.

General barriers to participation

Possible barriers to the involvement of older people in research of all kinds include physical and cognitive impairments, lack of transport, a lower threshold for burden,

distrust, changes in routine and negative beliefs about medication (Modey et al., 2008; Orwig et al., 2011). However, such factors do not apply to all older people and are not limited to older people. Suggesting that they do would amount to stereotyping. Higher costs linked to the recruitment and maintenance of older people in studies have also been cited as possible barriers to their participation in research (Cherubini et al., 2010).

With the necessary time, effort and perhaps financial investment, such factors could often be overcome. Adherence to recruitment methods and study protocols, which do not take into account the specific needs of older people (with or without dementia) as well as failure to build in additional costs into the design of studies for the recruitment of older people, could be considered as examples of ageism and structural discrimination. This is also not in keeping with the principles of dignity, respect and social inclusion.

Specific issues linked to the exclusion of older people from clinical trials

Failure to include older people in clinical and epidemiological studies may lead to inequities in healthcare (Choo, 1994). However, it has been suggested that people with poor health and older people may be particularly difficult to recruit in clinical trials. As Prof. Tom MacDonald from the University of Dundee's Medicines Monitoring Unit points out, "We can't get the people who are unhealthy to take part, and we can't get older people to take part. But they are the ones who need all the drugs" (quoted in Reynolds, 2001, p. 1338 – BMJ, 342, 2011).

The difference between older people and younger people participating in clinical trials is not simply numerical (i.e. the number of years' difference in age). Rather, it is the implications or consequences of age which are often perceived in a negative light due to comparison with the socially defined norm of the younger person. There may be differences between younger and older people with regard to:

- adherence (whether the person actually takes the medication as recommended),
- adverse reactions,
- pharmacokinetics and pharmacodynamics (biological effects in this case linked to age, e.g. affecting metabolism and sensitivity to medication),
- comorbidities (having additional acute illnesses and chronic conditions such as dementia),
- polypharmacy (increased use of medication/older people taking several different drugs each day) (EFGCP, in press; Orwig et al., 2011).

The above age-related differences often contribute towards the exclusion of older people from clinical trials. However, these are the characteristics of the majority of older people who will eventually be taking the drugs which hopefully will result from the clinical trials from which they were excluded. They are not the characteristics of the majority of those who took part in the study.

Another possible reason for excluding older people from clinical trials is that their inclusion might dilute the active treatment effect, thereby resulting in results which are not statistically significant (Cherubini et al., 2010). This has obvious implications for the development of marketable drugs but at the same time for fairness to the hundreds or thousands of participants who dedicate their time and energy to a study which may be inconclusive. Nevertheless, Sox and Greenfield (2009) criticise randomised clinical efficacy trials for attempting to create near ideal circumstances in order to determine whether the intervention could possibly work as this may result in many people (e.g. older people with comorbidities) being excluded and does not reflect the conditions in real clinical practice.

The scientific validity of research into the use of existing or experimental drugs which have not been tested on the populations using them is questionable. As Loewy (2007) points out, it would be inappropriate scientifically (and hence unethical as good ethics must start with good facts) to extrapolate the conclusions of a study based, for example, on 20 to 30-year-old white males to a 70-year-old black woman. People with dementia are entitled to have access to drugs which were tested on people of a similar age because the physiology of younger people (even younger people within the older age group) is likely to be different and therefore side effects and tolerability may be different. The EFGCP recently advised that all medicines "be tested on our real, very old, frail and multimorbid patients" (2012, p. 5). They further suggest that extrapolation on other patients and conditions is scientifically unsound and has to be abandoned as soon as possible.

If older people with dementia are excluded from research, they are denied the same opportunity as other members of society to participate in and contribute towards society, to express their views and ultimately, to benefit from drugs which have been scientifically tested on people with similar characteristics to themselves (contrary to most other groups in society). This is not in keeping with the principles of equity, solidarity and autonomy, and amounts to exclusion and discrimination. However, there is a growing awareness of the need to include them and of their right to be involved.

Areas where appropriate research involving or of relevance to older people is lacking

An important avenue of research, currently being developed, is that of pharmacogenomics. Pharmacogenomics is the field of research which focuses on the effect of genes on individual responses to medicines in terms of effectiveness and toxicity. For this reason, some pharmaceutical companies collect DNA samples which they then analyse alongside the results of clinical trials. This has led to advances, for example, in the effective treatment of HIV (where a genotyping kit has been developed) and in the domain of cancer (in connection with the breast cancer drug Herceptin®) (NIGMS, 2011). Further progress is needed in conditions predominantly affecting older people (e.g. in the domain of neuro-degenerative diseases such as dementia).

Another area of research attracting interest is comparative effectiveness research, which compares different available treatments or examines their impact on particular subpopulations such as people with other existing medical conditions or of the same age,

sex or ethnic group as a particular patient. This can be helpful because as Tinetti and Studenski (2011) point out, there are an infinite number of combinations of diseases and treatments and this makes the identification of a truly representative population very difficult. Comparative effectiveness research can be meaningful to doctors when trying to make a decision about or with a specific patient, particularly when treatments which are effective for one condition may exacerbate another condition in the same patient (Tinetti and Studenski, 2011; Institute of Medicine of the National Academies, 2009).

Pharmacogenomics and comparative effectiveness research are relatively new areas of research which could be beneficial to older people with dementia. In the interests of equity but also to avoid age-based discrimination, adequate funding must be provided for this particular population.

Reactions of patients towards failure to include older people in research

The PREDICT study (2000), which aimed at increasing the participation of older people in clinical trials, investigated how the low number of older people involved in such research was interpreted by lay people. A series of focus groups were held in which people with stroke, depression, heart failure, cancer, diabetes or dementia and their carers were asked about participation in clinical trials (Bartlam et al., 2010). Most people felt that leaving older people out of clinical trials amounted to ageism and a devaluation of older people in both scientific and social communities. Some were shocked that it was even possible for certain drugs, typically used for older people, to have been clinically tested on much younger populations. Other points raised in the PREDICT study, which could equally apply to other forms of research, is that older people are devalued and stereotyped as vulnerable (perhaps leading to over-protection) (Bartlam et al., 2010). This undermines their right and ability to take part in research.

Involving older people in all kinds of research and at all stages of the research

At the same time, it is important not only to involve older people in research but to involve them in research which results in knowledge that is meaningful to them and their doctors, such as comparative effectiveness research, bearing in mind that older people with comorbidities may have different priorities when it comes to outcome measures compared to those of the researchers. In a review of over 100 studies into conditions which are common in older people, only 27% mentioned outcomes which were of relevance to the older people such as quality of life or functional status (Covinsky, 2011). Whereas researchers may place their emphasis on disease specific outcomes, older people with multiple conditions may prioritize outcomes of a more individual or personal nature.

3.2.3 Involving people from ethnic minority and other "racialised" groups in research

According to the principle of justice, participants should have an equal opportunity to participate in research (Fondation Médéric Alzheimer, 2011). This means that they should not be systematically excluded on the basis of race, gender, religion or other personal characteristics unless this can be justified due to the nature of the research question (Fawcett and Garity, 2009). For example, it would be justifiable to exclude "white/Euro-

pean" or Indian immigrant carers from a study into the attitudes of Chinese immigrant carers towards state support but it would not be justifiable to exclude same-sex Chinese immigrant partners who are carers from that study.

Language barriers may prevent some people from ethnic minority groups or immigrants from participating in research. Researchers could be encouraged to take necessary steps to overcome this barrier (e.g. having interpreters or participant information sheets and consent forms in the language of potential participants from such groups). However, this would incur extra time and costs, which they might not have. It would be impossible to translate research materials into every possible language and each translation would ideally have to be translated and then back-translated (to see whether the translated version when translated back into English is very close to the original version). With some research materials, such as cognitive tests or other research tools (sometimes called research instruments), this would not be sufficient as the materials should ideally be validated and this would involve a study in itself. Certain well-known tests may already exist in other languages and already be validated but may be difficult to obtain.

In some countries, sign language is recognised as a language and in New Zealand, it is one of three official languages of the country (New Zealand Government, 2006). However, researchers may find it even more difficult to involve people with dementia who use sign language in research due to difficulties communicating and a lack of tools adapted to this particular group of people.

People from ethnic minority groups are poorly represented in published clinical trials (Mason et al., 2003). Their inclusion in other types of research is probably also low (Hulko, 2004). Some cultural groups (e.g. travellers ⁵) may be even more absent from research, perhaps based on a combination of factors such as accessibility, patterns of mobility, language and stigma.

It is debatable whether the voices of people with dementia are really being heard in the domain of research or whether the voices of certain groups of people (which Hulko describes as "racialised" people) such as older and disabled people, LGBT people, people on a low income and those with little or no education, are being ignored. (Younger people may also be somewhat excluded from dementia research as dementia is typically associated with older people and as younger people may be difficult to reach.)

Hulko (2004) points out that where these groups have been included in research, the focus has tended to be on comparative risk, incidence and prevalence, challenges in assessment and diagnosis, service provision and the meanings of dementia. There are very few accounts of their subjective experiences of dementia as the focus tends to be on the subjective experiences of white, middle-aged, well-educated people in the early stages of dementia with a supportive family (also, Phinney, 2008).

People with dementia from ethnic groups should be involved in the design of studies and the dissemination of the results as well as in their capacity as a research participant. It has

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⁵ The term "traveller" is a generic term used in England which refers to people from a range of different ethnicities, cultural groups and lifestyles including gypsies, traditional and new travellers, boat dwellers, and fairground and circus people. In other countries, a different term might be preferred. For further information, please refer to: http://gypsyromatraveller.com/gypsy-roma-traveller-culture.html

been suggested that in the case of studies involving people from different cultures, researchers should seek the advice of community leaders. However, others warn against assuming that the opinions of minority scholars and community leaders truly reflect those of all members of that community, suggesting that this amounts to paternalism (Fisher, 2006).

The very use of terms such as "race" and "ethnicity" fails to challenge racial stereotypes or examine the significance of these socially constructed labels (Standfield, 1993; Fisher, 2006). It also strips people of their personal identity, as they become a mere representative of a particular "race" to which they may even have little sense of belonging (Heath, 1995). For example, a British participant, who was born and educated in England, whose mother was French and father Pakistani, might be classed as "mixed Asian" in a particular study but she might consider herself as international, British, mixed British, Asian or British Asian.

Involving people from minority communities in research should also extend to the choice of research topic. Tyack (1995) points out that research into issues relating to various minority groups often reflects topics chosen by or identified as being problematic by people who are not members of those groups and often for economic or political reasons.

3.2.4 Involving people dying with or from dementia in research

Research with patients at the end of their lives can be extremely difficult. Morse (2000) described qualitative studies with seriously ill patients as "being the most difficult type of qualitative research because of the immediacy of their symptoms and fluctuating nature of their own personal realities." Nevertheless, it has been suggested that excluding patients who are at the end of their lives from clinical research is unethical and runs counter to the Declaration of Helsinki and that instead of asking whether they should be included in research, we should be asking on what grounds, if any, would it be considered ethical to exclude them (Alexander, 2010; Bradburn and Maher, 2005; Krouse et al., 2003).

It is important that research into end-of-life care is conducted amongst a group of participants with the same characteristics as those for whom the improvements in care are envisaged (Carasret et al., 2001). Studies involving people who do not have dementia or are not receiving end-of-life care would be unlikely to contribute towards the development or improvement of services for that group. For this reason, the participation of people who are dying with or from dementia is greatly needed. Furthermore, depriving them of the opportunity to take part in research could be construed as paternalism or injustice.

It has been suggested that participants in end-of-life research cannot benefit from the results of the research as they will no longer be around to do so and that they should therefore be left in peace. This presumes that they will not benefit from an intervention that is being studied during the study or from the personal satisfaction of being able to benefit others. Alexander (2010) suggests that such presumptions, for which there is no

supporting empirical evidence, may have hindered the development of appropriate palliative care to vulnerable groups.

Moreover, people with a limited prognosis are still people and as far as we know, have the same views about the potential value to the community of participating in research as do other people (Addington-Hall, 2002). Consequently, a person's prognosis should not be used as an excuse to deprive them of the right to decide whether or not to participate in such studies.

Reciprocity has been described as a universal element in sustaining human relationships (Gouldner, 1960) and as a basic social need which is largely ignored but may contribute towards self-esteem and dignity, as well as respecting autonomy (Vernooij-Dassen et al., 2011). As the disease progresses, it may become increasingly difficult to find opportunities to give something back to others or to society at large, particularly in the end stage when many people are dependent on others for their care. It would therefore be unethical to deny them this opportunity.

3.2.5 Recruitment and the involvement of third parties

Many studies are based on convenience samples or purposive sampling. This means that the participants are chosen on the basis of availability (i.e. because it was possible to reach them) or for theoretical or practical reasons and that they were not randomly selected. These are acceptable ways of recruiting participants and commonly used in qualitative studies where the need for a large, random sample is not necessary (i.e. for statistical purposes). Some quantitative studies also use convenience samples but this approach has implications for statistical analysis and the perceived value of the results.

However, such recruitment strategies may also have ethical implications. For example, gaining access to people in specific settings may necessitate the involvement of other people such as health and social care professionals and staff but these people may not be aware of or entitled to give information about people's diagnoses to third parties. Some may nevertheless do this, thereby violating the right to privacy and confidentiality. If they limit themselves to identifying people with memory problems, such people cannot be considered as necessarily having dementia as the two are not synonymous.

Alternatively, they may block access to potential participants. Managers in care homes, for example, might refuse permission based on concerns about disturbing residents or the belief that they would not be interested (Fisk and Wigley, 2000; Sherratt et al., 2007). Alternatively, refusals to cooperate may be based on stereotypes about dementia, concerns about how they or their staff might be affected by the study and paternalism. In a recent phenomenological study, for example, into the experience of patients with malignant wounds receiving palliative care, some patients were excluded from the study based on the unilateral decision of healthcare professionals who felt that it would be detrimental to their wellbeing. Yet those who did take part in the study all commented that it was a positive experience and that they appreciated having been able to tell their story (Alexander, 2010).

Addington-Hall (2002) suggests that such practices may limit participation in end-of-life research to a particular type of person and deprive others of the right to be heard. Even research which does not aim at representativeness in the statistical sense may strive to represent a diversity of views and therefore, such interference with the selection process could adversely affect the results.

The involvement of third parties can also be positive in that it may help to reduce feelings of anxiety, prevent coercive measures being used to recruit participants and facilitate access to certain groups of people with dementia (e.g. those living in residential care or institutions, those with Down's Syndrome and those from ethnic minority groups).

Attempts to recruit people with dementia for studies into end-of-life care may be upsetting to potential participants and their close family and friends if they had not realised that this is what they were receiving. Healthcare professionals may have been avoiding using these terms in order to help those concerned retain hope or cope emotionally. It is not always possible for researchers responsible for the initial contact to understand how someone interprets the treatment or care they are receiving. Even if a person has been told, they might not have taken in the implications of what was said. Healthcare professionals with experience interacting with people dying with or from dementia could be helpful in advising researchers on how to approach this topic with individual patients.

The involvement of third parties may therefore be beneficial in some cases, protecting the wellbeing of potential participants and hinder the recruitment process in others, depriving some people with dementia of their autonomy and disempowering them.

3.2.6 Involving carers

It is considered good practice to involve carers in studies in which people with dementia are participants. Advantages include ensuring the wellbeing of the person with dementia by preventing possible psychological harm, helping the person with dementia to communicate his/her views, helping ensure that informed consent is obtained and providing another perspective on the research topic (sometimes called triangulation). However, not all people with dementia and carers have harmonious relationships. There may be underlying power issues, the presence of the carer may hamper the person with dementia in expressing his/her views and insistence on involving carers may be interpreted as a devaluation of the contribution made by the person with dementia. Some people with dementia may want to participate in a study and object to the assumption that they will be accompanied (Pratt, 2002). In some cases, the involvement of the carer may amount to paternalism which erodes the personhood of the person with dementia (Cowdell, 2006).

3.2.7 Disclosure of the diagnosis through research and confidentiality issues

People may be involved in a study based on consent given by a third party and are not aware that they are taking part in the study. Whilst they may not be disturbed by the study, if other residents in group living arrangements are aware of the study and the topic of the study is sensitive (e.g. aggression, sexually inappropriate behaviour or incon-

tinence), they may devalue or even ridicule the participant. The consequences of this may be disturbing to the participant and this raises issues about the protection of the dignity of participants.

It is possible that researchers, simply by approaching somebody about possible participation in a study, may inadvertently disclose a diagnosis of dementia to a person who was not aware that they had dementia, and in some cases, such information may in addition be incorrect (Cowdell, 2006). In group living arrangements, depending on how people are approached and what is known by residents about the study, some people may feel devalued or stigmatized, either for having been approached or for not having been approached. Some residents who are not involved may perceive the participants as having more power or as receiving more attention and this may be psychologically disturbing.

3.2.8 Including people at all stages and types of dementia in research

A great deal of research involving people with dementia has involved relatively articulate people in the early stages of Alzheimer's disease. Those with other forms of dementia and in the more advanced stage of dementia have been largely excluded. This is perhaps as it requires much more effort to include them (Phinney, 2008) in terms of communication, consent and access. Yet their views, experience, behaviour and reactions are important. Standard methods for collecting data such as the interview or questionnaire may be difficult for people with more advanced dementia but excluding them from research fails to respect the principle of equity. Excluding people with lower scores on cognitive tests such as the Mini-Mental State Examination (MMSE) is not justifiable, as a lower score does not necessarily indicate the inability to communicate one's views (Cowdell, 2006).

Clearly, the choice of participants must be linked to the research question/hypothesis. For example, if researchers are interested in some aspect of the disease biology in people with mild dementia, they would legitimately want to recruit people with mild dementia for their study. The problem arises when the initial choice of topic is determined by obstacles which could in many cases be overcome.

Different approaches may be necessary to facilitate the participation of people with more advanced dementia in research. One such approach is that of observation in a natural setting. Kitwood (1997) advocated carefully attending to what people do and say as they go about their daily lives. This might involve interacting with them (e.g. accompanying them on a walk or carrying out a certain task such as preparing a meal with them). Such an approach could be used in the context of assessing people's needs with the aim of providing support but has also been used in the context of research (Sheehan et al., 2006) for which video or monitoring devices may be useful for the collection and analysis of the information obtained (Cook, 2003).

There is a need to be creative in the search for novel ways to include people with different levels of dementia in research. Finding new approaches to data collection is likely to involve addressing additional ethical issues (e.g. linked to privacy, confidentiality, trust and consent).

3.3 Recommendations on involving people with dementia

GENERAL INVOLVEMENT

People with dementia should be consulted during the design phase of research projects, in the definition of meaningful outcome measures and, if appropriate, concerning the initial choice of topic.

Such involvement should be meaningful and not merely a token gesture.

Depending on the nature of the research, researchers should consider involving people with dementia not only as participants but also as consultants and co-researchers.

Research should be encouraged involving people at all stages of dementia (from early to end-stage dementia) and with different types of dementia (including rare forms of dementia).

All participants in dementia research should be equally valued and respected.

INVOLVEMENT OF OLDER PEOPLE WITH DEMENTIA

Attempts should be made to include people with dementia from the older age group in all types of research.

When trying to recruit older people for research (including those who lack the capacity to consent), researchers should explain to those people, their carers, legal representatives or possible "gatekeepers" why it is important to include older people in research and why the same research could not be achieved with younger people or just with people who have the capacity to consent.

Study designs for medical research (e.g. clinical trials for drugs to be used in the treatment of dementia), which do not include an appropriate proportion of older people with dementia, should be challenged by funders, research ethics committees and peer reviewers of such research.

Clinical trials for drugs, targeted for future use by people with dementia, should be tested on samples which are truly representative of that group of people.

More research into comparative effectiveness and pharmacogenomics linked to dementia should be carried out.

INVOLVEMENT OF OTHER SPECIFIC GROUPS OF PEOPLE WITH DEMENTIA

Attempts should be made to include people with dementia from ethnic minority or other "racialised groups", and people with dementia with visual, auditory and intellectual impairments or with less common forms of dementia in research.

Researchers should draw up a plan of proposed actions or measures to ensure the recruitment of older people and other sub-groups of the population with dementia.

As such actions and measures may involve extra costs and time (e.g. for facilitators, interpreters and transport) this should be considered during the design phase.

As people have multiple identities, with various degrees of emphasis on different aspects of their identity, the relationship and dynamics between and within various racialised identities and people should be considered.

People from ethnic minority and other racialised groups involved in research should be recognised as representing more than their perceived ethnic or racialised characteristics (i.e. they may have many similarities with other people with dementia who do not share the same characteristics).

People from ethnic minority and other "racialised" groups should be included in a broad range of research topics.

Unless there are good reasons for not doing so, researchers should, where possible, translate research materials into other languages if this would facilitate the inclusion of people from ethnic minority or immigrant groups.

INVOLVEMENT OF THIRD PARTIES

Measures should be adopted to attract researchers from ethnic minority and other racialised groups to dementia research.

Researchers should encourage carers to support people with dementia in their participation in research, provided that the latter are in agreement.

It should not be presumed that people with dementia participating in research want their carer to participate or be present.

METHODS AND TOOLS

The development of tools to differentiate between different stages of dementia should be encouraged.

Researchers should take into account individual differences and use methods which are appropriate to the impairments of individual people with dementia.

Researchers should also attend to remaining capacities of individual people with dementia and consider methods which correspond to those capacities in order to facilitate the involvement of people with dementia in research.

Researchers should consider the use of data collection methods which do not automatically exclude certain groups of people with dementia.

Researchers should ensure that the tools they use are suited to particular groups (e.g. to illiterate people).

Researchers should consider the use of tools (such as the MMSE) which have been modified for people from different cultures and educational levels.

Researchers should be creative in developing approaches which facilitate the involvement of people with dementia with a wide range of characteristics.

Research ethics committees should encourage researchers in the development of appropriate and acceptable approaches to dementia research aimed at the inclusion of a wider group of people with dementia.



Informed consent to dementia research

4 Informed consent to dementia research

4.1 Background information about informed consent to dementia research

4.1.1 The necessity to obtain informed consent

Legal obligation

Within the context of medical treatment in the European Union, medical practitioners have a legal obligation to obtain consent before treating a patient and may be accused of physical assault should they fail to do so (Alzheimer Europe, 2009). In some countries, this obligation extends to medical research and in some countries there are either specific laws on research which cover the issue of consent or paragraphs in more general laws addressing the issue of participation in research. This is the case, for example, in Austria, Bulgaria, Cyprus, Denmark, Estonia, Finland, France and Germany but the emphasis is clearly on medical research such as clinical trials, experimental treatment in hospitals or accepting treatment by a student doctor.

The obligation to obtain consent for participation in research is, in addition, covered in numerous codes and declarations such as the Nuremberg Code (1946), the Declaration of Helsinki (1964-2008) and the Additional Protocol on the Convention of Human Rights and Biomedicine concerning Biomedical Research (2005) to name but a few.

Informed consent therefore represents an autonomous decision made by a competent person to authorise medical staff or researchers to involve him/her in a particular study, which for certain types of research (such as medical research) is also a legal requirement. Informed consent is increasingly becoming an ethical obligation for all types of research (e.g. for academic recognition of the validity of studies or for funding purposes).

Ethical motivation

Buchanan and Brock (1990) describe the two main values governing the need to obtain informed consent as being 1) to promote and protect the person's wellbeing, 2) to respect the person's self-determination.

The issue of personal wellbeing, which is also linked to personal benefit, will be discussed in section 5 of this report). With regard to self-determination, this term describes the desire to make important decisions about one's own life oneself. Generally speaking, the two are linked as it could be presumed that people tend to think that they are best placed to make decisions likely to affect their own wellbeing. However, this fails to be the case if they lack the capacity to judge what might contribute towards their wellbeing.

The terms autonomy and self-determination are sometimes used interchangeably but are actually quite different. Atkinson (2007) describes the difference between these terms as follows:

Autonomy is the capacity for self-government and self-determination: the ability to choose for oneself. (.../...) Self-determination requires an individual to have the capacity to formulate and carry out plans, desires and policies of their own devising. Self-government further requires the individual to take account of their own rules and values in making these choices. (Atkinson, 2007, p.83)

She further specifies that for a person to be able to exercise autonomy, in addition to the mental and physical capacities needed, there must be a social and political environment which recognises and promotes the value of autonomy and allows it to flourish.

From an ethical and legal standpoint, it is necessary to be able to assess whether informed consent can or has been given and this includes assessing a person's capacity to make a decision about participation in a particular study.

4.1.2 Determining whether a person has the capacity to give informed consent

The components of informed consent

Informed consent can be considered to have been given if a person (or his/her legal representative) after having been fully informed about the study, having understood the information provided and being capable of making a decision on the basis of that information freely agrees to participate in the study. Petrini (2010) describes the basic components for informed consent as being:

- The possession of competence
- Voluntariness (not having been forced to make a particular decision).
- The provision of information (clear and truthful information, covering amongst other things details of any potential risks, benefits and alternatives to participants).
- Enrolment (freely deciding to participate in the study on the understanding that the
 participant can withdraw at any time without having to justify his/her decision or
 suffering any negative repercussions).

Competence refers to the legal capacity to make decisions in a certain realm and may be legally defined or determined in court. This is usually but not always linked to cognitive capacity. For example, many people under the age of 18 may have the cognitive capacity to make medical decisions but are not considered legally competent to do so (DuBois, 2008).

There are different degrees of lack of voluntariness ranging from being subjected to research without having had any choice in the matter, being forced to participate on the basis of some kind of threat or deciding to participate on the basis of undue influence such as the need for money which results in overlooking the risks involved (DuBois, 2008).

It is the responsibility of researchers to ensure that potential participants have received all the information they need to decide whether to participate. Such information typically covers benefits, risks, inconvenience, tasks, the purpose of the study, participants' rights and the fact that the study departs from ordinary medical practice (Miller and Wilner, 1974). There may be additional information that is specific to a particular study or type of research such as the possibility of receiving a placebo or some degree of invasion of one's privacy. Such information may be provided orally but it is common practice to provide participants with a written participant information sheet and accompanying consent form.

Cognitive status and the ability to give informed consent

Part of the process of obtaining informed consent involves determining whether a person has the necessary competence. A person's cognitive status or score on an assessment of mental status (such as the MMSE) cannot be taken as sufficient proof of their ability to give informed consent (Orwig et al., 2011). The MMSE has also been criticised for its emphasis on a person's current ability to recall or manipulate facts and failure to address life experiences requiring long-term memory (Hellström et al., 2007).

Moreover, it is generally accepted that a person who is competent for the purposes of decision-making has the right to make a decision which other people may consider irrational. Competence does not equate with perfect rationality (DuBois, 2008). However, some people are not considered as having the capacity to make decisions at all, even foolish ones (Feinberg, 1986).

The criteria for competence

The assessment of competence involves paying attention to four main abilities (Appelbaum and Grisso, 1988; Mental Capacity Act, 2005):

First, the person must have sufficient capacity to understand the information. If the study involves a considerable degree of risk, more information must be provided, particularly about possible risks and benefits, and the potential participant must be able to understand such information.

Second, the person must be able to retain, use and weigh up such information long enough to be able to make a decision. In addition, they must also be able to understand what the decision is about, why they are being asked to make it, and what the consequences of making or not making that decision might be.

Third, possible benefits, risks and inconvenience linked to participating in research must be understood and weighed against the person's own values and goals, which means that the person must understand how participating might affect him/her personally (High, 1992 and Stanley et al., 1984 in Olde Rikkert et al., 1997).

Fourth, the person must have the ability to communicate his/her decision.

Giving informed consent to research is a complex process requiring cognitive skills which gradually deteriorate as a result of dementia, making such informed consent difficult and in some cases even impossible to obtain. Many people with dementia will, at some point, lack the capacities for reasoning and deliberation needed to fulfil some or all of these conditions for most medical decisions that need to be made, including

those related to research. On the other hand, many people with dementia have sufficient capacity to express their desire to take part in research and to engage in various consent discussions (Hougham, 2005). When determining whether a person has the necessary capacity, it is not the final decision that is important but rather the process that the person goes through to make that decision (Sessums et al., 2011).

4.1.3 Exception to the necessity to obtain informed consent

One of the only exceptions to the necessity to obtain informed consent for medical treatment is that of the emergency situation in which it is imperative to act immediately in order to save a patient from imminent danger or serious harm. This would rarely apply to the research situation in which interventions are carefully planned in advance and designed to provide some kind of new knowledge. However, in certain circumstances it might cover the use of experimental treatments or procedures in the acute care or clinical setting (or at the scene of an accident by paramedics) for people who are unable to consent (please see following section on ethical issues for more details).

4.1.4 Obtaining informed consent directly from people with dementia

The term "competence" describes the capacity to complete a certain task. It is always task-specific in that it relates to the capacity to perform a particular task, at a particular moment in time and under specified conditions (Buchanan and Brock, 1990). The area of competence of relevance to the involvement of people with dementia in research is that of decision-making capacity.

People may have varying degrees of capacity. In the case of dementia, it may even fluctuate not only because of dementia but also due to a range of psychosocial, situational, medical, psychiatric and neurological factors (Holzer et al., 1997) However, whereas capacity is not an all or nothing matter in that people may possess varying degrees of capacities (with regard to a particular task), competence is. There is a threshold for competence with regard to a particular task which someone either reaches or does not as the case may be (Buchanan and Brock, 1990). So a person is either competent or incompetent to make a decision about participating in a study. The importance of making such a distinction is to determine whether the potential participant should consent to participating in a particular study or whether somebody else should make that decision on his/her behalf. It is therefore relevant to the issue of informed consent.

4.1.5 Obtaining informed consent indirectly through advance directives

A person who fully lacks the capacity to consent to research could be for or against participating in research in general. It may be possible to determine what his/her wishes would have been by consulting his/her close family and friends or an advance directive for research.

Advance directives were developed in the 1960s in the United States of America. They were originally intended to be written by competent individuals who wanted to express in writing their wishes with regard to medical treatment they might eventually need in the event of an accident or illness which rendered them incapable of exercising self-

determination (Vollman, 2001). In this way, a person's autonomy could be extended into the future well beyond the point that they were actually able to exercise it. The concept of the advance directive has been further extended to the research situation in some countries but not in most. Amongst those which do not accept advance directives, some may accept consent to research from a proxy decision-maker (previously appointed by the person lacking capacity to make such decisions on his/her behalf). Advance directives may be legally binding or simply advisory depending on their legal status in each country and sometimes on the nature of the decisions to be made. Even in cases, where they are not legally binding, they may take on legal authority insofar as there is an obligation to consider the presumed will or previously expressed wishes of a person now lacking capacity.

4.1.6 Proxy decision making

Proxy decision making is often discussed in the context of healthcare decision making (e.g. linked to treatment or care decisions) and may be covered by laws or deontological codes. Proxy decision makers may, in some countries, be able to consent to research on behalf of people with dementia. If such consent can only be given by a legally appointed proxy decision maker, this may slow down the recruitment process.

In some countries, the appointment of a proxy decision maker is made by means of an advance directive whereas in others, it is a separate process. The principle of appointing a proxy decision maker is to give that person authority to make decisions on one's behalf at some time in the future. This is different to the principle of the advance directive which is to make a statement of one's wishes in future situations (Atkinson, 2007).

However, apart from the fact that people may use the advance directive to appoint the proxy, some people actually combine the two decision-making possibilities. This means that they express their wishes in the advance directive and also appoint a proxy decision maker with authority to override those decisions. This gives people the reassurance of having somebody who can be consulted in cases where there is some doubt as to how the wishes expressed in the advance directive correspond to a particular situation. It can also be useful in situations where there have been new developments or changes which might result in the person's previously expressed wishes not being applicable to the current situation.

4.2 Ethical issues linked to informed consent to dementia research

4.2.1 Information and capacity

4.2.1.1 The provision of information

It is the responsibility of researchers to ensure that relevant and adequate information has been provided in a manner that is suitable for the particular person, and that it has been understood and retained (Fondation Médéric Alzheimer, 2011). The provision of information in a way that the person does not understand may result in what Sessums et al. (2011) call "pseudo incapacity".

The common practice of providing a written participant information sheet and consent form can be particularly helpful for people with dementia who may forget what they were told by the time they are asked to sign the consent form. The participant information sheet can also serve as a reminder throughout the course of the research of what the study is about and what is involved.

Research ethics committees typically require a number of issues to be covered in the participant information sheet. This might, for example, include what the study is about, what participation would involve, what is hoped to be gained from such a study, the fact that the person can withdraw at any time and whether the participants are likely to benefit personally etc. Please see appendix 2 for a list of possible issues to be covered in a participant information sheet). An important issue, which is often overlooked, is that regardless of any personal benefit which might possibly result from participation, the purpose of research is not to benefit the participants. Such information about the difference between research and medical treatment is of paramount importance when obtaining informed consent to research from people with medical conditions, particularly those for which there is as yet no known cure.

4.2.1.2 The capacity to understand the information provided

People with dementia who participate in research do not always fulfil the criteria for consent despite it having been obtained because they have not understood the information provided. Agawar et al. (1996) carried out an interesting experiment involving people with dementia who had already consented to and were participating in a clinical trial, as well as their carers. Responses to a questionnaire revealed that out of 15 participants, only 3 realised that they might be receiving a placebo, 8 that they could withdraw at any time and 7 that they were participating in a research study. It could be that some of the participants had since forgotten the information they were given and upon which they based their decision (which nevertheless indicates the need for an ongoing consent process). The researchers conclude that if one were to apply the criteria for consent to treatment to consent to research, very few people would be able to take part but that at the same time, people with dementia represent a vulnerable group and need to be protected from exploitation.

In another study, the researchers emphasise the importance of the stage of dementia. 415 participants who had already given informed consent to a low risk, longitudinal study were tested for their understanding of the information they had previously been given. 250 participants had very mild, mild or moderate dementia and 165 did not have dementia. The responses from the participants suggest that those with very mild to mild dementia had understood the information but that in those with moderate dementia one third demonstrated poor understanding. The researchers found that presenting the information twice, improved the rate of understanding amongst people with mild dementia but concluded, based on their findings, that for people with moderate dementia, a carer should be involved in the process (Buckles et al., 2003).

The two above-mentioned studies suggest that people with moderate dementia might not have the capacity to understand the information provided as part of the informed consent process and that for some, the presence of a carer might be beneficial. They also raise questions about researchers' ability to assess capacity. However, although issues linked to capacity and the assessment of capacity may sometimes make it difficult to involve people with dementia in research, they do not rule out the possibility of such involvement.

4.2.1.3 The assessment of capacity

Tools have been developed to measure the capacity to consent to treatment and to clinical research such as the MacArthur Competence Assessment Tool for Treatment (MacCAT-T) and the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), which are sometimes recommended (Appelbaum and Grisso, 2001; Dunn et al., 2006; Kim et al., 2001). The MacCAT-CR covers understanding, appreciation, reasoning and expression of choice. However, it takes 15 to 20 minutes to complete and requires substantial training to administer it and to ensure its valid interpretation. Jeste et al. (2007) have developed a much shorter instrument for the assessment of decisional capacity for clinical research called the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC). They describe this tool as being easy to use and to score, taking less than five minutes to administer. The tool also enables researchers to identify participants who need more comprehensive assessment.

The MMSE, which according to Molloy and Standish (1997) takes about ten minutes to administer, is not always an accurate predictor of the capacity to give informed consent. Sessums et al. (2011) suggest that it may be a useful indicator in the case of people with an extremely low score and for those with extremely high scores, but for those in the grey zone in between those two extremes, it may have limited usefulness for the assessment of the capacity to consent.

In their discussion about tools to assess the capacity to consent to research and care, Moye and Marson (2007) point out that there may be differences in the type and rate of impairment of people with different conditions and that consequently, some tools may work less well in some conditions than others. They also draw attention to the way that the assessment of capacity is becoming a field of study in its own right.

As pointed out by Kim et al. (2001), an appraisal of cognitive capacity is not sufficient to come to a categorical decision about a person's capacity to consent to research. For such a decision, a score obtained by means of an assessment instrument is just one part of the process of obtaining consent, the other being clinical judgement. Researchers therefore need access to and expertise in the use of assessment tools for capacity as well as clinical experience.

However, the traditional competency-based approach fails to take adequate account of the situational aspect of capacity and the importance of interdependence and relationships (Dewing, 2007). It has been suggested, particularly by qualitative researchers, that the criteria for informed consent to research are heavily influenced by research ethics

committees, which tend to focus on bio-ethical principles, and that this may actually lead to the exclusion of older people with dementia from research (Dewing, 2007). Dewing suggests the need to develop and propose to research ethics committees alternative methods of obtaining informed consent which are neither exclusionary nor paternalistic.

4.2.1.4 Preserved abilities

As mentioned earlier, the assessment of capacity must lead to a decision as to whether or not the person is competent to consent to participation in research. A person with dementia may lack the necessary capacity to consent to research but retain the capacity to decide about various aspects of research and express preferences that are reasonable (i.e. compared to decisions on the same issue made by people with capacity). Kim (2011) highlights a particular study he carried out with his colleagues in which it was found that the preferences expressed by people with AD concerning different research scenarios (i.e. involving blood draw, clinical trial, PET scan and brain surgery) were similar to people in the control group for three of the scenarios. People who had more advanced AD were not reckless with regard to risk taking but actually more cautious than their less impaired counterparts.

This highlights the need to involve people with dementia in decision-making linked to research, not just by informing them of decisions and obtaining their assent but also in a more active way based on their remaining abilities. There is a risk that lay people who are not familiar with the concept of capacity in relation to dementia will not think it appropriate to involve people with dementia in this way.

4.2.1.5 Capacity for decision-making about end-of-life research

People with end-stage dementia are likely to have limited capacity to make decisions about some forms of research and/or have difficulty expressing their wishes. However, expression of their wishes is not impossible as not all people dying with dementia have end-stage dementia (Cox and Cook, 2007). In addition, some may have made advance directives in which they expressed a desire to take part in research or appointed a trusted person to make such decisions on their behalf.

In some cases, there may be fluctuations in participants' physical and mental condition. Perhaps one day, they feel able and motivated to take part but not the next day. Some may be receiving highly burdensome treatment for co-existing conditions, be experiencing extreme fatigue and experiencing distressing symptoms. Addington-Hall (2002) questions whether it is ethical to ask them to participate in research at such a time.

4.2.2 The timing and form of consent

4.2.2.1 Prior consent

Informed consent should be obtained before any research procedure is carried out. Depending on the type of research being carried out, informed consent may be a one-off procedure and a person may be asked to confirm having given consent in writing. This is also a legal matter in that obtaining informed consent may serve as a protection against possible prosecution for assault. In this respect, prior consent is a legal requirement for participation in research.

However, people with dementia may forget having consented to a study and not understand what is being asked of them or why. They may not realise that they are free to decide not to comply with the researchers' requests or to withdraw from the study. Some may even be unaware that such requests are linked to research rather than treatment.

4.2.2.2 Experienced and ongoing consent

People do not always realise how they feel about a particular intervention or procedure until they have experienced it, particularly in the case of repeated invasive procedures like blood tests but also for procedures which some people might find disturbing (e.g. indepth interviews on sensitive issues). People's opinions as to whether research involves minimal risk and burden may differ in that certain vulnerable populations, such as older people and perhaps also people with dementia, may have a different perspective to that of the researchers (Annas et al., 1986).

It may be helpful for participants to experience what is involved before they give full consent. "Experienced consent" involves obtaining informed consent in the usual way before the intervention or procedure and then seeking it again, perhaps a week later, when the person has had time to decide whether s/he would be willing to repeat such an experience. Another approach is to seek consent at regular intervals throughout the whole study (Milton, 2000; Pratt and Wilkinson, 2001). This has the advantage of reminding people with dementia that they are participating in a study and that they are free to withdraw at any time.

Olde Rikkert et al. (1997) tested out experienced consent in a sample of frail older patients attending a geriatric hospital in the Netherlands and participating in biomedical research. They identified three advantages to its use. First, the actual capacity to consent improved (i.e. to understand information about the study and weigh the possible risks and inconveniences). Second, it enabled a true assessment of risk and convenience. Third, it gave participants time to reflect before being asked to sign a written consent form. The researchers point out that it may be easier for a person not to sign a consent form than to withdraw from a study after having given written consent. This might particularly apply to people for whom it is important that others do not consider them as unreasonable or making a fuss. It could also be helpful in situations where people wrongly presume some form of obligation based on their experience of signing documents and making contracts in everyday life.

However, Welie and Berghmans (2006) draw attention to the lack of a control group in the above-mentioned study, which means that the improved capacity may have been due to factors other than the try-out of the study, such as the passage of time or having received the information twice. They also draw attention to a possible catch-22 situation in that capacity is also needed to consent to a try-out of the study and participants may not have such capacity. They state that whilst the standard for capacity to consent to try out part of a study is perhaps lower than the standard for capacity to consent to participate in the complete study, the rationale for participating in a try-out study may be more difficult for participants to grasp.

4.2.2.3 Layered consent

Sometimes, participants would like to take part in a particular study but have considerable concerns about some aspect of the procedure (e.g. giving blood, authorising the researchers to obtain genetic information or being interviewed in their own home). In some cases, it may be possible for the researchers to exempt some of the participants from some of the procedures. If so, "layered consent" might be possible. This involves participants consenting to certain parts of the protocol and not others (White, 2000).

4.2.2.4 Situations where rapid consent is needed

For some types of research (e.g. research into delirium), rapid consent is needed but problematic to obtain. According to Holt et al. (2008), participants in studies into delirium are likely to be considered as vulnerable due to impaired capacity to consent as well as the possible underlying causes for delirium. One such cause is dementia. Yet, delirium has an acute onset and tends to be short-lived (e.g., just a few days). Sufficient lucidity to consent (for people who would normally have such capacity) tends to occur towards the end of the period of delirium. It is therefore necessary to recruit participants rapidly. If a proxy is needed to make the decision, that person must be found and contacted immediately. Attempts to protect participants may be in direct contradiction with their right to be involved in research which is appropriate to their condition. According to Adamis et al. (2005 and 2010), stringent testing of capacity may exclude many people with delirium from research into delirium. Those who do take part are unlikely to be truly representative of people with delirium and this has implications for the generalizability of the results. In their own study, in which they compared different approaches to obtaining consent to research from people with delirium in an accurate medical ward, they found that using stringent criteria resulted in younger, less cognitively impaired participants. This may also apply to other forms of dementia research but in the case of delirium studies (and other research carried out in emergency situations), there may be insufficient time to obtain proxy consent.

In England, there are special rules in the Code of Practice of the Mental Capacity Act (2005) governing the participation of people unable to consent in "urgent treatment research" (Holt et al., 2008). In such cases, the researcher can obtain the authorisation of a medical practitioner who is not linked to the study (but could be the patient's doctor) or of the appropriate body for such decisions. Holt et al. (2008) recommend this approach, also in relation to non-treatment protocols involving minimum risk such as observational studies.

Another approach would be to try to obtain consent in advance from potential participants who are at risk of needing a particular urgent medical intervention or experiencing a particular symptom for which a study is envisaged (Kalisvaart et al., 2006). This might still be possible for many people with dementia or their legal representatives but such an approach might cause undue anxiety about the probability of a specific medical condition occurring.

4.2.2.5 Form of and procedure for consent obtained

Nowadays, it is increasingly common for researchers to obtain written informed consent and in some countries, such as the United Kingdom, they are obliged to do so in order to conform to the requirements of ethics committees. In the Clinical Trials Directive (2001/20/EC of the European Parliament and of the Council of 4 April 2001), it is stated that a decision to take part in a clinical trial must be written, dated and signed by the participant or his/her legal representative. It is further stated that people who are unable to write may, in exceptional circumstances, give oral consent in the presence of at least one witness. This process may contribute towards researchers treating the consent process as a one-off procedure or formality.

On the other hand, obtaining written consent, or at least making a detailed written record of consent given verbally, may help ensure that all relevant issues have been addressed and consented to. There is much more to consent than indicating whether one wishes to participate in a particular study. For example, consent may be needed to interview people, observe them or subject them to tests, to record interviews, to quote statements made by participants in future publications and to use data collected in case of subsequent loss of mental capacity or death. Consent forms also serve as proof that participants have been fully informed which is part of the process of obtaining informed consent. Participants can indicate on the form that they have been assured that data will be anonymised, that they are free to withdraw at any time and that they have been given a participant information sheet, had the opportunity to ask for any additional information they may require and that if so, such information has been provided. This structured and detailed approach to obtaining informed consent is generally considered as being in line with ethical requirements for research. Please see Appendix 1 for details of the kinds of topics covered in consent forms.

Nevertheless, it has been suggested that older people and people with dementia might be anxious and feel insecure or threatened when asked to sign a consent form even if they are interested in participating. Some researchers have proposed alternative methods such as verbal and behavioural consent (Bamford and Bruce, 2000; Bartlett and Martin, 2002; Cowdell, 2006; LaRue and Markee, 1995). Possibilities for alternative forms of consent must also be considered in the case of people with dementia with additional impairments (e.g. visual impairments and intellectual disabilities).

Research ethics committees sometimes require researchers to follow a set procedure to obtain informed consent which is clearly geared towards quantitative research and not adapted to many studies adopting a qualitative research methodology. For example in qualitative research, researchers can legitimately develop research tools, questions and even the consent process as the study progresses but in order to obtain ethical approval for the study, they may be required to submit final documents such as interview schedules, participant information sheets and consent forms and to state explicitly how participants will be selected and recruited (Allbutt and Masters, 2010). At the same time, the conduct of good quality research requires researchers to adopt appropriate methodologies and to apply them effectively. It is possible that overly rigid and restricted

approaches on the part of ethics committees might interfere with researchers' ability to achieve this or alternatively, result in unauthentic/misleading declarations which amount to paying lip service to the requirements of the ethics committees. This would surely not be in the interests of research participants.

4.2.3 Possible factors influencing informed consent

4.2.3.1 State of wellbeing

The performance of people with dementia on tests of cognitive performance may be influenced by a range of factors such as the time of the day, level of concentration and motivation. Cognitive processing may also be affected by a person's state of general well-being (Damasio, 2000). Consequently, tests which are carried out with minimal regard for the individual may affect the results obtained and lead to the unnecessary exclusion of some people with dementia from research due to low scores on various tests.

For this reason, Dewing (2007) advises researchers to find out how potential participants present themselves when in a state of wellbeing. She states that it may be necessary to find out about this from other people although clearly some people with dementia may object to being discussed in this way. Nevertheless, this may be easier to do in some settings than in others. For example, in a residential care home, it may be easier to adapt the process of obtaining consent to the individual but less so if the person needs to travel to an assessment or research centre.

Nevertheless, irrespective of the setting and even in the absence of personal knowledge about each potential participant, researchers can take measures to create a pleasant environment, be attentive to how the person with dementia is feeling and be as flexible as possible in organising the timing and place of the consent procedure.

Researchers must also be careful not to inadvertently disclose a diagnosis of which the potential participant is unaware whilst discussing possible participation in a dementia study (Blanchard, 2008). The disclosure of a diagnosis of dementia should be carefully planned and adapted to each individual.

4.2.3.2 Deception

In some studies, participants are not informed about the deception until after the study at which point they have the opportunity to consent to the data being retained and analysed for the purposes of the study. This is known as *post hoc* consent and the process of informing them as "debriefing". It implies that participants are asked to give informed consent either after having previously consented on the basis of ambiguous or misleading information or after having unwittingly participated in a study.

If participants do not know what the study is really about, it could be argued that they have not given informed consent (Dresser, 1981) and that the principle of veracity has not been respected (Fry and Veatch, 2006). They should therefore be informed about everything that might affect their decision with regard to possible participation in the study (Baumrind, 1976). Obtaining *post hoc* consent merely solves the issue of

whether it is ethically and perhaps even legally permissible to use the data obtained from participant. It does not address other issues linked to the wellbeing of participants linked to their actual experience of participating in the study, to the violation of their trust or to disrespect for their personal values. The ethical issues and justification for the use of deception in research is further discussed in sub-section 5.2.9 which addresses issues linked to protecting the wellbeing of people with dementia participating in research.

4.2.3.3 Coercion, power and undue influence

Increasing difficulties to provide informed consent but also to communicate their wishes during a study make people with dementia potentially vulnerable and at risk of coercion or exploitation (Fondation Médéric Alzheimer, 2011). Coercion in the context of research could involve one person intentionally making an overt threat of harm to the potential participant in order to obtain consent to a study. This is not limited to physical violence. It could also involve deliberately leading the potential participant to believe that his/her condition will deteriorate or that s/he will die if s/he does not take part in the study (Fawcett and Garity, 2009). Exploitation would involve mistreating or unfairly using a person for the benefit of other people (e.g. solely for the researchers' own personal goals).

Research ethics committees try to ensure that potentially vulnerable populations, such as children, people with incapacity and people in circumstances which severely restrict their liberty, are not exploited or forced to take part in studies. In some countries, this is explicitly stated in legislation on research or on involuntary internment (Alzheimer Europe, 2009). The issue of vulnerability is covered in more detail in section 5.2.7.

Researchers and doctors may be considered as figures of authority in their particular domain and hence accorded trust, which gives them a certain degree of power. Participants tend to go along with the rules and methods proposed by researchers which should reflect accepted practice within the research profession. However, whereas in the doctor/patient relationship, patients expect to be provided with medical expertise and services corresponding to their needs, this is not the case with the researcher/participant relationship in which the emphasis is on the creation of knowledge and not necessarily or essentially for the benefit of individual participants. (Benham, 2008). In the case of clinical research in which the researcher is a doctor and the participant is a patient, it may be unclear what reasonable expectations would be. Patients may become fully consenting research participants without understanding the difference between research and treatment. They may even be participating based on blind trust in their doctor. As a person with depression commented in a focus group on involving older people in clinical trials,

"If it was my doctor suggested it: "will you try this?" I'd say yes, but if anybody else asked me, I would probably say no." (Bartlam, Lally and Crome, 2010).

This highlights the important role that doctors can play in facilitating recruitment but raises questions about the inappropriate use of power.

However, power may also be exerted on individuals who are not generally considered as belonging to a vulnerable group. For example, researchers may obtain approval from a hospital or residential care home for a study involving interviewing or observing staff. Ideally, each member of staff should consent to their participation in the study and such a process may actually take place. However, there may be cases where members of staff feel under pressure to consent based on insecurity about their jobs or about future professional advancement within the organisation. In some cases, where a whole department is involved, they may be afraid of standing out as a trouble maker or of the consequences of having to be moved to a different department during the study.

There may also be reasons why carers would feel under pressure to take part in a study or to give proxy consent (e.g. if they felt beholden to the people organising the study for the support or care of the person with dementia or feared reprisals against the person with dementia if the latter was in residential care).

Sometimes, the involvement or presence of carers during the consent procedure may result in carers making certain decisions on behalf of people with dementia and consequently, those people with dementia not exercising independent will or making a free choice (Agawar et al., 1996). Whilst this is most unlikely to involve deliberate coercion, it raises concerns about voluntariness and the extent to which the carer helps as opposed to decides on behalf of the person with dementia, particularly as the carer might not have the legal authority to do so. Also, it cannot be presumed that the carer has the best interests of the person with dementia at heart.

4.2.3.4 Financial incentives

Sometimes researchers offer participants some form of financial remuneration. This might be intended as compensation (for their time, for expenses incurred or for risks or harms), as a mark of respect or gratitude or in order to motivate them to take part (DuBois, 2008). The actual amount paid is important and affects whether it is considered as undue influence or justifiable. For example, a payment of EUR 40 to a person living below the poverty line with no opportunity to earn money might lead them to participate and to overlook the possible risks involved, whereas for a person on a good salary, it would probably not. If the amount is too high, the participants may be inclined to try to please the researchers by providing the information they think the researchers want.

In some studies, participants are offered access to medical treatment or care that they would not be able to finance themselves but consider necessary. For a person with good health cover, this would not even be an incentive but to someone with no health insurance, it might be a deciding factor.

It could be argued that certain benefits such as money, treatment or care are clearly beneficial to those lacking them. However, it has been suggested that participation solely for financial or other related gain is an indication that the research is exploitive and that the participant is being used "merely as a means to somebody else's end" (DuBois, 2008). Consequently, when deciding what might be a reasonable amount to offer a person, it

is important to bear in mind that it is relative. There are likely to be differences between and within different groups of participants. On the other hand, it would be equally unethical to offer different amounts of money or benefits to different participants in the same study.

In their report on the ethical issues linked to tissue donation, the Nuffield Council on Bioethics (2011) suggests that altruistic donation prevents the exploitation of the poor and may help ensure good quality tissue. They report mixed views on the issue of ownership of the body with some people feeling that they "own" their bodies and consequently can sell it as one might sell parts of a car, and others feeling that the recognition of ownership rights amounts to an inacceptable objectification or commodification of the body.

Researchers sometimes offer donations to established charities or gift vouchers instead of money. These options make the exchange of actual money unnecessary and may appeal to the altruism of participants or place the emphasis on something pleasurable as opposed to compensation.

The offer of money or other kinds of incentives might also be offered to doctors for their assistance in recruiting patients for studies. This might create a conflict of interests between a doctor's willingness to help researchers and his/her duty to protect the best interests of his/her patients.

4.2.3.5 Doctors and possible ambiguity in their role in the research process

Where research is being carried out (or even just proposed to the patient) by medical practitioners there may be ambiguity between the role of doctor and that of researcher. In many countries, doctors are ethically bound by the Hippocratic Oath which states that treatment that is given should be in the best interests of the patient. As Berghmans and Ter Meulen (1995) point out, "The aims of conducting research are not primarily, nor exclusively to benefit the individual patient who is the research subject". They further state, with reference mainly to biomedical research, that the knowledge obtained from such research may be "beneficial for future patients but that there is seldom or never a direct benefit for the patient" (1995, p. 648). However, people with dementia should have the opportunity to contribute towards such knowledge in the medical domain as well as in other areas.

4.2.4 After informed consent has been given

4.2.4.1 Withdrawal from the study

It is understandable that some participants give informed consent and later find certain aspects of the study more unpleasant or burdensome that they had envisaged. Whilst researchers prepare a protocol which contains a step-by-step plan of the various procedures to be carried out, it is difficult to predict how people will experience or react to those procedures. For some studies, various parts of the procedure (such as the actual questions to be asked in an interview) are developed or adapted along the way. This is part of the research method adopted.

Even if the questions are known in advance, a participant may find the level of probing too deep and not wish to continue. S/he may also be disturbed by some of the questions and in some cases may experience distress even some time after the interview. There is a possible conflict of interests in that the researcher needs to protect the wellbeing of the research participant but the withdrawal of the latter from the study may result in inconvenience to the researcher or have implications for the analysis and presentation of the data.

Older people are more likely than younger people to withdraw from a study (especially those involving trial drugs or the effects of existing drugs) due to worsening health, complications, the effects of polypharmacy, changing residence, going into hospital and dying (Orwig et al., 2011). As most people with dementia are quite old, this must affect a great deal of dementia research irrespective of the additional factors linked to dementia such as confusion, loss of mental capacity involving difficulties with communication and complying with instructions etc. In studies using quantitative methods of data analysis, withdrawal from the study may affect the generalizability of the results, especially if the participants who withdraw are in some way different as a group to those who remain in the study (Orwig et al., 2011). Also a reduction in the number of participants involved in the study may affect the statistical power of the study, making it difficult for the researchers to claim that the results they found were not simply due to chance. On the other hand, statistical methods are available to deal with drop out from studies by adjusting for the missing data (Orwig et al., 2011). Nevertheless, there is a potential conflict of interests and a necessity to ensure that the wellbeing of participants is respected with regard to their possible desire to withdraw from the study.

Blanchard (2008) points out that there may be consequences for the participant of withdrawal from a study such as undesirable side effects or financial issues, and suggests that patients who withdraw from a study should be followed up.

4.2.4.2 When the participant loses capacity or dies before the end of the study

A person may agree to take part in a study and may have the capacity to consent but then lose that capacity during the study. This raises a few ethical questions such as: Should the person who has lost the capacity to consent continue to be involved in the study, who should decide on this matter and what should happen to data relating to that person that has already been collected? Similarly, a surrogate decision maker who consents to a study on behalf of a person with dementia may also lose capacity during the study and hence not be in a position to ensure that the rights of the person with dementia are being respected and that s/he is still willing to participate. Such problems should not normally arise if the person responsible for giving informed consent states his/her wishes with regard to this matter before the start of the study. Some research ethics committees specifically ask researchers to explain how they will address this issue when they initially apply for ethical approval for a study. A similar problem arises when a person dies before the end of a study in that it must be decided what to do with the data that has already been collected from that person.

4.2.4.3 Consent to data or human tissue being used for further studies

When researchers collect data or human tissue for the purpose of a study, once the study has ended that material is no longer used. In some countries, researchers are required by ethics committees to destroy it within an agreed period of time and in a specified way. However, the same data or tissue could often be used for additional research purposes. This would reduce unnecessary duplication, prevent wasting the time of additional participants and prevent exposing additional participants to unnecessary burden. However, researchers do not necessarily have the right to use data or tissue for additional research purposes.

Where this issue is not covered by law, an ethical dilemma exists. It could be argued that such data or tissue was given for a specific purpose which the participant felt was worthwhile and on that basis was willing to give consent to its use. An exception might be the *post mortem* donation of brain tissue for research. The participant might not be in agreement with the aims of the additional study or even object to other aspects of the study such as the researchers, other activities carried out by the research organisation or moral issues linked to the study.

Seeking additional consent for the reuse of the data or tissue is certainly not a mere formality and can be a major setback in longitudinal studies. It involves contacting every person who participated in the original study. In some cases, this might be thousands of people, many of whom will have moved house, not respond to requests for additional consent or no longer be motivated to contribute towards research. As many people with dementia are fairly old, depending on the timescale involved, some will have died. In addition, some may have had the capacity to consent at the time of the original study but may now lack that capacity. The researchers would then have to contact the person's legal guardian who may not know anything about the original study and in some cases, not have the legal right to consent. Moreover, whereas the consent procedure may have been thorough initially, as the revised procedure consists of consent to the reuse of data or tissue rather than to actual continued participation, there is a risk that the procedure may be somewhat superficial.

In some cases, human tissue may have been collected in the course of clinical care and not for the purpose of research but could, nevertheless, be valuable to researchers. According to Emanuel and Menikoff (2011), research may be hampered by lack of clarity concerning the use of leftover biomedical specimens from research or from clinical use and a simple one-off written consent procedure in hospitals might overcome this problem. In the case of clinical care, some patients may have undergone particularly burdensome procedures for the removal of the human tissue. It would be unethical to submit an additional person to the same degree of burden merely for the purpose of research. This may render some types of research impossible yet, paradoxically, research using those existing samples might eventually benefit future generations with the same condition.

4.2.5 The involvement of, or impact on, third parties

4.2.5.1 Involving carers in the consent process

Carers sometimes act as gatekeepers in that they facilitate or obstruct researchers' access to people with dementia. In some cases, they may even refuse to let the person with dementia take part in a study even though the person with dementia is displaying a clear interest in the study (Hellström et al., 2007). Whether they have the right to do so is a legal issue but such gatekeeping may be quite subtle and hence difficult to detect.

From an ethical standpoint, such action can be interpreted in at least two ways. Some carers may, for example, be exercising power and disregarding the wishes of the person with dementia. This might also be expressed in the form of not informing the person with dementia of opportunities to participate in research which have been communicated to the carer. This would be a case of failing to respect the autonomy of the person with dementia, not respecting him/her and not acting in his/her best interests. However, some carers may be genuinely trying to protect the person with dementia from harm and feel that they have a better understanding of the risks involved based on their capacity to fully understand everything involved and their in-depth knowledge of the person with dementia. The person with dementia may be unaware of the probable impact that participation in a particular study might involve but nevertheless have consented to it. If s/he objects to the interference of the carer, it may be a difficult situation for all involved.

4.2.5.2 Disturbance to people not directly involved in the study

In some cases, people may suffer certain inconvenience or disturbance for a study for which they are not the actual participants. An example of this would be a study which involved interviewing a person with dementia in their own home as the spouse of the person being interviewed could feel under pressure to tidy the house, offer refreshments and allow a stranger into his/her home.

In the healthcare or residential care setting, a study involving the use of surveillance or monitoring techniques for people with dementia might also affect the right to privacy of staff employed in those facilities yet they might not have a realistic option not to be filmed or monitored. Possible solutions include the temporary assignment of members of staff who object to a different unit (Sifford and Bharucha, 2010) or considering that a person who continues to work under such conditions has implicitly consented to the procedure (Carlson, 2001). However, in the first case, the employee may find the temporary assignment to another post disagreeable or fear negative consequences as a result of his/her decision. In the second case, it must be borne in mind that people do not all have the financial security to leave their job or sufficient opportunity and relevant skills to change their employment.

4.2.6 When the person with dementia cannot give informed consent

4.2.6.1 In the case of consent to research of no direct benefit to the participant

Whether or not people who are unable to consent should be involved in research is an ethical issue which was addressed in the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application

of Biology and Medicine (1997). The convention differentiates between research that is beneficial to the participant and that which is not, stating that the latter should not normally be carried out on people who are unable to consent.

For example, article 17, 1, ii states that the results of research must have the potential to produce real and direct benefit to the participant's health if s/he is unable to consent to the research. Article 2 of article 17 further specifies that in addition to certain standard requirements, exceptionally and under the protective conditions prescribed by law, research which does not have the potential to produce results of direct benefit to the health of the person concerned can nevertheless be carried out subject to further conditions being fulfilled:

- the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
- the research entails only minimal risk and minimal burden for the individual concerned.

The above guidelines are linked to biomedical research and the benefits mentioned are perhaps understandably linked to participants' medical condition or health. However, not all potential benefits are linked to health, even in the case of biomedical research. It has been suggested, for example, that there may be benefits linked to increased social interaction, human contact and other people taking an interest in one's problems, and that taking part in research may even give people a sense of meaning (Cassel, 1985). Berghmans and Ter Meulen (1995) describe these as "secondary interests" and assert that although they may be important, they are not sufficient in themselves to justify participation in a particular research project. For some patient groups, the "direct benefit" might occur many years later if an effective drug results from the study but in the case of dementia, this period of time might be too long for this to be a valid argument.

In the past, the terms therapeutic and non-therapeutic research were used and these were eventually replaced by references to direct benefit. However, the term direct benefit, as it is currently used, is perhaps somewhat limited and unrealistic. Furthermore, as different research projects have different objectives, the possibility for benefit and the type of potential benefit may differ from one study to the next.

4.2.6.2 Advance directives for research

Ensuring that the future participant understands the nature of research

Backlar (1998) highlights the necessity to ensure that the person who makes the advance directive for research fully understands the difference between being a patient and being a research subject. However, as advance directives are not necessarily drawn up in the presence of witnesses, have a variety of forms and may in some cases only be used several years after loss of the relevant capacity, it would be difficult to assess whether or not this was the case.

Making decisions about an unknown future activity

Consenting to future research in an advance directive may be more problematic than consenting to treatment in advance. As pointed out by Berghmans (1998), it is difficult to give consent for a future experiment which has not yet been devised and which, by the nature of research, is likely to be innovative.

Buchanan and Brock (1990) draw attention to the fact that advance directives do not leave any leeway for discussion contrary to contemporaneous decisions. With regard to research, the possible risks may be considerable and perhaps the actual condition or situation of the person who made the advance directive is different to that which s/he envisaged when it was written.

On the other hand, advance directives are written by people with capacity who can be informed of any possible risks linked to the use of advance directives and then make an autonomous decision.

The involvement of third parties

Backlar (1998) suggests that the person's treating doctor should not have any connection to future research in which the person having made the advance directive for research might participate. However, there may be occasions when it might be beneficial for the patient to be involved in research of which his/her treating doctor might be aware (e.g. in the case where a patient is not responding to existing treatment). It is therefore important to be clear about the kind of involvement on the part of the doctor that would be considered unacceptable and whether there could be exceptional circumstances.

An alternative to making an advance directive is to appoint in advance (e.g. by means of an advance directive) a proxy or trusted to person with responsibility for decisions relating to participation in research or to be consulted with regard to the interpretation of the advance directive for research (e.g. in case of ambiguity regarding the person's expressed wishes or for particular situations which the person might not have considered).

Personhood – deciding on whose behalf and with regard to which interests?

There are also a few issues linked to personhood and personal identity which challenge the whole issue of using advance directives, including for research purposes. For example, some theorists claim that the person who previously wrote an advance directive is the same person now as when s/he wrote it but his/her interests may have changed. Others suggest that at some point in time, the person can no longer be considered as the same person and consequently question the validity of the advance directive.

Experiential and critical interests within stages of one complete life

Dworkin (1994) proposes the integrity view of autonomy. This approach considers autonomy as a reflection of a person's integrity as opposed to being based on concerns for their welfare. He distinguishes between two types of interests: experiential interests (the things that people do because they like the experience of doing them) and critical interests (the things that if not satisfied would make a person feel that they were

worse off in some way or that life had been wasted such as having a close relationship or accomplishing a particular task or duty).

Dworkin claims that people with dementia in the later stages have no sense of a whole life with a past joined to a future and that they cannot have the projects or plans of the kind that leading a critical life requires. Furthermore, they are no longer able to act in a way that would make life more or less valuable. Consequently, although there may be a conflict between a person's precedent autonomy and contemporary experiential interests, there is no conflict with their critical interests as they perceived them whilst still competent. Whilst his views about interests and quality of life involve some degree of stereotyping and should be considered in that light, his conclusion is worth considering, namely that even though experiential interests seem to take precedence over critical interests in advanced dementia, it is no reason to ignore the critical interests a person had when competent.

Dworkin's view of a person with dementia seems to be one in which the person at a particular stage of their life has dementia, but this is just one stage in their complete life which has already involved different stages. As such, the stage they are now in, is affected by interests and concerns which transcend that stage and are important for their life as a whole. As such, the competent and incompetent selves are one and the same person. The critical interests, which previously gave meaning and coherence to life, are still important, even if at this particular moment in time, the experiential interests seem to be more in the foreground. Dworkin's account would seem to suggest that advance directives should still be respected even when the person has lost capacity because they are to be viewed as expressions of the critical interests a person has, which are relevant to their whole life. Failure to respect them would, in his view, constitute "an unacceptable form of moral paternalism".

Continuity between former and current selves – becoming a different person

Parfit (1984), on the other hand, describes a kind of psychological continuity between former and current selves which varies in terms of similarity to a greater or lesser degree. He argues that the two selves may become so radically different that they can no longer be considered as the same person and hence, the former self should not have decision-making power over the current self. Berghmans (1998) points out with regard to this theory that the degree of psychological continuity would probably be stronger in the case of early dementia compared to advanced dementia. However, this approach would justify the use of advance directives more in early stage than late stage dementia which is not something that people consider when they write such a directive. Also, such views would reduce the possibility of people consenting to end-of-life research which, to use Dworkin's terms, may be a critical interest for some people.

Protecting the former interests of a future "non-person"

Buchanan (1988) takes the view that an advance directive serves to protect the interests of the person with capacity who wrote it and not the experiential interests of "the non-person that succeeds them." The interests of the "former self" survive and extend to con-

cerns about the future self (even though this is no longer the self). Again, a distinction is made between the person somebody once was and the person they have become, which sometimes sounds remarkably inhuman:

"This interest survives not only his loss of the capacity for exercising a right of self-determination: it survives the loss of personal identity that results from the most severe and permanent dementia. Jones no longer exists yet his interest in avoiding the prolongation of the life of the body that was his survives him. It is the (surviving) interest of a (no longer existing) self in what happens to something (a living, sensing body) that is not that self. (Buchanan and Brock, 1990, pp 165-166)

Alzheimer Europe's position on the use of advance directives from 2006

In 2006, Alzheimer Europe produced recommendations on the use of advance directives by people with dementia in which we stated our view that consent to research expressed in an advance directive should be accepted as a valid expression of a person's wish to participate in such research (subject to certain conditions being fulfilled).

4.2.6.3 Values history

As part of future healthcare decision making, some people write what is known as a "values history". This is usually a written document in which people describe what is important to them, covering, for example, their values, beliefs and preferences. As such it is a very personal document. A person's views about participation in research could be included in such a document in varying degrees of detail. A values history can be written alongside or instead of an advance directive. Whilst a values history does not have any legal basis, it can be very useful in helping other people understand what is important to a person, particularly in situations where somebody has no close friends or relatives but also in the residential care setting. Such documents may therefore contribute towards self-determination and beneficence, and help ensure more people with dementia have the opportunity to participate in research if they so desire, at the same time avoiding people who would rather not participate, doing so.

However, the issue arises as to who should have access to a values history. The person who wrote it presumably realized that it would be read by people who did not know them sufficiently well to know what they would have wanted. On the other hand, it is likely that they had in mind professional medical and care staff. The person may have trusted somebody (e.g. the family doctor or a trusted person) with the tasks of giving the document to the appropriate person or people when needed. If not, there is a risk that the document will not reach the appropriate people or that the person's right to privacy will be violated.

4.2.6.4 Proxy decision making

Assessment of risk

To fulfil their role of proxy decision maker, a person should ideally have at least some understanding of dementia (Werner, 2001) as well as an understanding of the particular study being proposed and of the risks involved. In relation to an assessment of the risks of a particular treatment, Karlawish et al. (2000) found that proxy decision makers for

people with dementia differed in their assessment of risk depending on their relationship to that person. Adult children of people with mild dementia were willing to accept a greater degree of risk than were the spouses of the people with dementia. Muncie et al. (1997) also found that proxy decision makers tended to be overprotective. This may prevent important studies from being carried out. Some proxies clearly overlook possible risk, based on the belief that the study would not be allowed if it were not safe. This casts doubt on the ability of proxy decision makers, presumably with full capacity, to make sense of the information they are provided with (Sugarman et al., 2001). Where the intervention was minimal, such as one extra blood sample, and of minimum risk, some proxies even reported having forgotten having consented and not being sure what was treatment and what was research during their visits to the clinic. In addition, the responses of some reflected a belief in the goodness of research and of the doctors and institutions involved which does not reflect a great deal of objectivity in assessing the possible risks involved in a particular study.

Basis for decision making

As proxies are expected to act in the best interests of the person with dementia, this would not normally include consenting to research involving burden unless some kind of benefit was likely for the person with dementia. Yet the person with dementia may well have been in favour of participating in research despite certain types or degrees of burden or risk. Indeed, the opinions of proxy decision makers may be different to those of the people they represent. Often, they do involve the person with dementia in the decision-making process (Karlawish et al., 2001; Sugarman et al., 2001) but this does not necessarily mean that they always make decisions based on the perceived views of the latter, even though they clearly should.

Proxy decision makers are expected to make decision which reflect what the person would have preferred or, for issues which the person had perhaps never considered, which correspond to his/her values and interests, and to what makes life meaningful to him/her. They are expected to make authentic decisions (i.e. decisions which are congruent with the values of the person on whose behalf they are consenting) (Brudney, 2009; Sulmasy and Snyder, 2010). Kim (2011) emphasizes that an autonomous decision can only be made by the potential participant him/herself but that a proxy could make an authentic decision on that person's behalf.

This requires a great deal of knowledge about the person and also the ability to make decisions on that basis rather than on the basis of one's own values and wishes. Some people may be better at this than others. Proxy decision makers do not necessarily have such knowledge.

A study into the use of pressure relieving mattresses involving frail older people revealed that only 18% of those able to consent refused to take part in the study compared to a refusal rate of 45% from the proxies of those who were unable to consent (Mason et al., 2006). In a systematic review of end-of-life treatment decisions, inaccurate assessment of wishes by proxy decision makers was as high as 33% (Shalowitz et al., 2006). Several

studies into proxy decision making in the context of healthcare involving chronically ill or older people have concluded that family members are not very good at predicting or making the same decisions as their relatives (Ditto et al., 2000; Pruchno et al., 2006; Seckler et al., 1991; Upadya et al., 2002 in Atkinson, 2007).

A small scale qualitative study involving interviews with 49 proxy/AD patient pairs revealed that proxies often make decisions based on what they believe to be in the best interests of the people with AD, with altruism as a secondary reason (Sugarman et al., 2001). The results of this study also suggest that proxies are considerably influenced in the decision-making process by the hope that the person will benefit in terms of more time or a better quality of life. Even though they seem to understand that this might not be the case, many express the view that it is better to try something than do nothing and even something experimental rather than current treatment. This is clearly not based on what they think the person would have decided and much more on what might be best for him/her. On the other hand, the study also suggests that they are influenced by similar factors as the people they represent such as hope, desperation, trust and altruism. However, Atkinson (2007) draws attention to a study in which more successful judgements were made by proxy decision makers when they were asked to make a substitute decision rather than one based on "best interests".

Willingness to cede control to proxies

Many people with dementia are willing to cede future decision making to their proxies or families. In one study of 149 patient-proxy pairs, 82.9% of people with dementia (with capacity to consent to research) were willing to let their proxies decide on their behalf for future research instead of proceeding according to current directions of their own (Stocking et al., 2006). Amongst those who were not as keen on letting others decide on their behalf, some expressed their desire to maintain autonomy and some mentioned study-specific issues.

In another study involving telephone interviews with 246 people who had a close relative with dementia and who had previously taken part in clinical research, 81% stated a preference for giving advance instructions rather than letting someone decide on their behalf (Wendler et al., 2002). At the same time, 80% were willing to let their family enroll them in research with potential benefit even if this contradicted what they had written in an advance directive. Very few (13%) preferred to simply let their families decide about research in general yet of the 246 participants interviewed only 16% returned a completed research advance directive to a research centre after the interview.

These studies suggest that there are differences between people with dementia in their preferences regarding the involvement of proxies in future decision making about research. They also indicate an acceptance on the part of most people with dementia that their proxies or families might make decisions which are not similar to those they would (or even did) make themselves. This reveals great trust in proxies and low expectations about their ability to make decisions that they would have made themselves. However, as revealed in the second study, very few people wanted to let their families

decide about research on their behalf. The fact that many people state an interest in expressing their wishes in advance with regard to research, yet so few write advance research directives, is a clear indication that more work is needed to promote the use of such documents.

A German survey-based study involving 100 people with mild cognitive impairment (MCI) or mild AD, 99 relatives and 93 doctors revealed that people with MCI or mild AD had, on the whole, high levels of confidence in their own ability to make decisions and a considerable preference to make decisions themselves (especially social decisions) (Hamann et al., 2011). Those who were unsure of their decision-making capacity chose not to participate in decision making. The results also suggested that both relatives and doctors had difficulty predicting the preferences of people with mild AD or MCI, and that relatives wanted to play a greater role in decision making than required. This study was based on treatment decisions and social decisions (such as whether to stop driving and whether to go into a nursing home), and not on research. However, research and the reasons for wanting to take part in a particular study might be more medically or more socially orientated, and this might be reflected in the level of interest in participating in decision-making and the extent to which the involvement of relatives is desired by people with dementia.

Autonomy and exclusion

There is a risk that a known diagnosis of dementia may result in family carers being asked to consent on behalf of a person with dementia without having the necessary legal authority to give proxy consent to research and without attempts having first been made to assess the capacity of the person with dementia to consent (Fisk et al., 2007). Researchers may have difficulty (or anticipate difficulty) in obtaining informed consent from people with dementia to participate in research. Consequently, some researchers may be inclined to approach people with dementia who have a proxy decision maker with authority to consent to research. Others may seek to involve proxy decision makers due to concerns about the level of risk involved and possible litigation (Bravo, Paquet and Dubois, 2003; Vass et al., 2003).

This could lead to a lack of equity in that people with dementia who lack the capacity to consent to research and have no proxy decision maker may be excluded from research. These people also represent a sub-group of people with dementia whose voices may not be heard.

Burden on proxies

Often the proxy decision maker is the person's spouse but this is not always the case. Not all older people have a spouse or even relatives who could be the proxy decision maker. Some people may prefer to appoint a close friend as their proxy. Proxies may feel under pressure to take on this role if asked.

In a study carried out by Sugarman et al. (2001) (please see next sub-section for details), some proxies reported that decision making was burdensome and this depended to

some extent on the degree of risk involved, the level of invasiveness and the extent to which the person with AD was able to participate meaningfully in decision making. This in turn was often linked to the stage of the dementia and the extent to which the proxy or the person with AD had come to terms with the diagnosis. The burden on the proxy is often overlooked but ethical research involves protecting the wellbeing of all involved.

The existence of an advance directive for research could perhaps assist proxies in their decision making. The results of a comparative study by Stocking et al. (2007) of the usefulness of research advance directives for people with dementia and their proxies suggest that they did not facilitate enrollment, ease decision making or make proxies feel more comfortable with their decision. However, the researchers recognise several drawbacks to their study and recommend further research. Perhaps, the usefulness of value statements should also be explored.

Assent

Even when somebody with the legal authorisation to do so consents to research on behalf of a person with dementia, the ongoing assent of the person with dementia is invariably needed (Fisk et al., 2007). In the Clinical Trials Directive (2001), it is stated that the explicit wish of an adult who lacks the capacity to give informed legal consent, but is capable of forming an opinion and understanding, to refuse participation or to withdraw from a study should be considered by the researcher. However, expressions of assent may sometimes be misleading.

Sugarman et al. (2011) analysed interactions during a consent meeting between participants, companions and researchers in the context of a study of genetic markers for sporadic AD. They found that the vast majority of contributions within the discussion by the participants were positive statements indicating agreement and approval. Those of the companions were much more varied. The authors suggest that these affirming statements were perhaps simply a means of engagement and not a deliberate cognitive act or indication of the person's preferences or views about the proposed study. As such this does not constitute authentic assent. Whilst it is not clear from the study whether the companions were proxies, this study does have implications for how people with dementia who have proxies are involved in the informed consent process. It also highlights the possible danger in placing too much emphasis on obtaining assent at the risk of failing to find more meaningful ways of ensuring that people with dementia really do agree to participating in research.

Cooperation and capacity of proxies

Ethical problems may arise if there are doubts about the mental capacity of the proxy decision maker and where there is more than one proxy decision maker (Bramstedt, 2003). In some cases, relatives may be opposed to decisions made by an appointed proxy decision maker, yet due to their relationship to the person with dementia, their cooperation or assent to the study may be essential for the effective participation of the person with dementia.

4.3 Recommendations on informed consent to dementia research

ASSESSING THE CAPACITY TO CONSENT TO RESEARCH

A person should be deemed capable of consent unless proven otherwise.

The knowledge or belief that a person has dementia should be considered as reasonable grounds for doubt concerning his/her capacity to consent to research and to justify the assessment of his/her capacity.

A diagnosis of dementia (or the belief or presumption that a person has dementia) should never be considered as sufficient proof that a person lacks the capacity to consent to research.

Attempts should be made to ensure that researchers have access to relevant and appropriate tools for the assessment of the capacity to consent to research, as well as to training in how to use them.

Additional research should be carried out to develop and validate appropriate, short and reliable assessment tools.

Such tools should be validated on different groups of people with dementia.

THE PROVISION OF INFORMATION FOR THE PURPOSE OF CONSENT

Researchers should have the necessary skills to provide relevant information, communicate it in a manner adapted to the potential participant, respond to questions and facilitate the communication of the decision by the potential participant. Alternatively, they should appoint someone who has such skills.

Researchers should ensure that potential participants and their representatives understand the difference between receiving medical treatment and taking part in medical research, emphasising the fact that the main aim of research is not to benefit the individual participant.

Potential participants must be informed about other options (i.e. what treatment options are available, how alternatives might be better or worse than participating in the study).

When providing information, researchers should be aware of differences between participants, taking into account their cultural backgrounds and other factors such as level of education, linguistic matters, differences in perceived power, impairments and psychological state etc.

The use of visual or other aids should be considered if necessary.

Researchers should check whether the person with dementia has understood the information that s/he has been given about the study and his/her participation in it.

Potential participants should be provided with a participant information sheet and consent form. These two documents should be combined and each page contain a reference number for the study and a date.

Once signed, participants should receive a copy of the combined participant information sheet and consent form.

WILLINGNESS TO AND FACTORS AFFECTING CONSENT TO RESEARCH

Researchers must ensure that people who take part in research agreed to do so freely after having been given all relevant information, having understood this information and having received satisfactory responses to any questions they may have had.

Researchers should be aware of the possibility of undue pressure from relatives to prevent or persuade a person with dementia to take part in a study.

Staff or students in a hierarchical relationship to the researcher should only be asked to volunteer to participate in research carried out by that researcher if adequate measures have been taken to address the issue of coercion with regard to their recruitment.

Potential participants should not be rushed into signing the consent form and in any case, be given at least one week to think about the implications of participating and to ask any questions.

Exceptions to the time limit for reflection should be considered in the case of urgent or end-stage dementia research.

Cultural traditions should be respected. In case of doubt regarding the way to approach members of a particular cultural community, researchers should seek advice from people who are representative of the target population of the study.

When seeking consent, particular attention should be paid to environmental factors (such as noise level, time of day and lighting), wording and sentence structure, the avoidance of medical jargon and the amount of information provided at a given time.

The need to obtain consent for emergency research (e.g. into life-saving treatment or procedures) involving people with dementia who are unable to consent should be waived but assent from relatives sought.

If relatives are not available to consent to emergency research, researchers should proceed but if relatives are available and object, they should not.

ONGOING CONSENT AND WITHDRAWAL FROM THE STUDY

Informed consent should be obtained at various intervals throughout the study. This provides regular opportunities for participants to withdraw from the study.

It should be stated on the consent form, close to where participants sign that they consent to participate in the study, that they are free to withdraw at any time.

It may be necessary to support the person with dementia in the decision-making process. In cases where s/he lacks the capacity to consent but is nevertheless involved in research as a result of proxy decision making, his/her assent should be sought at regular intervals

Participants must be aware that they can withdraw from the study at any time, freely and without having to provide justification for their decision. In addition, researchers should be attentive to signs of distress linked to participation and, if necessary, check with the participant whether s/he wishes to withdraw from the study.

Researchers should follow up participants who withdraw from a study in case they are experiencing any negative effects from the study or resulting from their withdrawal.

Researchers need to be alert to signs of distress, be ready to stop the consent process with that person either temporarily or permanently, and to have envisaged a way to deal with distress following the consent procedure (e.g. by having a counsellor available).

Researchers should include a clause in the consent form in which the participant states whether s/he would like to continue participating in the study, should he/she lose capacity before the end of the study.

ISSUES SURROUNDING LOSS OF CAPACITY TO CONSENT

A person who loses capacity during a study, and did not indicate prior to the study his/ her wish to continue in the event of this occurring, should be withdrawn from the study.

Additional attention should be paid to a person's willingness to continue participating in the study if s/he loses capacity after having given valid consent (but previously consented to remain in the study in such case).

Researchers should be encouraged to include a clause on consent forms where participants can state whether or not their data can be used (for the purposes of the study to which they are currently consenting) in the event of their future/further incapacity or death.

INVOLVEMENT OF THIRD PARTIES IN THE CONSENT PROCEDURE

Attempts should be made to involve the spouse or partner in the consent procedure (e.g. through joint discussions).

If the study involves researchers entering a home, which is also the home of other people, the researchers should try to ensure that the other residents agree to this intrusion into their private sphere.

Objections and concerns from carers should be taken into consideration by the researchers out of respect for the carers and also as they may reflect legitimate concerns about the participation of the person with dementia in the study.

Researchers should not discuss with carers the participation of a person with dementia in a study if they know or could reasonably believe that the person with dementia would object to their being consulted.

If the person with dementia has the capacity to consent but the carer is strongly opposed to his/her participation, this should not prevent the person with dementia from participating in the study.

If the carer's consent is to be sought as the person with dementia lacks the capacity to consent, care must be taken to avoid making the person with dementia feel infantilized, humiliated or devalued.

ADVANCE DIRECTIVES FOR RESEARCH

People should be encouraged to consider writing an advance directive for research (in which they state whether they would or would not like to take part in research and state any particular preferences).

People should be encouraged to consider writing a values history, which could be combined with an advance directive for research.

When consenting to research in an advance directive, an indication should be provided of the type and level of risk/burden that would be acceptable as the actual nature of the future research is unlikely to be known when consent is given in the advance directive.

The current wishes of the person with dementia should be considered alongside those expressed in an advance directive covering research.

Researchers' own personal beliefs about personhood and the criteria for status as a person should not result in people with dementia having made an advance directive for research being denied the right to participate in such research.

A person's treating doctor should not propose the involvement of his/her patient in medical research, in which s/he has a personal interest, based on the latter having made an advance directive for research.

In exceptional circumstances and where such participation might be in the patient's best interests, the treating doctor should seek a second opinion from an independent doctor.

PROXY DECISION MAKERS

The assent of a person with dementia to participate in research should be sought if s/he lacks the capacity to give informed consent.

If possible, the opinion of the person with dementia about letting someone decide on their behalf should be sought before approaching a proxy decision maker for this purpose.

When appointing a proxy decision maker, people should strongly consider discussing their wishes and views about research with the chosen person.

Proxy decision makers should try to make decisions based on their understanding of what the person with dementia would have wanted rather than what they feel would be in his/her best interests.

Proxy decision makers should strive for authenticity (i.e. making decisions which conform to the known values of the person with dementia).

A proxy decision maker should not have a significant connection to the project (i.e. s/he should not be under the personal or professional influence of the research team).

A proxy decision maker should not directly benefit from the participation of the person with dementia in a particular study.

The proxy decision maker should be informed that s/he has been appointed and given the chance to refuse such appointment.

Proxy decision makers should be asked to declare any potential conflict of interests linked to providing consent on behalf of the person with dementia.

The person appointing a proxy decision maker should be aware of whether the proxy would have the legal authority to consent to research on his/her behalf and whether there would be any restrictions regarding the type of research to which the latter could consent.

Proxy decision makers should try to ensure the accurate interpretation of wishes contained in an advance directive or values statement if the person with dementia has made one.

Proxy decision makers should be involved in determining whether the research that is eventually proposed is in line with the wishes expressed in the advance directive.

If a proxy decision maker loses capacity, another person should be asked to take over the role as questions may arise during the study which necessitate further decisions being made.

If there are doubts about the capacity of a proxy decision maker when the initial decision is being made, an assessment of his/her capacity should be made.

ISSUES SURROUNDING THE FURTHER USE OF DATA

Researchers should obtain additional informed consent for any research involving the use of existing data or human tissue for purposes other than those for which informed consent was originally obtained.

Researchers should be encouraged to include a clause on the consent form where participants can state whether or not they agree to their data being used for possible future studies. A space should be provided for the participant to state any conditions attached to such additional consent.

RESTRICTIONS ON THE RIGHT TO PARTICIPATE IN RESEARCH

No individual should be denied the right to participate in research on the basis of their group membership.

The absence of perceived direct benefit should not serve as a justification to prevent people with dementia from participating in any kind of research.

A broader definition/understanding of the concept of direct benefit should be developed covering, for example, social benefit and personal satisfaction (e.g. linked to feelings and self-esteem).





Protecting the wellbeing of people involved in dementia research

5 Protecting the wellbeing of people involved in dementia research

5.1 Background information about the protection of wellbeing

Wellbeing is notoriously difficult to define. The World Health Organisation partly and indirectly defines wellbeing through its definition of mental health:

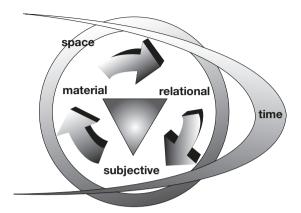
"Mental health is defined as a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community (WHO, 2011)."

This definition emphasises productivity and the ability to contribute to society. This is also reflected in several other definitions of wellbeing. Some, alternatively, define wellbeing as a state of being or feeling happy and healthy or as a good or satisfactory state of existence, sometimes linked to health and prosperity.

In this report, there are sections which address issues such as consent, involving people with dementia in research, considering risks and benefits and protecting their interests. Collectively, the points raised may contribute towards ensuring that it is possible for people with dementia, amongst others, to take part in research, without undue stress, exploitation or danger and in so doing both participate in and contribute to society. In this section of the report, we examine issues linked to the way that people with dementia participating in research are considered and treated. This is more directly linked to wellbeing in the sense of feeling good about oneself, in relation to others and with regard to society.

According to White (2008), wellbeing is also a dynamic process with material, relational and subjective elements which occur within a particular timeframe and geographical space. Please see figure 3 below.

Figure 3: Wellbeing as process (White, 2008)



People's understanding and perception of wellbeing may change from one moment in time to another (e.g. as people age, linked to changes in health and on the basis of people's experiences in life and on the people they encounter). Time in relation to the perception of wellbeing is not limited to the present time but also covers people's reflections about the past and expectations for the future (which may be affected by the experience of dementia). Perceptions of wellbeing may also be affected by their geographical location (the space in which one lives and moves about) (White, 2008).

Perceptions of wellbeing are socially constructed within cultural contexts. The relational dimension of wellbeing is very important and repeatedly occurs in people's definitions of wellbeing (White, 2008). However, there may also be cultural differences in the importance attributed to wellbeing. In a recent four-nation survey involving 431 adults from Canada, India, China and India, which explored factors which people consider "make for a good life", wellbeing and contentment was fourth out of the thirty most prevalent indicators identified (Tafarodi et al., 2011). It was not amongst the top ten most prevalent indicators for the Canadian participants whereas it was the third most prevalent for Indian participants, being cited more often than wealth, success and close and enduring friendships. This may indicate different interpretations of the term wellbeing as well as different degrees of importance attributed to it.

Nevertheless, people who participate in research are voluntarily contributing to society and irrespective of the importance that they assign to their own wellbeing, it is the duty and responsibility of researchers to protect participants' wellbeing and even to contribute towards it if possible. Participating in research can and should be a positive experience.

5.2 Ethical issues linked to the protection of wellbeing

5.2.1 Dignity

Dignity is an important ethical issue in research and is linked in some way to certain other ethical principles such as respect for privacy and confidentiality, the sanctity of life, respect for justice and inclusiveness, and respect for vulnerable research participants. It has been described as the cardinal principle of modern research ethics and as a principle which aspires to protect the multiple and interdependent interests of the person - from bodily to psychological to cultural integrity (Health Canada, 2007). Hellström et al. (2008) suggest that excluding people with dementia from research is an affront to their dignity whereas including them in research may enhance their dignity of personal identity.

Nordenfelt (2002) identified four types of dignity: Menschenwürde, the dignity of merit, the dignity of moral stature and the dignity of identity. Menschenwürde is the dignity that is inherent in being a human being. This German term reflects the undeniable value of human beings regardless of their social, mental or physical properties. Another term that is often used is "basic dignity". People have the same degree of Menschenwürde throughout their whole lives and it is something that cannot be taken away from a person (Nordenfelt, 2002).

The dignity of merit applies to people who are considered as having achieved excellence or distinction such as a high rank (Nordenfelt, 2002). This may be formally bestowed on a person or informally achieved by artists, athletes or scientists but nevertheless acknowledged and respected. This kind of dignity can be acquired and lost. In the context of research, people with dementia can be officially recognised for their contribution to society, in some cases officially by means of public recognition, in other cases, on a more personal basis through the gratitude of those involved in or likely to benefit from the study. For many people who take part in research, their participation is anonymous and part of a global effort which is worthy of merit but unfortunately not always acknowledged.

Another type of dignity is that of moral stature which is linked to the respect that people have for themselves and to their own dignified conduct, as well as to respecting other people's rights (Nordenfelt, 2002). As a person's capacities in various areas of everyday life gradually decline as a result of having dementia, the social roles they have or could have may be adversely affected. The opportunities to reciprocate or to engage in activities which they considered worthwhile and beneficial to others may be reduced. Being able to benefit other people through participation in research may, for some people, contribute towards their sense of self-respect. However, some research methods may result in people's deficiencies being highlighted or in attention being drawn to behaviour which might be considered by the participants or other people as undignified. This need not be the case even for studies involving measurement of various capacities, provided that the researchers are sensitive to the need to protect the person's dignity.

The dignity of personal identity is described as the kind of dignity that people attach to themselves as integrated and autonomous people who have their own history, future

and relationships with other people (Nordenfelt, 2002). This type of dignity is dependent on other people in that a person's perceived value and worthiness that is reflected back in the context of interaction. It can therefore be considered as an attribute that can be subjectively felt but also something which can be denied, ignored, withheld and violated. Examples of failure to respect a person's dignity of personal identity include not treating somebody with respect, belittling, ridiculing or humiliating them, ignoring or insufficiently acknowledging them, seeing them as a member of a group rather than as a unique individual, and/or physically or mentally transgressing their personal space (Holmerová et al., 2007; Jacobson, 2007; Mann quoted in Horton, 2004). Such acts could occur in a wide range of settings, including the research setting. For further issues of relevance to the dignity of personal identity, please see sub-section 5.2.4 on personhood.

Nordenfelt (2002) explains that the dignity of personal identity is also objective because it can be violated even in cases where a person is not aware of the violation or even no longer alive. This has implications for the respect of people with end-stage dementia who may have reduced self-awareness and also for the way that a person's body is treated in the case of post mortem brain tissue donation and research. The respect of the individual dignity of people with dementia, in general and especially in such circumstances, is equally important for the wellbeing of their relatives and loved ones.

5.2.2 Integrity

Integrity refers to a kind of wholeness. According to the Danish philosophers, Rendtorff and Kemp (2000) integrity has two moral dimensions. The first consists of a created and narrated coherence of life, in the form of a coherent and complete life story, which should not be violated. The second consists of a personal sphere for experience, creativity and personal self-determination (Ebbesen and Pedersen, 2008). Some people with dementia may have difficulty communicating their life story and protecting or promoting their personal sphere. It may be difficult for researchers to understand the integrity of each person with dementia they encounter but they can reflect on whether their treatment of the person might in some way fail to respect their integrity. On the other hand, researchers may also be instrumental in promoting or respecting the integrity of research participants through the use of certain research methods, such as narrative interviewing, participant observation and ethnographic research, which focus on the whole person and provide a means for experience, creativity and self-determination.

5.2.3 Respect

Respect can be reflected in both behaviour and attitudes towards other people. Respect might include having consideration for another person's feelings, refraining from offending him/her, and being polite and courteous toward him/her. There may be certain cultural differences between different groups in society as to what is considered as respectful (e.g. depending on cultural background, age and education).

Nevertheless, acts of consideration and attitudes which reflect genuine interest in a participant's wellbeing are likely to be appreciated such as offering the person a seat, not keeping him/her waiting for longer than needed, the tone of voice used, provid-

ing refreshments, asking how the person is feeling and even offering a little gift as a token of appreciation at the end of a study. Accepting gestures of hospitality (e.g. when interviewing in the participant's home) may also be an important sign of respect. Treating participants with respect is important for the ethical conduct of research in that it is linked to personhood and dignity and may in addition have an effect on the quality of data collected.

5.2.4 Personhood

The importance of relationships

Personhood is at the core of several ethical principles and, like dignity, has a fundamental inherent character as well as one that is socially constructed and maintained. There is a huge ethical debate on the topic of personhood, covering for example, the role of consciousness, rationality and psychological and biological continuity, with possible implications for the legal status of a person (e.g. relating to the validity of advance directives). A full discussion of these issues is beyond the scope of this report in which the emphasis is quite simply on the relational aspect of personhood, namely the way in which people are recognised and treated as unique human beings as opposed to animals or inanimate objects.

For some people, personhood may be linked to spiritual beliefs (e.g. that a person has a unique essence). This is perhaps more common in the Judeo-Christian tradition. In Hindu, Buddhist and Native American cultures, many people believe that a person is reincarnated as another person or animal after death or that a person embodies the spirit of ancestors or animals (Goodfellow et al, 2003). In such cases, personhood may be understood slightly differently.

Interdependence has been described as a necessary condition of being human. This emphasizes the importance of relationships (Kitwood and Bredin, 1992). Buber (1970) identified two different ways in which people relate to one another, which are also of relevance to the maintenance of personhood in people with dementia. The I-It mode of relating is one in which a person relates to the other in a cool, distanced, non-involved way which fails to fully acknowledge the individuality of the other as the other is objectified. The I-Thou⁸ mode of relating involves meeting the other person in a genuine human exchange (i.e. an authentic and meaningful encounter or dialogue). People with dementia may eventually lose the capacity to create and encourage a genuine human exchange. If, in addition, they have become an object in the eyes of other people, their personhood may be jeopardized.

Depersonalisation

In the context of care, Kitwood (1990) drew attention to processes and interactions which depersonalize people (described as "malignant social psychology"). Examples include infantilizing, disempowering, intimidating, labeling, stigmatizing, outpacing (going too fast for a person with dementia), invalidating (failing to validate the subjectivity of the person with dementia), banishment (being physically or psychologically separated from contact with other people) and objectification. These ways of relating to people with

dementia could all occur in the research setting. This is quite clear from the following examples of objectification and intimidation which were provided by Kitwood (but in relation to care):

"The dementia sufferer" is not treated as a person; that is, as one who is an autonomous centre of life. Instead he or she is treated in some respects like a lump of dead matter, to be measured, pushed around, manipulated, drained, filled, dumped etc.

"The dementia sufferer is made afraid by such processes as head scans or psychological assessments, these being carried out in a somewhat impersonal way, by professionals who are powerful and competent. Sometimes intimidation includes threats, or actual physical assault." (Kitwood, 1990, 38-39).

Objectification and cognitive separation

According to Kitwood and Bredin (1992), objectification involves a clear division being made between us (members of the so-called normal population) and them (people with dementia), whereby they are considered as being "in a bad way for they are afflicted with a primary degenerative disease in the grey matter" whilst we are "basically sound, undamaged, competent, kind". Link and Phelan (2001; 2006) used the term "cognitive separation" to refer to the process (which they also defined as a component of stigma) whereby people with a socially salient attribute come to be seen as fundamentally different. Some researchers have explored this concept in the form of dis-identification, which is the extent to which a certain group of people are considered as being different to oneself (Servais and Saunders, 2007). This process of cognitive separation from certain groups of people, which can in the extreme lead to objectification, may serve the psychological function of protecting people from existential anxiety and helping them to continue believing in a stable, orderly and just world in which they identify with the ingroup and convince themselves that they are very different from the out-group (Lerner, 1980; Novak and Lerner, 1968; Solomon et al., 1991).

The relationship between researchers and participants

In most forms of research, there are at least two distinct groups, namely the researchers and the participants. This does not necessarily imply an "us" and "them" relationship involving processes of cognitive separation. It is merely the result of the agreed temporary relationship between the two parties. After the research, most participants will return to their everyday lives and will no longer be a separate group. However, some participants are already perceived by many people, including the researchers, as being an identifiably separate group (e.g. based on age, cultural identity or health conditions such as dementia). This may be important for the purposes of obtaining appropriate support but may also increase the likelihood of cognitive separation, objectification and loss of personhood.

In addition, the process of research may involve subjecting people to batteries of tests, observing them, measuring response times or reactions, taking samples and so on. This can be done with consideration and respect, thereby respecting the personhood and dignity of the participants. However, as highlighted by Kitwood such treatment may also

lead to the objectification of the person. In his "involutionary spiral of the dementia process", Kitwood (1990) described how various ways of relating to people with dementia may lead to a diminished sense of personhood as well as shame, low self-esteem, social withdrawal and depersonalisation.

Researchers have different motives for carrying out research. Some are working towards the award of an academic degree, some are carrying out research in the context of their work (practitioner-researchers) and for some, research is their actual profession. Researchers therefore have their own personal interests such as the need to make a living, to obtain research grants, to publish in peer reviewed journals, to be officially recognised and to advance in their professional careers in addition to their interest in the research topic itself. There is a need for researchers to be cognizant of both the needs and values of the research participants with whom they are engaged and to have regard "not only to the content of research, but also to the process" (Kitwood, 1995).

5.2.5 Confidentiality

Anonymity

In qualitative studies involving interviewing (either face to face or by telephone), people reveal information about how they think, feel and act to the researcher carrying out the study or in some cases to people who have been trained to collect such data on behalf of the researcher. In most cases, participants will have been assured that their identities will not be revealed and that the information they provide will be anonymised. This means that in addition to the use of pseudonyms (i.e. using a special code or name instead of the person's real name), any information which might make it possible for another person to identify a particular participant will be changed. This is important in cases where quotes are included in published articles which anyone might pick up and read.

In studies involving surveys or questionnaires, it may also be possible to provide anonymity with regard to the researcher. This means that people can send completed questionnaires to the researcher without revealing their identity. This may result in greater honesty but makes it difficult to protect the wellbeing of participants. The questions asked may be disturbing to some people but the researcher would not know this. Even if s/he detected this in the response to open-ended questions or spontaneous comments on the form, the researcher would not be able to contact the person.

Information about third parties

In the course of an interview a person may reveal information about another person (sometimes spontaneously). Although such information would also be anonymised, the researcher may know that person and then knows information that that person might not have wanted to disclose. Although the researcher would hopefully treat such information with the same degree of confidentiality, it nevertheless represents an infringement of the right to privacy of other people as they did not consent to such disclosure (Hadjistavropoulos and Smythe, 2001).

Focus groups

Focus groups consist of focused discussions amongst homogenous groups within a group setting, facilitated by a moderator. People tend to disclose more about themselves to people who resemble them in various ways than they do to people who differ from them (Jourard, 1964). Self-disclosure is also facilitated by the existence of a non-threatening environment and perhaps in some cases due to being amongst relative strangers rather than personal acquaintances (Krueger and Casey, 2009). This is ideal for researchers who are interested in obtaining rich, meaningful data for their study but the researchers cannot guarantee that all members of the focus groups will respect the principle of confidentiality. Sometimes people may find that they know other members of the focus group and this may hamper self-disclosure and at the same time make anonymity within the group impossible.

Information about illegal behaviour

Sometimes, especially if they have been assured anonymity, participants may reveal information about behaviour that is unlawful or unethical (such as cheating in exams, stealing or abusing a vulnerable person). There may be less likelihood of this occurring if people are warned in advance but in some cases, people may unwittingly reveal such information. The researcher is then faced with a dilemma. On one hand, s/he promised the participant anonymity and confidentiality and should respect this promise (i.e. be trustworthy and honest) and on the other hand, s/he is ethically bound to report serious cases of abuse or other significant crimes. He/she may also be bound by deontological rules. This touches on the researcher's sense of integrity as a researcher and member of society.

Sometimes, in applications for ethical approval, researchers are asked to explain how they would handle such situations, should they occur. This forces researchers to consider the possibility of this occurring and to have the necessary measures in place.

Storage of data

Often auditory or video recordings are made of interviews and usually a written transcript is made of the whole interaction. Some researchers literally label and cut up statements before sorting them into categories. Nowadays, the whole process of qualitative analysis has become much more sophisticated and several computer packages exist which facilitate the management of data. Consequently, the transcript and even video recordings of the interaction are usually transferred onto computers. This raises questions about access to various stored records (on paper, on film, on auditory recorders, in word format and on computerised qualitative data analysis packages). The data gradually become dispersed and researchers must consider who should have access to each source of data and how to ensure that unauthorised people do not.

At the same time, there is a need to ensure that data are stored for a sufficiently long period. In order to serve as proof of the findings in case of dispute, the original data (e.g. the voice recording or samples) should be stored beyond the end of the study. Researchers might also want to save data for possible further research which this then raises the

issue of consent for the further use of research data (which has been addressed elsewhere in this report).

5.2.6 Privacy

What is privacy?

Privacy covers issues related to the control and management of personal information about somebody's thoughts, body and experiences (Fawcett and Garity, 2009). In the context of the person's body, information could perhaps be understood as including somebody else seeing that person's body. The control and management of privacy by the person concerned depends to some extent on the situation or context, as well as his/her personal values and experience. There may also be cultural differences linked to what is considered acceptable or appropriate.

Privacy in observational research

In some forms of research, such as ethnographic or field research, the researchers are interested in observing naturally occurring behaviour and conversations. Sometimes (e.g. in participant observational studies), the researchers interact directly with the participants, sometimes joining them in their daily activities, whereas in others they remain separate and observe or record behaviour from a distance.

Observing other people's behaviour represents an intrusion into their privacy. This is perhaps not so much the case when they are in the public domain (e.g. sitting in a park, waiting for a train or shopping) but there is a difference between passively watching people go about their daily lives and systematically studying their observed behaviour. Researchers must obtain consent if they want to observe people for the purposes of a study, either in person or by means of recording equipment. However, for some studies the people who are to be observed lack the capacity to consent or even assent to being observed. Their relatives or legal advisors may have consented to an observational study. They might not necessarily have explained to the person concerned that s/he is being observed.

Some people may not mind being observed and even appreciate the attention. Others may object to being observed or consent to it but then feel very uncomfortable about it and have a feeling that their privacy is being invaded (Parrot, 2002).

Provided that people know that they are being observed (and also where and when) and have the opportunity to consent and withdraw from the study, there should not be an ethical problem. The problem arises, when they are not aware of this or did not consent to it.

Observational research raises issues of dignity and respect. To a greater or lesser extent, people generally like to have some control over the image that they present to other people. One's image is a reflection of one's identity and may affect the way that one is treated by others. According to Goffman (1959), people manage their appearance and behaviour (in a similar way to actors taking on various roles and performances)

and people cooperate with each other in supporting each other's social identities and performances. People with dementia may find it increasingly difficult to manage their performance. Video recording without their consent results in a record being made of a performance which they might have preferred not to share.

In group settings, some people may have consented to being observed or filmed for research purposes but others not. However, it may be difficult for the researchers not to film them too and may occasionally interact with them. This may make some people with dementia feel uneasy and perhaps distrustful of the researchers. After all, how can they be sure that they are not also being studied? Also, even if they are not, they have nevertheless been filmed without their consent and that film may be seen by other people. They have no control over the diffusion of images that have been taken of them.

Privacy in the context of qualitative interviewing

When people consent to being interviewed, they should normally already have some idea of the topic that will be discussed. However, there are different approaches to qualitative interviewing ranging from very structured, to semi-structured, to unstructured. Sometimes participants will just have an idea of the general topic, sometimes they may already know the precise questions that they will be asked. One of the features of qualitative interviewing is that it is flexible so researchers may spend more time on some issues and less on others, follow up hunches, test out their understanding of what the person means and focus on novel issues that a person raises which are relevant to the topic.

Consequently, participants do not always realize until the questioning starts how deep or probing the questions will be. Some may find the depth of probing disturbing but have difficulty expressing why or stopping the interview, particularly if the interview is taking place in their own home. Some people may only start to feel uneasy about the depth of disclosure after the interview.

It is quite common for people with dementia to be interviewed in the presence of their carer as the latter can help the person to understand the questions or communicate their thoughts to the researcher. The presence of a carer may also be helpful in detecting fatigue, stress or discomfort and help bring the interview to a premature end. The researcher should also be attentive to such factors but having less knowledge about the participant might fail to detect the relevant signs. In some cases, researchers might be equally interested in the views of the carer and that is the reason for the presence of the carer (although clearly the two could be interviewed separately in that case).

A drawback to having the carer present is that it could interfere with the right to privacy of the person with dementia. It cannot be presumed that all couples share all their thoughts and feelings with each other. Moreover, depending on the topic, the presence of the carer may result in certain information being withheld which would not be conducive to good research but is an issue which researchers need to take into account when designing their study and in particular how to collect data.

5.2.7 Vulnerability

Vulnerable groups and what we mean by vulnerability

A wide range of vulnerable human research participants have been identified in several reports and international documents on ethics and research. Those which might be relevant to people with dementia include people incapable of giving consent, people in nursing homes, ethnic and racial minority groups, older people, people with limited capacity or freedom to consent or to decline consent, people who will not derive benefit from participation, people for whom research is mixed with clinical care, the very sick and the institutionalized (Hurst, 2008). Vulnerability may also be contextual and influenced by dynamic processes which are not permanent. For example, a person may be more vulnerable at certain times of the day, in certain environments, after a couple of hours' discussion or after an operation. Researchers cannot be expected to know specific circumstances which might render individual people vulnerable. Consultation with carers would therefore be beneficial.

Hurst (2008) draws attention to issues of particular importance when considering the protection of vulnerable research participants such as those linked to consent, harm and fairness. These issues are in fact relevant to all research participants but in the case of vulnerable research participants, depending on the particular feature which leads to them being considered as vulnerable, additional efforts may be needed to protect them. Consequently, the protection of vulnerable research participants does not address additional ethical issues; it simply increases the efforts needed to ensure that general ethical issues are adequately addressed for certain groups of people in order to reduce the likelihood of those people incurring additional or greater wrong (Hurst, 2008).

In the case of dementia, the main issues which might result in people with dementia (as a group, not individually) being considered as vulnerable are age, cognitive impairment, being dependent on others for care and/or being a resident in a long-term care institution. Additional factors may co-exist based on being a member of an ethnic minority group, gender, physical disability, sexual orientation and living situation (e.g. being homeless, a prisoner or nomadic). Research participants who have end-stage dementia represent yet another sub-group (this is further discussed in section 8 on end-of-life research). The particular vulnerability of people with dementia might therefore be linked to factors such as them not understanding the risks involved, giving invalid consent, being coerced to consent, not being respected (due to ageism and the stigma generally associated with mental disorders), not being consulted at all, being in a less powerful position, being denied access to participation or alternatively being exploited. This will vary depending on the situation of each individual and the severity of his/her dementia. Also, some studies may just involve people with dementia from a particular sub-group (e.g. people with dementia in institutional care, over a specific age, just male or just female, from an ethnic group etc.).

People in the last stage of a terminal illness have been described as especially vulnerable as they are faced with many losses, confronted with overwhelming burdens, may be afraid and may be experiencing unpleasant symptoms. Whenever a person is dependent

on another for his/her treatment, care and wellbeing, there is a risk of that person feeling under pressure to participate in a study. Raudonis (1992) describes participants in end-of-life research as "a captive audience" but this could equally apply to other kinds of research carried out in institutional settings. Participants may be afraid that failure to cooperate will result in the loss of their place in a palliative care unit. People dying with or from dementia may be dependent on others involved in the research for the appropriate and timely administration of pain relief or to take care of their basic needs (Addington-Hall, 2002). They may be afraid of the consequences of non-compliance with the researcher's requests and feel that having agreed, they no longer have any choice. Such fears may also apply to carers who are asked to consent on behalf of a person with dementia, particularly when the person is receiving care and treatment in a hospital or hospice where they cannot be present all the time.

Risks linked to categorizing groups of people as vulnerable
Several arguments have been put forward against a group-based approach to vulnerability.

First, it detracts somewhat from the perception of the potential vulnerability of all human beings (as being capable of suffering) as well as of the increased vulnerability of individuals based on reasons which are not immediately evident.

Second, it focuses on the groups concerned and highlights a particular attribute (i.e. being vulnerable). This could be interpreted as those groups having or being "the problem". Another way of looking at vulnerability would be in the context of relationships between people. Hurst (2008) describes vulnerability as a two-way street also involving researchers who have a duty to avoid identifiable wrongs.

Third, the reference to groups contributes towards overlooking similarities and differences between both groups and individuals. For example, many groups require the same type of protection, some people belong to more than one group and some members of a group may need additional protection with regard to certain issues but not others (DuBois, 2008).

Fourth, there is a risk of stereotyping vulnerable research participants. This might involve attaching additional attributes (such as weak, needy, powerless etc.) which devalue those groups of people and may lead to unfair treatment or discrimination. Stereotypes are inaccurate generalizations which exaggerate and distort similarities and ignore the differences between people from various identifiable groups. Linking vulnerability to particular groups may also reinforce existing stereotypes associated with those groups (e.g. that people with dementia are totally incapacitated).

Finally, there is a risk that categorizing people as vulnerable might result in their overprotection. This would prevent them from exercising their autonomy and having an equal right to take part in research. It could also interfere with the advancement of science and at the same time prevent people with dementia from benefiting from the results of research into their condition, care and treatment (Hurst, 2008). Types of vulnerability and a non-group-based approach to vulnerability

An alternative non-group based approach to vulnerability involves assessing people for specific vulnerabilities and heightened risks. A specific condition or diagnosis (e.g. dementia) would alert researchers and justify them in assessing people with that condition for different types of vulnerability insofar as they relate to their study (DuBois, 2008). Six types of vulnerability have been identified by the National Bioethics Advisory Commission (2001). These are: cognitive or communicative vulnerability, institutional vulnerability, deferential vulnerability, medical vulnerability, economic vulnerability and social vulnerability.

5.2.8 Transparency and official recognition of researchers and studies

Researchers are not always recognisable as such. They do not tend to have official cards proving their status as a researcher, although most principal researchers would have documents proving that they had been granted ethical approval, governance approval or funding. This should be stated in the participant information sheet which all potential participants should receive as part of the informed consent process. However, very few people would ask to see copies of such authorisation.

Some researchers have academic posts, student identification or proof that they are a member of a recognised organisation (e.g. a pharmaceutical company, government body or advocacy group) which is carrying out research. When the researcher is a medical professional (e.g. a doctor or nurse), it may be unclear that s/he is also a researcher.

In observational/ethnographic research, the role of the researcher may be somewhat ambiguous in that it may be unclear who is a researcher and who is not. The researcher might, for example, participate in the research in the guise of a member of staff (e.g. observing people with dementia or even other members of staff). In some studies, researchers may actually be members of staff (e.g. in day care centres or nursing homes) who use data routinely collected during their daily work or during specific periods of observation. Ethical issues linked to transparency, but also to dignity, privacy and autonomy, therefore need to be addressed when carrying out research of this kind.

Sometimes, people with dementia and carers are asked for their opinions or advice (e.g. about services, care, support or other relevant issues). This may involve filling out a questionnaire, being interviewed or perhaps taking part in a focus group. It may represent a worthwhile attempt to improve some aspect of the lives of people with dementia or their carers (e.g. to develop useful assistive technology or improve services) but not fulfil the strict criteria for it to be classed as research. Such attempts to involve service users in the creation, development or improvement of services should be seen in a positive light provided that the nature of the questioning or involvement is clear to all involved.

A distinction can perhaps be made between scientific or academic research and what is sometimes called "market research" (which is an organised event to gather information about markets or customers). The involvement of people with dementia and carers in such studies is questionable when the purpose is solely for the commercial gain or

personal interest of a company or individual and when this is not made clear or when the person with dementia lacks the necessary capacity to understand this. However, if information about the nature of the proposed involvement is provided and understood by the person with dementia or any other person who is asked to participate, they can make an informed decision about participation and may have reasons for wanting to be involved.

As has already been mentioned in sub-section 4.3, it is essential that people with dementia (or their legal representative if one has been appointed) understand the fundamental difference between research and treatment and that they are aware that they are consenting to research when this is the case. In some cases, researchers are not clear about this distinction either.

Research ethics committees often encourage researchers to involve patients and carers in the various stages of research such as the conceptualization and design of the study, and the dissemination of the results. Consulting people with dementia and carers in the initial development of the study and when drafting the protocol would take place before ethical approval was sought. As such, their involvement could be better described as co-researcher or advisor than as participant or subject. This has implications for the protection of their wellbeing. Although they would be involved in research, they would not have received a participant information sheet or signed a consent form, would not necessarily know in advance what to expect and would not benefit from the results of the reflection on ethical issues which is part of the process of seeking ethical approval for a study.

5.2.9 Deception

What is deception?

Deception was used fairly extensively in social psychology studies in the 1970s and 1980s (DuBois, 2008) but is not used as much nowadays (Hertwig and Ortmann, 2008). When used, it often involves lying (providing information that is untrue) and concealment (not revealing the purpose of the study or the identities of various people involved in the study) but there are other forms of deception such as exaggerating, making understatements and making indirect, ambiguous or misleading statements (Buller and Burgoon, 1996). Day et al. (2011), who carried out qualitative interviews with people with dementia about the use of lies and deception in dementia care, report that some people with dementia made a distinction between blatant lies and little white lies, the latter being associated with deceptive acts which are more subtle in nature.

Some researchers use deception but opt for controlled transparency in which participants are not deceived or tricked but the information provided just covers the essential details that participants need to know in order to make an informed decision.

Deception may also occur where people agree to take part in a study because they believe that it will be beneficial to them. This is called the therapeutic misconception. This may be due to their failure to understand the difference between treatment or care

and research and not involve any kind of deliberate deception. However, it is the duty of researchers to ensure that potential participants have understood this distinction.

Arguments in favour of the use of deception

Deception about the purpose of the study has been justified on the grounds of social desirability. This means that there is a risk that if participants know everything about the study, they may give responses or try to behave in a way that they think will be perceived as socially desirable or acceptable by the researcher. However, irrespective of whether deception is used, other reactions are possible. According to Tashakkori and Teddlie (1998),

- some participants will try to be helpful by behaving in accordance with what they think the researcher wants,
- some participants will be negativistic or suspicious and deliberately do the opposite of what they think the researcher wants, and
- some will try to act and answer authentically.

The use of deception in research is still accepted by the American Psychological Association (APA) provided that 1) the study is of significant value, 2) that non-deceptive procedures are not feasible, 3) that deception would not cause pain or severe emotional distress and 4) that participants are informed of the deception at the latest at the conclusion of the data collection, so that they can withdraw their data if they so wish (DuBois, 2008).

Benham (2008) argues in favour of deception in social-behavioural research based on a presumed "enrichment benefit". He describes this as a unique opportunity to gain insight into oneself or others based on conditions or methods to which people do not normally have access. This is, of course, based on researchers revealing the deception and the results of the study to the participants afterwards, which is probably not always the case.

It is possible that for people with limited capacity or whose capacity deteriorates during the course of the study or before the results are made available, the concept of deception may not be fully understood or its revelation may come too late. Also, some might be unable to gain insight into themselves or others due to cognitive impairments. Depending on the duration of the study and the speed of cognitive decline of participants with dementia, debriefing may be impossible for some participants.

Nevertheless, it is possible that the total prohibition of all forms of deception in research would prevent researchers from carrying out many important studies which would have been beneficial for society (Kimmel, 1998) and such prohibition could therefore be considered as immoral (Christensen, 1988).

Arguments against the use of deception in research

Baumrind (1976) argues that the benefits to society are often over-estimated and the costs to the individual and society underestimated. In line with a personalist approach to ethics, which places greater value on the life and integrity of the person than on any

function that the person might be called upon to serve, and as ethical theories do not tend to condone deception as a principle of action, Baumrind concludes that deception is unacceptable within research and that researchers who use deception are taking advantage of people's implicit trust (Baumrind, 1964 and 1976). She further states:

"Only by acting in accord with agreed-upon rules, keeping promises, and avoiding deceit can human beings construct for themselves a coherent, consistent environment in which purposive behavior becomes possible. Thus, the long-range good that truth-telling promotes facilitates self-determination or authority over one's own person." (Baumrind, 1976, 23-11)

This seems to be particularly relevant in the case of dementia research in which some participants may be struggling to make sense of their everyday lives, as well as venturing into the unfamiliar domain of research.

Other criticisms of the use of deception are that it fails to respect participants, may result in loss of trust, may harm participants and may foster insincerity amongst participants which would be counterproductive to researchers and that other approaches should be found (Baumrind, 1964; Sieber, 1982 in DuBois, 2008). It has also been suggested that deception in research may wrong people (NHS, 2009). This has connotations of injustice, violation and being discredited.

With regard to psychological wellbeing, deception may result in feelings of incongruence, perhaps resulting in people feeling that they have acted in a way which is not in keeping with their values. Guidelines (e.g. from the American Psychological Association) suggest that deception should not be used if it would be likely to cause severe emotional distress. There must be some measure of severe emotional distress which is meaningful to people with dementia and which takes into account the difficulties they may experience communicating their distress. Feeling tricked or deceived may be particularly worrying for people who are dependent on others for their wellbeing and care as is the case for many people with dementia. Moreover, if the distress occurs after the study, there may be no measures in place to help the participant deal with it.

Clare (2003) draws attention to emotion-based coping strategies which are often used by people with dementia (such as denial or normalization of the illness or symptoms) and how the discovery of a lie may inhibit such strategies by forcing people to face their illness.

The study by Day et al. (2011) into the attitudes of people with dementia regarding lies and deception in dementia care suggests that the impact of lies and deception may differ according to who is using such practices, the stage of dementia of the person on the receiving end, whether s/he is aware of the lie and whether it is in his/her best interests. The participants felt that lying elicited distress or anger due to the impact on relationships or self-concept, and that they found it patronising or demeaning, implying that they were perceived as a person with dementia rather than a "normal" person. Whilst this

study was small scale, it suggests that the use of lies and deception may be perceived differently by people who have dementia than by people who do not.

Carers may also feel misled, disappointed and distressed if they find out that the person with dementia will not benefit from the study which s/he is already taking part in. The subsequent lack of trust in researchers by people with dementia and their carers may damage the reputation of individual researchers or research organisations and even the research profession in general with possible consequences for the recruitment of participants for other studies (Epley and Huff, 1998; Ortmann and Hertwig, 1998).

The whole issue of possible harm caused by deception is unclear. Some researchers argue that research participants do not perceive deception as being harmful and that some even enjoy the experience of such studies and their educational benefits more than studies not involving deception (Christensen, 1988). They nevertheless suggest that the use of deception is more likely to be perceived as unethical in studies investigating private behaviours. Hertwig and Ortmann (2008) suggest that there are many factors influencing possible distress caused by deception such as how well a person tolerates loss of control and being fooled, his/her expectations about honesty within research and the extent and nature of the deception. They conclude that further research is needed to clarify the impact of deception on research participants.

5.3 Recommendations on the protection of personal wellbeing

PROTECTION AGAINST HARM

Researchers should have at least a basic understanding of dementia.

Lay people (including carers of people with dementia) should be encouraged to sit on research ethics committees and to be actively involved in the assessment of dementia research.

Lay people and professionals who sit on research ethics committees should be provided with any necessary training (e.g. linked to ethics, research or dementia).

Researchers should envisage the possibility of participants experiencing emotional or psychological harm and ensure that any person who is exposed to their research materials or data collection processes knows whom to contact for support. This could be a member of the research team with the appropriate training and skills or perhaps a counsellor or relevant association.

Participants should have the full contact details of a person whom they can contact in case of dissatisfaction with any aspect of the study. The contact person should be somebody who is not directly involved in the data collection and analysis but is knowledgeable about the study and has the means to deal with possible problematic situations.

DIGNITY, INTEGRITY AND RESPECT

Respecting the dignity of people with dementia and carers (and other research participants) should include polite, respectful behaviour (e.g. being considerate, attentive and well-mannered), and respecting individuality and cultural traditions.

Researchers should use appropriate language when speaking to or referring to people with dementia. Terms such as "demented" and "suffering from dementia" should be avoided.

Researchers should, through their own behaviour and attitudes, strive to promote and protect the dignity of people with dementia even in cases where it seems that the latter are not concerned or lack awareness or insight.

The protection of the dignity of research participants should extend to the body of the deceased person in the case of post-mortem research.

Measures to promote the wellbeing of research participants should focus on what is positive and desirable, rather than concentrating solely on what is lacking and negative.

As wellbeing is encompassing and holistic, as well as a subjective experience, attempts should be made during and after the research to assess how people feel or felt about the experience.

The use of standard feedback forms and quantitative measures, which can be completed anonymously, should be considered. This may be particularly helpful in eliciting criticism and discontent.

Qualitative methods and approaches involving direct, meaningful interaction with participants should also be considered for the purposes of obtaining feedback about participants' wellbeing but also as a means to actively contribute to their wellbeing and communicate to them that they are valued.

PERSONHOOD

Researchers should try to meet people with dementia in a genuine human exchange, even in the absence of verbal communication.

This may require familiarization with verbal and non-verbal communication techniques in order to facilitate interaction.

Researchers should be aware of and if necessary challenge processes and interactions in the context of research which risk depersonalizing people with dementia.

PRIVACY AND CONFIDENTIALITY

Strategies to ensure privacy and confidentiality should be included in the research protocol.

Participants should be informed in advance that if they participate in the study, whilst confidentiality would be assured, the researcher would have to consider taking appropriate action if informed of criminal acts.

VULNERABILITY

People with dementia should not be labelled in a blanket fashion as vulnerable.

The diagnostic label of dementia should justify the assessment of people with dementia for specific vulnerabilities in relation to a specific study as they may be more vulnerable than others.

TRANSPARENCY

Principal researchers should have some means of proving their status as researcher and of identifying their research assistants or co-researchers.

A system should be developed by independent or academic research ethics committees to provide researchers having obtained ethical approval with a means of identification, which participants can verify.

Measures should be taken to ensure that participants understand whether they are being asked to participate in research or in other activities such as service user-involvement, consultation or "market research."

DECEPTION

The use of deception, particularly with participants who have dementia, should be avoided and only used in exceptional circumstances.

Even in exceptional circumstances, the use of deception should only be considered if:

- an alternative design which would not involve deception is not possible;
- the study does not entail more than minimal risk;
- there is a sound scientific justification for the use of deception;
- · participants will be debriefed after the study;
- other people or representatives from the target group of participants have been consulted in the design of the project.

If deception is used in a study, participants should have the right, once debriefed, to request that any data collected from them be excluded from the study.



Risk, benefit, burden and paternalism

6 Risk, benefit, burden and paternalism

6.1 Background information about risk and burden

Risk is sometimes described as ranging from minimal to greater than minimal with various degrees of risk between those two poles such as a minor increase over minimal risk (Alzheimer's Association, 1997, American Psychological Association, 1981). Risk is often discussed along with burden and balanced against possible benefit. There are limits to the degree of risk and burden that is considered acceptable for research involving people who are unable to consent, with greater restrictions being placed on research which does not entail personal benefit.

A risk is generally considered as being low if it does not exceed that associated with the kind of routine medical or psychological examinations that are typical for people from the same group as the participant (e.g. a person with dementia). The US Department of Health and Human Services (2011) defines minimal risk as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests". The International Ethical Guidelines for Biomedical Research of 2002 allow for levels of risk which are slightly higher than those linked to routine medical or psychological examinations if there is an overriding scientific or medical rationale for the increased risk and provided that an ethical review committee has approved the study. An example of a high risk would be that detected in the phase II trials into the AN-1792 Alzheimer vaccine in which 6% of participants developed severe brain inflammation resembling meningoencephalitis which led to the trial being abandoned in 2002.

Benefit, which has already been discussed in relation to the issue of consent, is also relevant to the assessment of risk. Perceptions of risk are often balanced against perceptions of possible benefit. As mentioned earlier, the definition of benefit is often too narrow to take fully into account the kinds of benefits that are possible and important to people participating in dementia research, such as spiritual, emotional or psychological benefit.

Burden, like risk and benefit, is subjective as it depends on people's values, what they are willing to tolerate and what they do and do not find acceptable. Examples of possible burden include having to fast before research interventions, travelling to the research centre in bad weather or when one has reduced mobility, accepting changes in one's daily routine, carrying out activities or tasks which are stressful, boring or repetitive, experiencing performance anxiety when asked to perform cognitive tests, having to spend long periods of time waiting or filling out forms and so on.

Paternalism is relevant to the issue of risk as it is one approach to minimizing risk. Paternalism usually involves the intentional restriction of a person's freedom (e.g. the freedom to decide for oneself) on the grounds that the restriction will protect or promote that person's wellbeing (Jansen and Wall, 2009). Usually the restriction applies to the person

whose own good is allegedly being protected. However, in the case of indirect paternalistic interference, it may apply to other people (Dworkin, 1972 in Jansen and Wall, 2009). An example would be the refusal to grant authorisation to researchers to carry out a particular study in order to protect the wellbeing of willing participants (Jansen and Wall, 2009).

6.2 Ethical issues linked to risk, benefit and paternalism

6.2.1 Balancing personal risk and benefit to society

The two following quotations reflect different positions regarding the possible gain to society and the risk or burden on/to participants.

"...ethics is a matter of principled sensitivity to the rights of others ... Ethics say that while truth is good, respect for human dignity is better, even if, in the extreme case, the respect for human dignity leaves one ignorant of human nature." (Blumer cited in Dench et al., 2004, p4).

"It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries." (Celsus cited in Sodeke, 2005)

The first statement emphasizes human rights and dignity, and clearly suggests that the pursuit of knowledge at all costs is unjustified and undesirable. It suggests that we must not lose sight of the safety, interests and wellbeing of the research participant through the relentless pursuit of knowledge. The second statement, which was made by a 1st century physician, seems to suggest that suffering may be justifiable if a greater number of people benefit from it but also that it may be more acceptable to allow certain groups or categories of people to suffer for the benefit of others who are considered more worthy. Whilst criminals may have had few or no rights in the days of Celsus, the same argument could all too easily be applied to other groups of people who become marginalized or devalued based on a range or combination of factors such as age, mental health status, prognosis, gender, ability to contribute towards society, sexual orientation and ethnicity.

In the International Ethical Guidelines for Biomedical Research of 2002, benefit to society is defined as being "generalizable knowledge". This reflects a positivist approach to research. Whilst these guidelines are clearly linked to biomedical research, it is important to bear in mind that generalizability is not the main aim of qualitative research. Whilst the results of a small-scale qualitative study may have relevance to other groups of people sharing similar characteristics, this is something that readers can decide for themselves based on the details provided by the researcher. It is not determined by statistical analysis.

The risk of considering one group of people as sufficiently unworthy as to justify their suffering for the good of the rest of society may be higher if members of that group are stigmatized or lack the power or capacity to protect their own interests, hence the necessity to ensure that people with dementia who take part in research are sufficiently protected. On the other hand, care must be taken to respect the autonomy of people

with dementia and to avoid stereotyping them as defenseless victims, treating them as children and even limiting their opportunities to contribute towards research.

6.2.2 Making sense of risk

Historically, risk was considered as something that could be either good or bad, resulting in loss or gain, but Lupton (1999) claims that it has been transformed into something that is entirely negative. Within the social and healthcare system, risk has often been viewed as something that is objective and measurable (Kemshall, 2000), whilst others argue that it is socially constructed and value-laden (Lupton, 2005). Risk can also be perceived as opportunity in that it may result in change.

When weighing up the seriousness of possible risk, the possibility of such an outcome occurring should also be considered. In everyday life, for example, certain drugs for relatively trivial health problems have possible side effects which although extremely rare would be devastating if they occurred. Yet large numbers of people take them every day either without reading the information leaflets or in full knowledge of the risk involved. The likelihood of certain risks occurring may be affected by the situation in which one lives (i.e. whether a person lives alone or has the support of family, friends and the local community).

As a unique individual, each person with dementia has his/her own perception of danger and of the level of risk that s/he is willing to take. Having dementia may even be an additional motivation to take part in research (e.g. to benefit relatives and other people who may develop dementia in the future or as a means to contribute to society in some way). However, as the disease progresses, the capacity to give informed consent to research is likely to deteriorate. For many people, another person will eventually be consulted whose assessment of acceptable risk may determine whether or not they participate in research.

In the context of consent to research, none of the interventions are actually necessary for the participants (except perhaps in the case of emergency research) and people with dementia are considered as being potentially vulnerable research participants. There is therefore a risk of overprotecting people with dementia, infantilising them and depriving them of their autonomy. This could in the long run deprive people with dementia of the possibility to benefit from the results of studies into their particular condition. In some cases, such over-protection may reflect concerns about litigation processes in case of harm as well as genuine concern for the wellbeing of research participants.

6.2.3 The perspective of risk and benefit at the end of life

Glannon (2006) suggests that the relative significance of a possible benefit or risk depends on one's perspective. With regard to a particular study, outsiders and the potential participants may consider the possibility of benefit occurring and the possible risks involved differently. A person with dementia receiving end-of-life care may place great value on even the fraction of a hope of benefit despite an awareness of a much greater probability of harm occurring, including the emotional consequences of having one's

final hopes shattered. In such cases, focusing on an improbable but possible benefit (even though this is not the purpose of research) would not be a therapeutic misconception as the person would be fully aware of what was likely and what was at stake.

With regard to benefits which are not directly linked to health, Casaret, Jason and Karlawish (2000) point out that when people are approaching death, the things that they find important may change. They may, for example, place a greater value on dignity, meaning, control, strengthening relationships and addressing unfinished business of a personal nature. In the case of people with advanced dementia, the expression of such concerns or priorities may be difficult but this does not mean that they do not exist. Participating in research may, for some people with dementia, correspond to these new priorities (e.g. by providing meaning or enabling them to feel part of something). For others, it might actually interfere with current goals and priorities (e.g. by taking up valuable time they might prefer to spend with relatives or friends).

Similarly, a person who is very close to death might not assess the possibility of serious risk in the same way as a person who has not yet reached that stage. Some risks may be considered as being more significant and others less so (Casarett, Jason and Karlawish, 2000). This would depend greatly on the individual as well as on his/her awareness of his/her prognosis.

6.2.4 One-off or continuous assessment of risk and burden

Robley (1995, in Aita and Richer, 2005) points out that many qualitative studies are unpredictable and that this does not permit a proper evaluation of the benefits/risks ratio which in turn raises concerns about the rights of participants. This is because qualitative research tends to be a flexible and iterative process in which the data is analysed continuously rather than at the end of the data collection process. This may lead to insights which are fed back into the process and may lead to changes in the way data are collected or in any other aspect of the research process (Maxwell, 2005). Whilst ethical approval may have been sought and obtained from the appropriate ethics committees prior to the study, such approval often fails to take into account the iterative nature of qualitative research. Committees therefore oblige researchers to provide precise details (such as interview schedules) and describe various aspects of the study and then grant or refuse approval on that basis. This may result in researchers feeling uneasy about their own scientific integrity and could be interpreted as a failure to accept the validity of research based on the interpretivist paradigm. Obtaining research ethics approval and governance approval (e.g. from government health services) can be an extremely lengthy process (at least in the UK) and it would be impractical to submit every change along the way to additional approval (although there may be procedures in place for "substantial amendments").

6.2.5 Proportionality

It has been suggested that studies which clearly do not involve more than minimal risk should perhaps be dealt with more expediently than those involving a higher degree of risk by the IRB (an institutional review board which is a committee that performs ethical review of proposed research) (Emanuel and Menikoff, 2011). It is further suggested that as for many studies the main potential risk is linked to the confidential handling of data, it should be possible for research to commence immediately after the study has been registered and after a one-page form has been submitted accompanied by a commitment to observe data-security protections. However, whilst the ethical review of safety issues does seem exaggerated and clearly inappropriate for many studies, there are other ethical issues to be considered by ethics committees. The National Research Ethics Service (2011) defines its objectives as follows: "to facilitate ethical research that is of potential benefit to participants, science and society/.... to provide robust, ethical review of proposed research via Research Ethics Committees (RECs). These independent committees put the rights, safety, dignity and well-being of research participants at the centre of their decision making." Consequently, there may be a need to simplify the approval process for projects involving minimal risk but not at the expense of ensuring the pursuit of good science.

6.2.6 Paternalism

Jansen and Wall (2009) consider the arguments for and against paternalistic interference in the context of research. First, they argue that paternalistic interference (in clinical trials) is only ever justifiable in the case of studies which impose a serious risk of harm to participants or if the therapeutic benefits do not outweigh any risks of harm. This argument could perhaps also apply to other types of research, such as psychosocial research which might involve psychological risks. According to the principle of distributive fairness, research involves risks as well as benefits which should be shared equally amongst members of society in the sense that specific groups of people should not have an unequal share of these (neither harms nor benefits). Jansen and Wall (2009) identify four different types of harm which paternalistic interference may help protect against: physical harm, psychological harm, social harm and economic harm.

The main arguments against paternalistic interference are that individual liberty (the right to decide for oneself) should take precedence over issues related to welfare and distributive justice and that paternalism is insulting to the individual whose liberty is being restricted (Jansen and Wall, 2009). These arguments are mainly relevant to people who have the capacity to make their own decisions about research and the level of risk they are willing to take (which would nevertheless include many people with dementia, at least but not necessarily limited to those in the early stage), even if such decisions seem foolish.

Miller and Wertheimer (2007) suggest that a person who appears to be willing to seriously endanger his/her life or wellbeing for the sake of science must be insufficiently informed or be subject to some form of "autonomy bearing pressure". However, it must be borne in mind that people may be taking part in research for altruistic reasons which could be considered as a good reason. Taking part in the same study out of self-interest might be considered as a bad decision in view of the risk to oneself. Bearing in mind the fact that foolish decisions are ethically acceptable provided that the person has sufficient capacity, this is no reason to impose restrictions on participation. Also, there is no reliable

method of ascertaining whether a person wants to participate in a study for altruistic reasons or for self-interest. Another category of participant might include people who have no concern for their own personal wellbeing. This might be attributed to depression but could presumably exist in the absence of any disorder.

Jansen and Wall (2009) argue in favour of paternalistic interference on the grounds that it is unfeasible to have different rules and levels of protection for different research participants as it would be necessary to determine for each person which set might be applicable. A level of protection that is too lax would put the people who are at greater risk of making a bad decision at a disadvantage. Stricter regulations are therefore justifiable.

The second argument outlined by Jansen and Wall is that paternalistic interference is insulting in that even if it does not violate the right to autonomy, it implies that the potential participant is not capable of making a decision. They argue that this is an unfair assumption as regulations are not targeted at individuals and cannot therefore be justifiably perceived as a personal insult. Nevertheless, it may still be argued that it is unfair to restrict the liberty of some people for the sake of protecting the interests of others which could be perceived as an individualist approach which does not recognise the value of distributive fairness.

6.3 Recommendations on risk, benefit and paternalism

People with dementia (and their carers, provided that the person with dementia agrees), should be involved, to the greatest extent possible, in assessing the level of risk they are willing to take and the level of burden they are willing to accept when designing studies.

An inventory of possible risks and burdens should be made for each study.

Researchers should be transparent about potential risks and burdens, and communicate these to participants in a way that the latter can understand.

Strategies should be devised to address or minimize risk and burden.

Researchers should strive to find the right balance between protection and the promotion of autonomy.

Paternalistic practices and attitudes should be avoided.

People with dementia should not be treated like children or stereotyped as helpless.

It should be recognised that zero risk may be a worthy aim in the development of medication but that it is not necessarily realistic or even desirable in all other aspects of people's lives.

Researchers should have an insurance for any harm resulting from the research.

Potential participants should be invited, if possible, to speak about possible expected benefits linked to participation in a particular study and details of their responses should be noted.

Participants should be asked after the study about their experience of it (including details of benefits and burdens) and details of their responses noted.

Details of the responses from participants (or in some cases their proxies) about the perceived risks, benefits and benefits of participation should be taken into consideration by researchers when designing subsequent studies.



Medical research

7 Medical research

7.1 Background information about clinical trials

7.1.1 What are clinical trials and how are they controlled/governed?

A clinical trial is a biomedical/health-related study into the effects on humans of a new medical treatment (medicine/drug, medical device, vaccine or new therapy), sometimes called an investigational medicinal product (IMP). Before a new drug is authorised and can be marketed, it must pass through several phases of development including trial phases in which its safety, efficacy, risks, optimal use and/or benefits are tested on human beings. Existing drugs must also undergo clinical testing before they can be used to treat other conditions than that for which they were originally intended.

Organisations conducting clinical trials in the European Union must, if they wish to obtain marketing authorisation, respect the requirements for the conduct of clinical trials. These can be found in the Clinical Trials Directive ("Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, 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").

There are also guidelines to ensure that clinical trials are carried out in accordance with good clinical practice. These are contained in the "Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products" (also known as the Good Clinical Practice or GCP for short). This document provides more concrete guidelines and lends further support to the Clinical Trials Directive.

The London-based European Medicines Agency (EMA) has published additional, more specific guidelines which must also be respected. These include guidelines on inspection procedures and requirements related to quality, safety and efficacy.

Copies of the above-mentioned documents in 22 languages can be found at: http://ec.europa.eu/enterprise/pharmaceuticals/clinicaltrials/clinicaltrials_en.htm

The protection of people participating in clinical trials (and in most cases in other types of research) is further promoted by provisions of:

- the European Convention on Human Rights and Biomedicine (Oviedo Convention, Act 2619/1998),
- the Additional protocol to the Oviedo Convention concerning Biomedical Research
- the Nuremberg Code of 1949,

- the revised Helsinki Declaration of the World Medical Association regarding Ethical Principles for Medical Research Involving Human Subjects,
- The Belmont Report of 18 April 1979 on the Ethical Principles and Guidelines for the Protection of Human Subjects of Research.

7.1.2 What are the different phases of trials?

Testing an experimental drug or medical procedure is usually an extremely lengthy process, sometimes lasting several years. The overall procedure is divided into a series of stages (known as phases) which are described below.

7.1.3 Pre-clinical testing

Clinical testing on humans can only begin after a pre-clinical phase, involving laboratory studies (in vitro) and tests on animals, which has shown that the experimental drug is considered safe and effective.

Whilst a certain amount of testing can be carried out by means of computer modelling and by isolating cells and tissue, it becomes necessary at some point in time to test the drug on a living creature. Animal testing is an obligatory stage in the process of obtaining regulatory approval for new drugs and medicines, and hence a legal requirement (EU Directive 2001/83/EC relating to Medicinal Products for Human Use). The necessity of carrying out prior testing on animals is also stated in the World Medical Association's "Ethical Principles for Medical Research Involving Human Subjects.

In order to protect the well-being of research animals, researchers are guided by three principles which are called the 3Rs:

Reduce the number of animals used to a minimum

<u>Refine</u> the way that experiments are carried out so that the effect on the animal is minimised and animal welfare is improved

Replace animal experiments with alternative (non-animal) techniques wherever possible.

In addition, most countries will have official regulatory bodies which control animal research. Most animals involved in research are mice. However, no animal is sufficiently similar to humans (even genetically modified ones) to make human testing unnecessary. For this reason, the experimental drug must also be tested on humans.

7.1.4 The main phases of clinical trials

Clinical trials on humans can be divided into three main phases (literally, phase I, II and III). Each phase has specific objectives (please see below) and the number of people involved increases as the trial progresses from one phase to the next.

7.1.5 Phase I trials

Phase 1 trials are usually the first step in testing a new drug or treatment on humans after successful laboratory and animal testing. They are usually quite small scale and usually involve healthy subjects or sub-groups of patients who share a particular characteristic. The aims of these trials are:

- to assess the safety of experimental drugs,
- to evaluate any possible side effects,
- to determine a safe dose range,
- to see how the body reacts to the drug (how it is absorbed, distributed and eliminated from the body, the effects that it has on the body and the effects it has on biomarkers).

Dose ranging, sometimes called dose escalation, studies may be used as a means to determine the most appropriate dosage, but the doses administered to the subjects should only be a fraction of those which were found to cause harm to animals in the pre-clinical studies.

The process of determining an optimal dose in phase I involves quite a high degree of risk because this is the first time that the experimental treatment or drug has been administered to humans. Moreover, healthy people's reactions to drugs may be different to those of the target patient group. For this reason, drugs which are considered to have a potentially high toxicity are usually tested on people from the target patient group.

There are a few sequential approaches to phase I trials e.g. single ascending dose studies, multiple ascending dose studies and food effect.

In <u>single ascending dose studies</u> (SAD), a small group of subjects receive a very low dose of the experimental drug and are then observed in order to see whether that dose results in side effects. For this reason, trials are usually conducted in hospital settings. If no adverse side effects are observed, a second group of subjects are given a slightly higher dose of the same drug and also monitored for side-effects. This process is repeated until a dose is reached which results in intolerable side effects. This is defined as the maximum tolerated dose (MTD).

<u>Multiple ascending dose studies</u> (MAD) are designed to test the pharmacokinetics and pharmacodynamics of multiple doses of the experimental drug. A group of subjects receives multiple doses of the drug, starting at the lowest dose and working up to a predetermined level. At various times during the period of administration of the drug, and particularly whenever the dose is increased, samples of blood and other bodily fluids are taken. These samples are analysed in order to determine how the drug is processed within the body and how well it is tolerated by the body.

<u>Food effect studies</u> are investigations into the effect of food intake on the absorption of the drug into the body. This involves two groups of subjects being given the same dose of the experimental drug but for one of the groups when fasting and for the other after a meal. Alternatively, this could be done in a cross-over design whereby both groups receive the experimental drug in both conditions in sequence (e.g. when fasting and on another occasion after a meal). Food effect studies allow researchers to see whether eating before the drug is given has any effect on the absorption of the drug by the body.

7.1.6 Phase II trials

Having demonstrated the initial safety of the drug (often on a relatively small sample of healthy individuals), phase II clinical trials can begin. Phase II studies are designed to explore the therapeutic efficacy of a treatment or drug in people who have the condition that the drug is intended to treat. They are sometimes called therapeutic exploratory trials and tend to be larger scale than Phase I trials.

Phase II trials can be divided into Phase IIA and Phase IIB although sometimes they are combined.

Phase IIA is designed to assess dosing requirements i.e. how much of the drug should patients receive and up to what dose is considered safe? The safety assessments carried out in Phase I can be repeated on a larger subject group. As more subjects are involved, some may experience side effects which none of the subjects in the Phase I experienced. The researchers aim to find out more about safety, side effects and how to manage them.

Phase IIB studies focus on the efficacy of the drug i.e. how well it works at the prescribed doses. Researchers may also be interested in finding out which types of a specific disease or condition would be most suitable for treatment.

Phase II trials can be randomised clinical trials which involve one group of subjects being given the experimental drug and others receiving a placebo and/or standard treatment. Alternatively, they may be case series which means that the drug's safety and efficacy is tested in a selected group of patients. If the researchers have adequately demonstrated that the experimental drug (or device) is effective against the condition for which it is being tested, they can proceed to Phase III.

7.1.7 Phase III trials

Phase III trials are the last stage before clinical approval for a new drug or device. By this stage, there will be convincing evidence of the safety of the drug or device and its efficacy in treating people who have the condition for which it was developed. Such studies are carried out on a much larger scale than for the two previous phases and are often multinational. Several years may have passed since the original laboratory and animal testing.

The main aims of Phase III trials are:

to demonstrate that the treatment or drug is safe and effective for use in patients in the target group (i.e. in people for whom it is intended)

to monitor side effects

to test different doses or different ways of administering the drug

to determine whether the drug could be used at different stages of the disease

to provide sufficient information as a basis for marketing approval

Researchers may also be interested in showing that the experimental drug works for additional groups of people with conditions other than that for which the drug was initially developed. For example, they may be interested in testing a drug for inflammation on people with Alzheimer's disease. The drug would have already been proven safe and obtained marketing approval but for a different condition, hence the need for additional clinical testing.

7.1.8 Open label extension trails

Open label extension studies are often carried out immediately after a double blind randomised clinical trial of an unlicensed drug. The aim of the extended study is to determine the safety and tolerability of the experimental drug over a longer period of time, which is generally longer than the initial trial and may extend up until the drug is licensed. Participants all receive the experimental drug irrespective of which arm of the previous trial they were in. Consequently, the study is no longer blind in that everybody knows that each participant is receiving the experimental drug but the participants and researchers still do not know which group participants were in during the initial trial.

7.1.9 Post-marketing surveillance studies (phase IV)

After the three phases of clinical testing and after the treatment has been approved for marketing, there may be a fourth phase to study the long-term effects of drugs or treatment or to study the impact of another factor in combination with the treatment (e.g. whether a particular drug reduces agitation).

Usually, such trials are sponsored by pharmaceutical companies and described as pharmacovigilance. They are not as common as the other types of trials (as they are not necessary for marketing permission). However, in some cases, the EMA grants restricted or provisional marketing authorisation, which is dependent on additional phase IV trails being conducted.

7.1.10 Expanded access to a trial

Sometimes, a person might be likely to benefit from a drug which is at various stages of testing but does not fulfil the conditions necessary for participation in the trial (e.g. s/he may have other health problems). In such cases and if the person has a life-threatening or serious condition for which there is no effective treatment, s/he may benefit

from "expanded access" use of the drug. There must, however, be evidence that the drug under investigation has some likelihood of being effective for that patient and that taking it would not constitute an unreasonable risk.

7.1.11 The use of placebo and other forms of comparison

The main purpose of clinical drug studies is to distinguish the effect of the trial drug from other influences such as spontaneous change in the course of the disease, placebo effect, or biased observation. A valid comparison must be made with a control. The American Food and Drugs Administration recognises different types of control namely,

- placebo,
- active treatment with a known effective therapy or
- dose-comparison,
- no treatment,
- historical treatment (which could be an adequately documented natural history of the disease or condition, or the results of active treatment in comparable patients or populations).

The EMA considers three-armed trials (including the experimental medicine, a placebo and an active control) as a scientific gold standard and that there are multiple reasons to support their use in drug development¹⁰.

Participants in clinical trials are usually divided into two or more groups. One group receives the active treatment with the experimental substance and the other group receives a placebo, a different drug or another intervention. The active treatment is expected to have a positive curative effect whereas the placebo is expected to have zero effect. With regard to the aim to develop more effective treatments, there are two possibilities:

- 1. the experimental substance is more effective than the current treatment or
- 2. it is more effective than no treatment at all.

According to article 11 of the International Ethical Guidelines for Biomedical Research (IEGBR) of 2002, participants allocated to the control group in a trial for a diagnostic, therapeutic or preventive intervention should receive an established effective intervention but it may in some circumstances be considered ethically acceptable to use a placebo (i.e. no treatment). In article 11 of the IEGBR, reasons for the use of placebo are:

- 1. that there is no established intervention
- 2. that withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms
- that use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.

7.2 Ethical issues linked to clinical trials

7.2.1 The use of placebo and the issue of irreversible harm

It has been suggested that clinical trials are only acceptable in ethical terms if there is uncertainty within the medical community as to which treatment is most suitable to cure or treat a disease (National Bioethics Commission of Greece, 2005). In the case of dementia, whilst there is no cure, there are a few drugs for the symptomatic treatment of dementia. Consequently, one could ask whether it is ethical to deprive a group of participants of treatment which would have most likely improved their condition for the purpose of testing a potentially better drug (National Bioethics Commission of Greece, 2005). Can they be expected to sacrifice their own best interests for those of other people in the future? It is also important to ask whether not taking an established effective intervention is likely to result in serious or irreversible harm.

In the 2008 amended version of the Helsinki Declaration¹¹ (World Medical Association, 1964), the possible legitimate use of placebo and the need to protect subjects from harm are addressed.

"32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option." (WMA, 1964 with amendments up to 2008)

The above is also quite similar to the position supported by the Presidential Commission for the Study of Bioethical Issues (PCSBI) (2011). In its recently published report entitled "Moral science: protecting participants in human subjects research¹²", the Presidential Commission argues largely in favour of a "middle ground" for ethical research, citing the work of Emanuel and Miller (2001) who state:

"A placebo-controlled trial can sometimes be considered ethical if certain methodological and ethical standards are met. It these standards cannot be met, then the use of placebos in a clinical trial is unethical." (Emanuel and Miller, 2001 cited in PCSBI, 2011, p. 89).

One of the standards mentioned is the condition that withholding proven effective treatment will not cause more than minimal harm.

7.2.2 The importance of placebo groups for drug development

The ethical necessity to include a placebo arm in a clinical trial may differ depending on the type of drug being developed and whether other comparable drugs exist. For example, a placebo arm would be absolutely necessary in the testing of a new compound for which no drug has yet been developed. This would be combined with comparative arms involving other alternative drugs which have already been proven effective. For studies involving the development of a drug based on an existing compound, a comparative trial would be necessary but not necessarily with a placebo arm, or at least with a smaller placebo arm. Nevertheless, the EMA emphasises the value of placebo-controlled trials in the development of new medicinal products even in cases where a proven effective drug exists:

"forbidding placebo-controlled trials in therapeutic areas where there are proven, therapeutic methods would preclude obtaining reliable scientific evidence for the evaluation of new medicinal products, and be contrary to public health interest as there is a need for both new products and alternatives to existing medicinal products." (EMA, 2001).

In 2001, concerns were raised about the interpretation of paragraph 29 of the 2000 version of the Helsinki Declaration in which prudence was called for in the use of placebo in research trials and it was advised that placebo should only be used in cases where there was no proven therapy for the condition under investigation. A document clarifying the position of the WMA regarding the use of placebo was issued by the WMA in 2001 in which it was made clear that the use of placebo might be ethically acceptable even if proven therapy was available. The current version of this statement is article 32 of the 2008 revised Helsinki Declaration (quoted in sub-section 7.2.1).

The PCSBI (2011) highlight the importance of ensuring that the design of clinical trials enables the researchers to resolve controversy and uncertainty over the merits of the trial drug and whether the trial drug is better than an existing drug if there is one. They suggest that studies which cannot resolve such questions or uncertainty are likely to be ignored by the scientific community and this would be unethical as it would mean that people had been unnecessarily exposed to risk without there being any social benefit.

7.2.3 Reasons for participation

People with dementia who take part in clinical trials may do so for a variety of reasons. One possible reason is that they hope to receive some form of treatment that will improve their condition or even result in a cure. This is sometimes called the "therapeutic misconception". In such cases, clinical trials may seem unethical in that advantage is being taken of the vulnerability of some of the participants. On the other hand, the possibility of participating in such a trial may help foster hope which may even enable a person to maintain their morale.

A review of 61 studies on attitudes to trials has shed some light on why people participate in clinical trials (Edwards, Lilford and Hewison, 1998). In this review, it was found that over 60% of participants in seven studies stated that they did or would participate in clinical trials for altruistic reasons. However, in 4 studies, over 70% of people stated that they participated out of self-interest and in two studies over 50% of people stated that they would participate in such a study out of self-interest. As far as informed consent is

concerned, in two studies (which were also part of this review) 47% of responding doctors thought that few patients were actually aware that they were taking part in a clinical trial. On the other hand, an audit of four further studies revealed that at least 80% of participants felt that they had made an autonomous decision. There is no proof whether such perceptions were accurate or not. The authors conclude that self-interest was more common than altruism amongst the reasons given for participating in clinical trials but draw attention to the poor quality of some of the studies reviewed thereby suggesting the need for further research. It should not be necessary for people to justify why they are willing to participate in clinical trials. Reasons for participating in research are further discussed in section 3.2.4 insofar as they relate to end-of-life research.

In a series of focus groups organised in 8 European countries plus Israel and covering six conditions including dementia, helping others was seen as the main reason why people wanted to take part in clinical trials (Bartlam et al., 2010). In a US trial of anti-inflammatory medication in Alzheimer's disease in which 402 people were considered eligible, of the 359 who accepted, their main reasons for wanting to participate were altruism, personal benefit and family history of Alzheimer's disease.

7.2.4 Random assignment to study groups

As people are randomly assigned to the placebo or the active treatment group, everyone has an equal chance of receiving the active ingredient or whichever other control groups are included in the study. There are possible advantages and drawbacks to being in each group and people are likely to have preferences for being in a particular study group but randomization means that allocation is not in any way linked to the best interests of each participant from a medical perspective. This is not an ethical issue provided that each participant fully understands that the purpose of research is not to provide a tailor-made response to an individual's medical condition and that while some participants benefit from participation, others do not.

There are, however, medical issues to consider. In the case in double-blind studies, neither the participant nor the investigator knows to which groups a participant has been allocated. Consequently, if a participant encounters medical problems during the study, it is not immediately known whether this is linked to the trial drug or another unrelated factor, but the problems must be addressed and possible contraindications avoided, which may necessitate "de-blinding" (DuBois, 2008).

Although many people would perhaps like to benefit from a new drug which is more effective than existing drugs, people have different ideas about what is an acceptable risk and different reasons for taking part in clinical trials. People who receive the placebo are not exposed to the same potential risks as those given the experimental drug. On the other hand, they have no possibility to benefit from the advantages the drug may offer. Those receiving a drug commonly considered as the standard therapy are not necessarily better off than those receiving a placebo as some participants may already know that they do not respond well to the accepted treatment (DuBois, 2008).

If people who participate in a clinical trial are not informed which arm of the trial they were in, valuable information is lost which might have otherwise contributed towards to treatment decisions made after the clinical trial. Taylor and Wainwright (2005) suggest that "unblinding" should occur at the end of all studies and so as not to interfere with the analysis of data, this could be done by a person who is totally independent of the analysis. This would, however, have implications for open label extended trials as in that case participants, whilst better equipped to give informed consent would have more information than the researchers and this might be conveyed to researchers in an *ad hoc* manner.

7.2.5 Open label extension trails

Open label extension studies (mentioned in sub-section 7.1.8) seem quite fair as they give each participant the opportunity to freely consent to continuing with the study in the full knowledge that s/he will receive the experimental drug. However, Taylor and Wainwright (2005) have highlighted a couple of ethical concerns linked to the consent process, the scientific value of such studies and issues linked to access to drugs at the end of the prior study.

With regard to consent, they argue that people may have had a positive or negative experience of the trial but do not know whether this was due to the experimental drug, another drug or a placebo. They may nevertheless base their decision whether to continue on their experience so far. For those who were not taking the experimental drug, their experience in the follow-up trial may turn out to be very different. Also, if they are told about the possibility of the open label extension trial when deciding whether or not to take part in the initial trial (i.e. with the implication that whatever group they are ascribed to, in the follow-up study they will be guaranteed the experimental drug), this might induce them to participate in the initial study which could be considered as a form of subtle coercion. Finally, researchers may be under pressure to recruit as they can only recruit people in an open label extended trial who took part in the initial study. This may lead them in turn to put pressure (even inadvertently) on participants to continue with the study.

The scientific validity of open label extension trials is questioned by Taylor and Wainwright (2005) on the grounds that people from the experimental arm of the first study who did not tolerate the drug would be unlikely to participate in the extension trial and this would lead to bias in the results. In addition, open-label trials often lack a precise duration other than "until the drug is licensed" which casts doubt on there being a valid research purpose.

The above authors suggest that open label extension studies are dressed up marketing activities which lack the ethical justification for biomedical research which is the prospect of finding new ways of benefiting people's health. However, it could be argued that the aim of assessing long-term tolerability of a new drug is a worthwhile pursuit and if conducted in a scientific manner could be considered as research. Moreover, not all open label extension trials are open-ended with regard to their duration. The main problem in

interpreting open label extension studies is that little is known about the natural course of the disease.

7.2.6 Protecting participants' well-being at the end of the clinical trial

Some people who participate in a clinical trial and who receive the experimental drug experience an improvement in their condition. This is to be hoped even if benefit to the health of individuals is not the aim of the study. However, at the end of the study, the drug is not yet licenced and there is no legal right to continue taking it. This could be psychologically disturbing to the participants in the trial and also to their families who may have seen a marked improvement in their condition.

Taylor and Wainwright (2005) suggest that the open label trials may serve the purpose of prescribing an unlicensed drug on compassionate grounds, which whilst laudable, should not be camouflaged as scientific research. Rather governments should take responsibility and set up the appropriate legal mechanisms to make it possible for participants whose medical condition merits prolonged treatment with the experimental drug to have access to it.

7.2.7 Minimising pain and discomfort

Certain procedures to which people with dementia or their representatives consent may be burdensome or painful or simply worrying but in accordance with the principles of autonomy or justice/equity, people with dementia have the right to participate. The fact that they have made an informed decision to participate and are willing to tolerate such pain or burden does not release researchers from the obligation to try to minimise it. For example, if repeated blood samples are going to be necessary, an indwelling catheter could be inserted under local anaesthetic to make it easier or medical staff should provide reassurance about the use of various scanning equipment which might be worrying or enable the person's carer to be present. In order to minimise fear, trained personnel are needed who have experience dealing with people with dementia. The advice of the carer, if there is one, could also be sought.

7.2.8 Drug trials in countries with less developed safeguards

Clinical trials are sometimes carried out in countries where safeguards are not well developed and where the participants and even the general population are likely to have less possibility to benefit from the results of successful trials. For example, some countries have not signed the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (1997) (referred to in section 4.2.6.1). The participants in those countries may be exposed to possible risks but have little chance of future medical benefit if the trial is successful. Yet people in countries with stricter safeguards for participants (which are often richer countries) stand to benefit from their efforts and from the risks they take, as they are more likely to be able to afford the drugs once developed. This raises ethical issues linked to voluntariness because there may be, in addition to the less developed safeguards, factors which make participation in such trials more attractive to potential participants. Such practices

also represent a lack of equity in the distribution of risk, burden and possible benefit within society and could be interpreted as using people as a means to an end.

Parallels can also be drawn to the situation whereby people in countries where stem cell research is banned profit from the results of studies carried out in countries where it is permitted or to the results of studies carried out in countries where research ethics are slack or inexistent.

For a detailed discussion of the ethical issues linked to the involvement in research of people in other countries, particularly lower and middle income countries where standards of protection may be lower, please refer to the afore-mentioned report by the Presidential Commission for the Study of Bioethical Issues.

7.3 Recommendations about clinical trials

Researchers should consider including a placebo arm in clinical trials when there are compelling and sound methodological reasons for doing so.

Researchers should ensure that patients are aware that the aim of a randomised controlled trial is to test a hypothesis and provide generalizable knowledge leading to the development of a medical drug or procedure. They should explain how this differs from medical treatment and care which are aimed at enhancing the health and wellbeing of individual patients and where there is a reasonable expectation that this will be successful.

Researchers should ensure that potential participants understand that they may be allocated to the placebo group.

It should not be presumed that the treating doctor or contact person having proposed the participant for a trial has been successful in communicating the above information.

Researchers conducting clinical trials may need training in how to ensure effective communication with people with dementia.

Appropriate measures should be taken by researchers to minimise fear, pain and discomfort of participants.

All participants should, when possible, preferably have the option of receiving the experimental drug (if proven safe) after completion of the study.

Pharmaceutical companies should not be discouraged from carrying out open-label extension studies but this should not be the sole possibility for participants to access the trial drug after the end of the study if it is proving beneficial to them.

In multi-centre clinical trials, where data is transferred to another country in which data protection laws are perhaps less severe, the data should be treated as stated in the consent form signed by the participant.

7.4 Background information about epidemiological research

Epidemiology is the study of disease distribution in populations and of factors which affect the distribution of such disease. The emphasis is on the health of the entire population rather than the health of individuals (Childress et al., 2002). This may be measured in terms of incidence (the number of new cases or deaths which occur in a specified time, usually one year) or prevalence (the total number of new and existing cases at a given time).

Researchers explore environmental and personal characteristics which vary by place, time and sub-group of the population in their search for relationships between these various factors and diseases. The interest of epidemiological researchers is in determining the likely cause of a particular condition or disease in order to be able to determine what the best response might be. Epidemiological research is concerned with correlations and not causal relationships. Researchers in this domain generate theory and make educated, informed assertions about which relationships are causal and in what way, based on their findings. This approach is sometimes called general causation (as opposed to specific causation) (Wikipedia, 2011).

To do this, they tend to use observational methods which include the study of available statistics, the careful questioning of patients, systematic routine medical history taking of patients and control groups, small and large scale case studies, large scale cohort studies where a group of people are monitored over a long period of time, and experimental studies such as randomised controlled trials (Gale Encyclopedia of Public Health, 2011).

With case control studies, researchers take two groups (one with the condition and one without) and look back to try to determine which factors they experienced or were exposed to. Cohort studies, on the other hand, take two groups, neither of which have the condition, but are different in some significant way (e.g. linked to alcohol consumption or smoking) and over time observe the incidence of the condition of interest on each group.

As the factors explored are extremely diverse, epidemiology draws on numerous domains such as microbiology, physics, engineering, town planning, immunology and genetics, to name but a few.

7.5 Ethical issues linked to epidemiological research

7.5.1 The attribution of responsibility and "blaming the victim"

According to the attribution theory of Weiner et al. (1988), people tend to make three attributions about a perceived group difference (which could include a medical condition such as dementia or, of relevance to the next sub-section, a person's genetic status). First, they consider controllability (i.e. whether the person had any control over contraction of the disease or the situation occurring). Second, they make attributions about responsibility (i.e. whether the person had any control over this and could have prevented it from occurring as if so, s/he may be considered responsible for his/her current situation/condition). Finally, if it is thought that the condition/situation could have been prevented, the person may be blamed for not having done so. This process of attribution has been shown to have an impact on the emotional response to people with a particular perceived group difference and on the behavioural response towards those people.

Research which uncovers causal relationships between various factors and dementia (whether these be environmental, genetic, life style or other) may have a double effect in that in addition to enabling people, in some cases, to take precautionary measures to prevent or delay onset of the disease, or to make plans for the future, it may result in a lack of sympathy towards people who may be blamed for having dementia.

7.5.2 Raising false hopes

Just as some people may readily blame others for their condition, others may be overly optimistic about their chances of preventing a particular condition from occurring. In both cases, this may be based on the interpretation of the results of epidemiological studies (amongst others). This requires ethical reporting of the results of studies (please see sub-section 10 on the publication and dissemination of research).

7.5.3 Avoiding common pitfalls

Epidemiological studies, and various types of longitudinal cohort studies, carried out by public health researchers, often cost a lot of time, effort and money. Such studies require considerable effort and dedication on the part of the participants. They may be asked to fill out endless questionnaires, be submitted to batteries of tests and have to regularly monitor or record their behaviour or information about themselves. Anything which disrupts the effective conduct of the study could therefore have consequences for all concerned in terms of a wasted personal or financial investment.

Common pitfalls to such studies include bias, confounding factors (i.e. possible alternative explanations for the correlations) and an insufficient sample size. It would be unethical to expend such considerable resources without having taken the necessary measures to address these issues.

7.5.4 Communication of findings

Epidemiological researchers have an ethical responsibility towards society and in some cases towards particular communities to communicate their findings in a timely and

appropriate manner so that people can benefit from the information (Coughlin, 2006). Findings must therefore be communicated after appropriate scientific peer review in a way that is understandable to those most likely to be concerned by such information. In some cases, those most concerned by particular findings, may be members of communities with specific characteristics (e.g. based on residency rights, living conditions, language and cultural beliefs and practices) which serve as a barrier to the communication of findings by conventional means.

7.5.5 Individual rights, societal benefits and paternalism

The need to balance the rights and wellbeing of the individual research participant with the perceived potential benefit to society applies to research in general, including dementia research. In the case of studies which explore various factors which may be common in certain cultural groups or amongst certain groups in society rather than in others, research findings may eventually result in restrictions being placed on the former which restrict their autonomy. Smoking is an obvious example. In some cases, there may be valid arguments linked to the protection of the wellbeing of other members of society (i.e. those who do not smoke), whereas in other cases, restrictive measures may eventually be taken by the state which simply affect the individual rights of those engaging in the activity or exposed to a particular factor. Attempts by the state to change habits of diet, exercise and smoking etc. may be covert or overt.

Depending on specific circumstances, this could be construed as the rightful role of the state to protect its citizens or as paternalism. According to Lappe (1986), the moral justification of various compulsory public health interventions, is dependent on the expected benefit to the public, the degree to which individual rights are restricted in order to achieve that benefit and that balance between the risks and harms to participants (Coughlin, 2006). However, the responsibility for change should perhaps not always lie with the general public. Findings could also suggest a need for the government to take constructive and voluntary measures to facilitate lifestyle and other changes which would be protective or promote the better health of the population (e.g. incentives to promote a healthy diet, increase exercise or promote social inclusion).

7.5.6 Non-research public health activities

Non-research public health activities occur when governments take action in the context of emergency situations in which an imminent health threat to the population has been detected (e.g. during the SARS epidemic). Sometimes, such action might seem to closely resemble research. According to Coughlin (2006), the difference lies in the purpose of the study. Non-research public health activities are generally aimed at rapidly determining the nature and magnitude of a problem, whether sufficient data is available to take action and whether causative factors can be detected so as to enable governments to rapidly implement appropriate measures. Another type of non-research public health activity is the regular, on-going surveillance of data pertaining to the frequency and distribution of diseases and health conditions in the population (Coughlin, 2006).

Activities may also be a combination of research and surveillance. In their 2007/2008 scientific report, the National Creutzfeldt-Jakob Disease and Surveillance Unit (NCJDSU) described their activities as follows:

"Surveillance and scientific research are both integral and interdependent components of the monitoring and investigation of Creutzfeldt Jakob Disease (CJD). Surveillance of variant and sporadic CJD by the National CJD Surveillance Unit (NCJDSU) provides data that are essential for informing a significant number of scientific research projects carried out in a wide range of professional fields at the NCJDSU, elsewhere in the UK, Europe and the world. While surveillance underpins this research, the findings of the research can also in themselves play an important role in surveillance, for example by providing sensitive and specific methods of diagnosis or by indicating specific risk factors to examine." (NCJDSU, 2008, p.5)

The aim of such research is not to produce data which is generalizable to other populations, not to contribute to general knowledge about the condition and not to ask new questions or generate theory; the main aim is to deal with a current situation and the findings of such activities may well benefit those directly participating in the activities or the target population (Coughlin, 2006; Goodman and Buehler, 1996; Snider and Stroup, 1997). On the other hand, such activities may involve a research component even if this is not the main aim.

Similar methods may be used and the same rigorous approach to scientific research adopted. The question remains as to whether such activities are carried out ethically. In other words, as such activities are carried out by the state and in the light of an imminent danger or long-term threat, how are people's rights and wellbeing protected? There may be some differences with regard to consent to participation (particularly voluntariness, being fully informed and coercive measures), privacy, confidentiality, dignity, stress and stigmatization).

There is also a power issue. The fact that such activities are organised by or through the state may have an impact on their perceived legitimacy and how the results are interpreted by the public (negatively or positively).

7.6 Recommendations on epidemiological research

Great care and sensitivity should be taken in the communication of the results of epidemiological research in order to reduce the likelihood of fear, stress and blame, and the stigmatization of those groups most affected by the findings.

Efforts should be made to ensure the timely communication of findings to the widest possible audience.

Efforts should be made to ensure the timely communication of findings to the group of people most likely to benefit from such knowledge in a way that is meaningful, credible and understandable to them.

In the case of sub-groups of people with dementia, with whom it is difficult to communicate, assistance from representatives or facilitators should be sought.

Ethical standards should be established for non-research public health activities involving the voluntary participation of the general public.

Governments should be transparent about their role in research or non-research activities.

Research protocols should address potential risks and possible solutions linked to the continuation of the study over a sufficiently lengthy period and to future challenges to the validity of the results of each study.

Researchers involved in epidemiological studies should consider the possible future implications of their work on present and future populations.

7.7 Background information about genetic research

The Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) is of relevance to research, treatment or diagnosis affecting an individual's genome and covers areas such as human dignity, the rights of people concerned and the way that such treatment, diagnosis or research is carried. In the general preamble to the Declaration it is stated:

"Recognizing that research on the human genome and the resulting applications open up vast prospects for progress in improvising the health of individuals and of humankind as a whole, but emphasizing that such research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics."

Two types of genetic characteristics might be identified in the course of research, namely genetic mutations and a person's genetic susceptibility.

In an extremely limited number of families, Alzheimer's disease is a dominant genetic disorder. It is transmissible and known as familial Alzheimer's disease (FAD). The first gene to be identified was the amyloid precursor protein (APP) on chromosome 21 but this is limited to approximately 20 families. In most cases, the mutation occurs in the presenilin-1 gene on chromosome 14. In a very small group of families, the fault is in the presenilin-2 gene on chromosome 1 (Lovestone and Gauthier, 2001). On average, half the children of an affected parent will develop the disease. For the members of such families who develop Alzheimer's disease, the age of onset tends to be relatively low, usually between 35 and 60. It is important to bear in mind that these genes are associated with the early onset, or familial form of the disease occurring in late middle age and that more than 90% of cases of Alzheimer's disease occur in the 65+ age group (Eisenstein, 2011).

In 2009 and 2010, a genome-wide association study led to the discovery of additional gene variants of CR1, CLU and PICALM, and in 2011 of the gene variant BIN 1 (all of which are believed to affect the development of late onset Alzheimer's disease (Eisenstein, 2011; Vaughn, 2011).

There is no single gene responsible for all cases of Alzheimer's disease. However, everyone risks developing the disease at some time and it is now known that there is a gene which can affect this risk. This gene is found on chromosome 19 and it is responsible for the production of a protein called Apolipoprotein E (ApoE). There are three main types of this protein: allele $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ and as every person inherits two alleles, six combinations are possible. The $\epsilon 4$ allele, although uncommon, makes it more likely that Alzheimer's disease will occur and at an earlier age. Just one copy would increase the likelihood fourfold, whereas two copies would lead to a tenfold increase in risk (Eisenstein, 2011). The $\epsilon 2$ allele, on the other hand, is believed to offer some degree of protection. However, the $\epsilon 4$ allele does not cause the disease, but merely increases the likelihood. For example, a person of 50, would have a 2 in 1,000 chance of developing Alzheimer's disease instead of the usual 1 in 1,000, but might never actually develop it.

There is no way to predict whether a particular person will develop the disease. It is possible to test for the ApoE4 gene mentioned above, but such a test does not predict whether a particular person will develop Alzheimer's disease or not. It merely indicates that s/he is at greater risk. There are in fact people who have had the ApoE4 gene, lived well into old age and never developed Alzheimer's disease, just as there are people who did not have ApoE4, who did develop the disease.

Nevertheless, researchers may be interested in a person's genetic status, even if this is limited to his/her susceptibility to develop dementia, as it may affect the drug they are testing or lead to the development of more targeted and hence more effective drugs (i.e. which will be more effective for some people than others). However, whilst research into genetic status or susceptibility is of vital importance for the development of medication for dementia, the outcome of such research could have negative implications for some groups of people.

7.8 Ethical issues linked to genetic research

In 2001, Alzheimer Europe produced a position paper on genetic testing in which it recognised the importance of research into genetic factors linked to dementia (which might further our understanding of the cause and development of the disease and possibly contribute to future treatment). At the same time, it cautioned against the use of any genetic test for dementia unless such test was known to have a high and proven success rate either in assessing the risk of developing the disease (or not as the case may be) or in detecting the existence of it in a particular individual. Alzheimer Europe did not, at that time, consider the ethical issues linked to genetic research.

7.8.1 Emotional disturbance or benefit

A person who discovers by any means that s/he possesses a gene known to result in dementia may suffer emotional distress which is why genetic counselling is so important. In the case of badly conducted research, there is a risk of the person finding out about his/her genetic status "in passing" (e.g. based on allocation to a particular group or if it was used as a criterion for inclusion in a study), without there being any provisions for genetic counselling. On the other hand, for some people, genetic testing resulting in a normal result may spare people and their relatives the stress of not knowing and years of uncertainty. This would of course only apply to genetic tests which had been reliably shown to be capable of predicting future disease (please see sub-section 7.8.6 on mere susceptibility).

In most cases, genetic information is probabilistic (White, 2000). However, Leibowitz (1999) points out that people react very differently to the perceived risk of disease based on statistical probability. Whereas some people will interpret 45% probability as meaning that they are less than likely to be affected, others will treat a 3% probability as practically a diagnosis. She concludes,

"Genetic information on an individual level has the potential to change people's lives through the infinitely powerful mechanisms of the mind. The danger lies in distortion and despair; the hope lies in a realistic understanding and appreciation of life." (Leibowitz, 1999).

However, as people are likely to react very differently and unpredictably with regard to personal risk, one might ask whether it is justifiable to risk psychological harm in the sole interests of research.

7.8.2 Possible impact on relatives

In the case of forms of dementia which are genetically inherited from parents, the identification of that gene in one person could have a dramatic impact on the lives of other family members who did not necessarily receive the counselling that the person participating in the research received. There are very few families in which dementia is genetically inherited but this does not make it any less of an ethical issue. Moreover, should there be an increased interest in carrying out research on this particular group of people, the problem would occur more frequently.

In "pedigree studies", which study the incidence and progression of a disease in families, pressure may be exerted within families on certain relatives to take part in a study which might eventually reveal unexpected information about their risk of developing that disease (White, 2000). This raises the issue of voluntariness, which is an important condition for informed consent.

7.8.3 Discrimination and stigmatization

An obvious risk linked to identifying a person's genetic status or susceptibility is that they may suffer some form of discrimination if such information was disclosed to a third party (e.g. in the domain of healthcare, insurance, banking or housing). As long as a person

does not know such information, s/he does not risk such discrimination (provided that confidentiality is maintained by the researchers), but once known, the person may be legally obliged to reveal it in certain circumstances and thereby suffer the consequences. This might include not being able to obtain a loan or travel insurance, or having to pay higher insurance premiums. As significant advances are made by researchers every year, it cannot be known at a particular moment in time the predictive value or implications of specific genetic information nor how society will respond to such knowledge. Even in the absence of actual discrimination, a person with a particular genetic status or susceptibility may feel stigmatized and suffer the consequences of anticipated discrimination. This could be the case not only for the person who was tested but also any of his/her relatives who are equally concerned by the results of the test.

On the other hand, Anderlik and Rothstein (2001) argue that singling out genetic information for special protection (please see sub-section on genetic exceptionalism) may actually increase the likelihood of stigma through the implication that such information must be particularly shameful.

7.8.4 "Genetic literacy"

In its position statement on genetic testing for late-onset Alzheimer's disease, the American Geriatrics Society (2000) draws attention to the fact that very little if anything is known about the "genetic literacy" of older adults. Many left school before DNA was discovered and before prenatal genetic testing became available. They may therefore be less familiar with genetic concepts and have more difficulty grasping the issues at stake such as what they are agreeing to and the implications of having or not having access to the results of any genetic test administered in the context of research.

7.8.5 Genetic exceptionalism

Genetic exceptionalism is the belief that genetic information is qualitatively different from other forms of medical or personal information. This is generally accompanied by the belief that such information should be treated differently in law (Dow, 2009) and may have implications for research. This is reflected in article 4 of the International Declaration on Human Genetic Data (UNESCO, 2003).

Article 4 – Special status

- (a) Human genetic data have a special status because:
 - (i) they can be predictive of genetic predispositions concerning individuals;
 - (ii) they may have a significant impact on the family, including offspring, extending over generations, and in some instances on the whole group to which the person concerned belongs;
 - (iii) they may contain information the significance of which is not necessarily known at the time of the collection of the biological samples;
 - (iv) they may have cultural significance for persons or groups.

(b) Due consideration should be given to the sensitivity of human genetic data and an appropriate level of protection for these data and biological samples should be established.

There may also be strongly held beliefs that genetic information is inherently unique and symbolically equated with the uniqueness of the individual. Its protection may therefore be seen by some as a reflection of respect for individuals as unique members of the human species (Dow, 2009). Shah (2001) criticises such assumptions, suggesting that health and identity cannot be reduced to the sum of our genes. Moreover, health insurers typically have access to non-genetic medical information which may have predictive value (such as a history of past tuberculosis in one's family). Legislation to protect genetic information has been described as under-inclusive and leading to inequity as it is based on the fact that whilst genetic risks transcend social class, many non-genetic risk factors (e.g. environmental factors) frequently do not (Suter, 2001).

According to Dow (2009), genetic exceptionalism may lead to a paternalistic approach to genetics and the application of the "precautionary principle" which implies that when potential adverse effects of an activity are not fully understood, such activities should not be proposed (United Nations World Charter for Nature, 1982) or should require proof of cost-effectiveness in the light of perceived threats of serious or irreversible damage. He argues that whilst there is a need to protect people, there is a risk that genetic exceptionalism might lead to regulations which deny the public the tremendous benefits that might result from research into how genetic information predicts disease and improves medical outcomes.

Anxiety about the possible implications on insurance contracts of knowing one's genetic status may prevent people from taking part in research or lead to hostility against such research. Insurance companies may also be concerned about the possible asymmetry of information resulting in adverse selection (i.e. people with a high risk, which is unknown to the insurer, purchasing more insurance). Joly et al. (2003) point out that the restriction of access to genetic information may even be counter-productive in that life insurers are interested in covering a maximum number of applicants. Having access to genetic information might actually fuel research by the insurance industry to broaden the insurability of the general population by gaining more precise information about the link between genetic tests and mortality rate. Rather than proposing greater protection of genetic information, Joly et al. (2003) propose the use of moratoria, codes of conduct established in collaboration with the general public and transparency on the part of insurance companies.

7.8.6 Mere susceptibility

Where the genetic information obtained is only linked to the likelihood of a person developing Alzheimer's disease (his/her ApoE4 status), the risk of discrimination and stigmatization is still present. People carrying the allele associated with the highest risk of developing dementia may never actually develop dementia and people carrying the allele associated with the lowest risk of developing Alzheimer's disease might develop

it. As genetic susceptibility status is not a biomarker in that it cannot determine with any degree of certainty that a person will develop Alzheimer's disease and there is as yet no cure for Alzheimer's disease, Alzheimer Europe stated in its position of genetic testing that it was not in favour of promoting the use of such tests. We felt that the results of susceptibility testing could cause considerable distress to some people who do not fully understand their basis and limitations, particularly if the tests were to become widely available without there being adequate provisions for genetic counselling.

7.8.7 The right to be informed

Within the context of research, which is by definition based on uncertainty, the value of susceptibility testing may be justifiable. It may, for example, contribute towards the development of more targeted drugs. However, is it morally right for researchers to withhold information about a person's genetic status which indicates the presence or likelihood of a medical condition? Even if the research participant never develops that condition, they might want to make certain changes in their lives based on that information (e.g. making informed decisions about their future care and treatment or delaying the possible or certain development of the condition by adapting their lifestyle habits). It is stated in article 5c of the The Universal Declaration on the Human Genome and Human Rights (1997) that each individual has the right to decide whether to be informed or not of the results of genetic examination and that the resulting consequences should be respected.

There is also the issue of transparency. Participants should be informed if researchers take genetic samples for use in any study (e.g. one which is not directly related to genetics but for which such data may be useful in comparing different sub-groups). In some cases, such information is not essential to the main study, although beneficial to the future development of drugs which are more targeted to individuals. In such cases, layered consent might be useful (White, 2000).

7.9 Recommendations on genetic research

Research affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risk and benefits pertaining thereto.

Genetic researchers should abide by laws pertaining to this type of research.

Researchers should try to avoid contributing towards the coercion of relatives to take part in certain forms of genetic research.

No genetic samples should be taken or genetic information recorded without the awareness and informed consent of the participant (or his/her legal representative).

As genetic testing may have implications for family members, potential participants should be encouraged to involve relatives in the consent process.

Researchers should ensure that participants fully understand explanations about genetics and genetic research, starting with the terms they use.

No prior knowledge, even of the most basic aspects of genetics, should be assumed.

Researchers should be careful that explanations of their findings do not mislead the general public, and lead to panic or false hopes.

The insurance industry should be dissuaded from the inappropriate use of information about the genetics of dementia until cause and effect relationships have been scientifically established.

The insurance industry should, in the event of emerging but inconclusive evidence of genetic or other factors affecting the development of dementia, respect a moratorium.



Research into end-of-life care

8 Research into end-of-life care

8.1 Background information about research into end-of-life care

In 2008, Alzheimer Europe produced recommendations on the good end-of-life care of people with dementia based on the work of a multi-disciplinary working group comprised of experts in the field of palliative care, medicine, psychiatry and psychology, as well as carers, in collaboration with the board of Alzheimer Europe and its member associations (Alzheimer Europe, 2008).

In its recommendations on good end-of-life care, Alzheimer Europe stated its opinion that a palliative care approach should be adopted for people with end-stage dementia as attempts to cure and prolong life are inappropriate for them. It nevertheless respected the right to individual choice and emphasised that palliative care is not limited to the actual end of life but should be introduced in a seamless manner, overlapping and complementing good dementia care. In this way palliative care is not restricted to the last days or months of life even though the provision of palliative care services may increase towards the end of the person's life. Palliative care and end-of-life care are therefore not synonymous. A definition of each is provided below.

8.1.1 Definition of palliative care

Alzheimer Europe's working group on good end-of-life care agreed on the following definition of palliative care, which is adapted from and closely resembles that developed by the World Health Organisation in 2002.

"Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. Palliative care:

- 1. affirms life and regards dying as a normal process;
- 2. intends neither to hasten nor postpone death;
- 3. does not aim to prolong life;
- strives for a good death (the least distressing passage partly due to the relief of suffering from pain and other distressing symptoms)
- may however be used in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications;
- 6. integrates the psychological, religious and spiritual aspects of patient care;
- 7. offers a support system to help patients live as actively as possible until death;

- 8. aims to enhance the quality of life of patients;
- 9. offers a support system to help family and friends cope during the patient's illness and in their own bereavement:
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- 11. is an attitude, a philosophy and a method which should be possible in any environment."

8.1.2 Definition of end-of-life care

End-of-life care is the care provided to people at the end of their lives. It may involve a palliative approach but not necessarily. People may want to pursue all available medical options (including treatment for other conditions they may have in addition to dementia).

People with dementia who are dying are not all in the final stage of dementia (Lynn and Adamson, 2005). The end of life is difficult to define as dementia does not follow the kind of steady, linear trajectory that is common to many other terminal conditions. Cox and Cook (2007) identify three distinct groups of people with dementia who may need end-of-life care. These are:

- People who reach the end of life but die from some other identifiable condition, such as cancer, before reaching the final stage of dementia.
- People who reach the end of life with a complex mix of mental and physical problems but where the effect on brain functioning is not as advanced.
- People who reach the end of life and die of the complications of dementia, such as end-stage dementia.

Alzheimer Europe's working group on good end-of-life care defined the end-of-life as being a matter of days or weeks before the actual moment of death (Alzheimer Europe, 2008). This definition is not dependent on any particular stage of dementia. Clearly, good end-of-life care must, by definition, be ethical and much of what applies to good end-of-life care applies to research into end-of-life care and to the involvement of people who are dying with or from dementia in it.

8.2 Ethical issues linked to research into end-of-life dementia care

8.2.1 Insufficient research into the end-of-life care of people with dementia

Palliative care services dedicated to the specific needs and situation of people with dementia (and their carers) are not very common throughout Europe. In the United Kingdom, for example, two thirds of patients with cancer who die receive some form of palliative care compared to only one out of twenty non-cancer patients (which includes those with motor neurone disease and AIDS) (Hospice Information Service, 2001 and Addington-Hall and Higginson, 2001).

Staff in palliative care centres and those who provide palliative care at home may therefore be less familiar with issues specifically related to the care of people dying with or from dementia. Similarly, healthcare staff providing end-of-life care or treatment in hospitals or at home are perhaps not sufficiently trained in dementia care or in communicating with people with dementia.

In addition to increasing access to palliative care for people with dementia, research is needed to develop and improve the quality of end-of-life care in general (i.e. including but not limited to palliative care). This might include the development of more effective pain scales, as well as measures to increase comfort and assess quality of life in end-stage dementia. Research of no direct medical benefit is also important for the advancement of knowledge which may improve the care and treatment of people with end stage dementia in the future.

Dementia is not always recognised as a terminal condition. Consequently, it is not always recorded as the actual cause of death on the death certificate, or at least not as the main cause of death, even when this is clearly the case. This may have an impact on the acquisition of medical knowledge about the final stage of dementia and on the ability to accurately predict the end-of-life of people with dementia. Research is therefore needed to develop indicators of the final prognosis, with the ability to predict the last weeks and days of life as this has important consequences for the care and treatment provided.

8.2.2 Conflicting views and interests

Whereas with end-of-life care, the emphasis is on the patient, as explained earlier, one of the aims of palliative care is to provide a support system to help family and friends cope during the patient's illness and in their own bereavement. Taking up the time and energy of the person with dementia in his/her last moments of life may deprive families of precious time with that person. This would be particularly relevant if the person with dementia was in residential care, hospital or a hospice and if relatives and friends lived some distance away. Addington-Hall (2002) argues in favour of respecting the principle of autonomy (which would mean letting the patient decide) but encouraging him/her to discuss the issue with his/her family or close friends. If the person lacks the capacity to decide and did not previously express his/her wishes, there would be a risk of close relatives and friends deciding on behalf of the person with dementia against his/her participation either directly or by blocking potential researchers' access to him/her.

8.2.3 Stereotyping and devaluation

There is a danger that blanket judgements will be made about the value or quality of life of people in the advanced stages of dementia, but also generalizations about what is good for people with end-stage dementia. Such judgements and generalizations may be well intentioned but fail to respect the individuality of each person with dementia.

There is also a risk of failing to recognise the personhood of people with advanced dementia due to stereotypes about awareness, capacity and the ability to communicate. This can happen at any stage of dementia but in the end stage, it may be more

likely. In some cases, their failure to recognise loved ones, difficulties communicating and changed physical appearance and behaviour may make it difficult for families to consider them as the same person or in the extreme as being a person at all. This puts the person with dementia in an extremely vulnerable position.

8.3 Recommendations on research into end-of-life care

The issue of recording dementia as the cause of death on death certificates should be addressed.

Stereotypes about people who are dying with or from dementia (e.g. linked to wellbeing, quality of life and capacity) should be challenged.

Research should be carried out to develop more precise indicators of the end of life for people with dementia.

Research should be carried out to develop appropriate end-of-life care and treatment for people with dementia (including palliative care).

It should not be presumed that people with dementia would not want to participate in end-of-life research.

Researchers should approach people who are dying with or from dementia (and their carers) about research with great sensitivity, paying attention to possible signs that they do not want to discuss the issue or that they are either not aware of, or in denial, about their prognosis.





The donation of brain and other tissue

9 The donation of brain and other tissue

9.1 Background information about the donation of brain and other tissue

A lot of research can be carried out on living people but some of it cannot. As it is not yet possible to reproduce the human brain in the laboratory and as it would be unacceptable to take samples of the brain whilst the person is alive, researchers are very much dependent on post mortem donations of human tissue.

Such tissue is needed not only from people who had dementia but also from people who did not. The brain tissue of people who did not have dementia (known as control tissue) enables comparisons to be made with the tissue from people with dementia. Control tissue is often much less readily available than that from people with dementia, but both are needed. In addition, brain tissue from people with other conditions affecting the brain can also be used within dementia research as it can help determine what makes dementia different from other neurological conditions (Brains for Dementia Research, 2011).

9.2 Ethical issues linked to the donation of brain and other tissue

9.2.1 Consenting to donation

The donation of one's body parts and tissue, including the brain, is generally considered as an act of altruism and is in keeping with the principles of solidarity and reciprocity. This may be on the part of the person with dementia or of the person who is responsible for making the decision. Depending on legislation, which may differ from one country to the next, a person may be able to consent to brain tissue donation in an advance directive or through a previously appointed legal representative or officially recognised "trusted person". Some people may be in the early stages of dementia but dying from another condition such as cancer or heart disease. Others may not have dementia at all but may be suffering physical or emotional pain in connection with their terminal condition.

In the case of people with dementia who might be able to consent (i.e. perhaps they have another terminal condition), one could ask what level of capacity is needed to be able to consent to post mortem brain tissue donation. For those who did not make such a decision themselves during their lifetime, one might ask what the best interests are of a person who is no longer alive. Consenting to the donation of brain and other tissue for dementia research is a sensitive issue. Questions about donation may make people with dementia aware of information about their condition for which they are not prepared or that they are not willing to acknowledge. Such attempts may interfere with coping mechanisms based on denial or hope. This may also be the case for their relatives and close friends.

In their comprehensive report on donation for medicine and research, the Nuffield Council on Bioethics (2011) considers the degree of information considered necessary for post mortem donation. They argue that minimal information could be justified (particularly as people may not want to hear all the details about the process), provided that it is very clear that it is/was the donor's wish to donate and that the person has had the opportunity to ask for any additional information s/he may require. If not in accordance with the person's wishes, taking body parts from him/her would amount to treating his/her body as a means to others' end (Nuffield Council on Bioethics, 2011). Understanding the person's wishes is therefore of paramount importance.

9.2.2 The timing of consent

Brain and other tissue donation, like organ donation in general, could be considered by people well in advance of their probable death. When this is not the case, people are likely to be asked about it around the time of death.

Decisions must be made rapidly as brain tissue must be removed very soon after death if it is to be in an optimum condition and hence of greatest use for researchers. Timing is therefore essential but also problematic. If contact with families and friends is handled badly, they may feel under pressure to make a decision. If they are approached whilst in a state of great distress, their consent might not be truly informed as they may not have taken in all the information that they were given, may not have been able to weigh up the pros and cons of the options available and may have failed to understand the procedure for the removal of the brain tissue.

9.2.3 Psychological and emotional wellbeing

Based on an extensive literature review, the Nuffield Council on Bioethics (2011) highlights some of the main concerns that people have in connection with post mortem donation, namely that less effort will be put into resuscitation attempts, that more organs will be taken than agreed, that it will lead to disfigurement and that contemplating one's own death may bring bad luck (the jinx effect). There may also be cultural or religious norms linked to how a person's body should be treated, which those approaching potential donors should be aware of. People may also have spiritual beliefs of a more personal nature (i.e. which are not linked to an established religion). All these issues may affect the psychological and emotional wellbeing of people who are approached in connection with brain and other tissue donation, even if they eventually decide against donation.

In keeping with a palliative care approach, the wellbeing of relatives and close friends of people with dementia who have donated brain and other tissue (either through a personal decision or on the basis of a proxy decision) should also be protected before and after the extraction of the tissue. There may be cases where the person with dementia clearly expressed his/her wish to donate but his/her family did not realise or feel uneasy about his/her decision.

9.3 Recommendations on the donation of brain and other tissue

People with dementia who appear to have the capacity to consent to the donation of brain and other tissue should be approached with great sensitivity, bearing in mind the possible impact of such a discussion on their psychological wellbeing.

Great sensitivity should be exercised when approaching their close friends and/or their relatives in connection with a request to donate the brain or other tissue of the person with dementia.

Whenever possible, obtaining consent to the donation of brain and other tissue should be a process, which takes place over a period of time, allowing the person with dementia to come to terms with the issue, ask questions, receive answers, reflect, discuss with others and eventually make a decision for or against donation.

The decision to donate, if made, should be reassessed over time if possible.

The provision of information to potential donors and proxy donors about the process should be adapted to the requirements and interest of the person concerned, bearing in mind his/her perceived willingness to receive it.

Potential donors and proxy donors should be provided with as much information as they require and not obliged to hear details that they would find disturbing.

Those responsible for obtaining consent to the donation of brain and other tissue should be knowledgeable about the procedure (i.e. how the procedure is carried out, by whom, where and when) and be able to communicate this with sensitivity if required.

Signs that the person with dementia does not want to discuss the topic should be respected and the issue not pursued any further.

The possible benefit of the person with dementia informing relatives and close friends of his/her decision to donate his/her brain or other tissue should be discussed.

In view of the need for a fairly rapid decision, hospital staff and researchers (or their trained representatives) with the relevant expertise, should be readily available for discussion concerning a possible donation of brain or other tissue.

Despite time constraints, families and relatives should not be placed under pressure to consent to the donation of brain or other tissue.

Relationships are not always straightforward and people should not feel obliged to justify their decisions or reactions vis-à-vis their relatives and friends.

Psychological support should be available to people with dementia as well as relatives and close friends who have been approached in connection with the possible donation of brain or other tissue from the person with dementia.

The extraction of brain or other tissue should not interfere with religious, cultural or spiritual practices or beliefs.

Those responsible for obtaining consent to the donation of brain and other tissue as well as researchers and anyone handling the tissue should be knowledgeable about and respectful of religious and cultural norms of donors.

Brain and other donated tissue should be anonymised.

Researchers should never know the identity of the donor.

Donated brain and other tissue should be extracted, transported and stored appropriately.

Donated brain and other tissue should be handled and disposed of respectfully.

Maximum use should be made of brain and other tissue.

Donated brain and other tissue should not be used for commercial purposes or sold to other researchers.

Institutions authorised to receive donated brain and other tissue should have a clear policy of how such tissue is used.





Publication and dissemination of research

10 Publication and dissemination of research

10.1 Background information about the publication and dissemination of research

Research into dementia is, or should be, carried out for specific reasons. Usually, the aim is to answer a question, which, once known, may improve the lives of people with dementia and their carers or future generations of people with dementia and carers. Even research carried out for academic reasons (e.g. for the purposes of obtaining qualifications) should be worthwhile. Consequently, it is important to share the findings of such studies so that the potential gain to society can be as widespread as possible. Other reasons include respect for the people who participated in the studies, avoiding the unnecessary duplication of studies and enabling researchers to build on the existing body of research, thereby enabling them to constantly progress in their search for knowledge and understanding.

There are various methods of dissemination, which are partly determined by the type of research and those responsible for the research. Typically, researchers try to publish the results of their studies in peer-reviewed journals. The peer reviewers, who are usually respected scientists in the relevant field of research, do not check the researchers' actual raw data and calculations but they verify that the research was carried out correctly and was accurately reported (based on the information provided by the researchers). There is therefore a certain element of trust involved but well-conducted research should provide a trail of evidence, which others can follow in order to see how the researchers arrived at their conclusions (Krueger and Casey, 2009).

Other means of dissemination include speeches and poster presentations at conferences, information on websites, brochures and books, articles in magazines and newspapers, and governmental or non-governmental reports. The various means of dissemination may reflect different target audiences or the backgrounds of the researchers. The audiences of such disseminated information may be influenced in their assessment of its accuracy and credibility by how and by whom it is reported. On the whole, the general public does not have access to specialised peer-reviewed journals as they are expensive and not readily available. Consequently, they often hear about the results of studies through secondary reports (e.g. on television, through the Internet or in newspapers and magazines).

10.2 Ethical issues linked to the publication and dissemination of research

10.2.1 Conflicts of interests based on financial issues

It is important that those reporting the results of their research are open about any information about themselves which might lead other people to suspect their motives or question their objectivity. Such information represents a potential conflict of interests but does not automatically imply that the researchers lack objectivity or integrity.

A potential conflict of interests would include researchers having received sums of money or presents from organisations which could be seen to benefit from the findings. An example might be a researcher who has received money or gifts from an organisation specialising in vitamin tablets reporting the findings of a study which suggests the benefits on cognition of certain vitamin tablets. Another example would be a researcher reporting on a clinical trial for a drug produced by a company in which s/he has shares.

Researchers may be under pressure from the institutions which employ them to have successful studies as those institutions may be dependent on the findings of those studies for subsequent funding (Seigel, 2003).

Other financial issues include the source of funding for a project. The findings of a study into the health benefits of milk, if financed by the milk industry, might, for example, be considered misleading were such information not openly declared. On the other hand, some people might find it perfectly logical that the milk industry would be interested in funding such a study (rather than one into the benefits of meat). The issue is not about which organisations should fund research but rather about being transparent about funding.

Whilst the pharmaceutical industry clearly has financial interests in discovering and developing drugs, those financial interests are completely transparent and understood by the general public. Moreover, the relationship between the companies and the general public is one of mutual benefit. Companies are clearly interested in proving that their product is effective and safe, and the general public is interested in having such products if and when they need them. The companies comply with stringent controls which help ensure that any conclusions they draw are accurate and based on the application of a rigorous scientific methodology. The good conduct of scientific research requires that measures are taken to avoid bias.

10.2.2 Academic interests and other outcome preferences

Seigel (2003) prefers to use the term "outcome preferences" due to the pejorative connotations of the term "bias" and as it has another meaning in the context of statistics. Sometimes, even in the absence of direct financial concerns, researchers may have outcome preferences. In the academic domain, for example, some researchers may be under overt or covert pressure to publish a certain number of articles per year and such publication may be linked to their career advancement (Maj, 2008). Zaki (2011) describes this as the "publish or perish" culture. As studies which do not produce results in support of the hypothesis or research questions are difficult to publish, this creates an undesirable pressure on researchers to produce certain results.

Prestige and peer recognition may add to this pressure to obtain significant and meaningful results. As noted by Seigel, "Fleming is not likely to have been celebrated for screening a host of potential antifungal agents, all found to be inert" (2003, p.3420).

The desire to improve health may also result in a particular outcome preference. Whilst such a desire is commendable, great care is required to ensure that researchers remain

objective and that those involved in the secondary reporting of research results present such findings in a realistic manner.

Researchers' commitment to a hypothesis or allegiance to a particular school of thought may also lead to outcome preferences (Coughlin, 2006; Maj, 2008; Seigel, 2003) which in turn may even lead to what Charles Babbage (1782-1871) described as "cooking", namely retaining only those results that fit the theory and discarding others (Al Bareeq and Fedorowicz, 2008). In some cases, the firm belief in a particular theory could be based on years of research. Challenging such beliefs and having the courage to question one's own previous work may be difficult for some researchers but a necessary requirement for good science.

Certain official bodies, which carry out or fund research, may have a preferred outcome (e.g. linked to policy, service provision or legislation) and want to approve documents and have the opportunity to comment on various drafts before they are published. This itself is not unethical. However, it would be unethical if such organisations censored the findings, only allowed the publication of those which supported their arguments, distorted arguments, rejected certain interpretations of the results by the researchers and/ or delayed publication (Royal College of Psychiatrists, 2001).

10.2.3 Conflict of interests amongst publishers

Maj (2008) argues that just as researchers may have conflicts of interest, so too might those responsible for publishing such research or reporting on it. Writing in the context of medical and psychiatric research, Maj draws attention to the possible impact of the non-financial interests of publishing organisations as well as individuals or organisations acting as referees or evaluators of research for such journals. These might include strong political commitments, allegiance to particular schools of thought and even protection of their own research from perceived criticism. It is perfectly defensible to have strong political interests and to be heavily influenced by a particular school of thought. However, if such factors are not known or there is no balance in terms of publishers with alternative political views, there may be an imbalance in the publication of research, resulting in a biased portrayal of knowledge and the unnecessary duplication of studies.

10.2.4 Integrity of publishers and researchers

It would be unethical to publish inaccurate research findings based on studies involving the use of fraud, the fabrication of results, the falsification of data, plagiarism (Al Bareeq and Fedorowicz, 2008) or unethical practices such as failing to obtained informed consent. For studies involving participants with dementia, this would include failure to consider appropriate methods to obtain consent from people with dementia before resorting to proxy consent.

10.2.5 Publication of negative or inconclusive findings

The publication of negative or inconclusive findings may be hampered by a reluctance on the part of publishers to publish such findings as well as on the part of researchers to be publicly associated with such studies. Some researchers would gladly publish such

results but find it difficult to find publishers. However, as mentioned above, failure to publish negative or non-conclusive findings (or much delayed publishing) may result in the duplication of research and exposing additional participants to risk and burden. Furthermore, it would be misleading and hence unethical to publish one study which was successful and to refuse a further nine which were inconclusive or negative involving the same chemical compound or intervention.

In addition to the misleading nature of such information, the failure of nine studies, if known, might affect the readiness of people to participate in a new study. This would clearly be problematic for the researchers but does not justify withholding such information.

Results which do not support the hypothesis of a particular study or which provide an inadequate or conflicting response to the research question are valuable in terms of the acquisition of knowledge. They might point to new hypotheses or research questions, or suggest the need for changes to future research protocols or choice of methods.

Negative findings are also of interest to lay people in their everyday lives. Many lay people react to the information they receive directly or indirectly about possible preventive measures and should be able to rely on researchers to give them the full picture with regard to research findings. For example, the publication of a study which suggests that certain food supplements or substances, used by lay people to prevent dementia, have no effect whatsoever, may help prevent those people from being misled, from wasting money in health shops and from having a false sense of security.

10.2.6 Gift and ghost authorship

According to the International Committee of Medical Journal Editors (ICMJE), also known as the Vancouver group, an "author" is generally considered to be someone who has made substantive intellectual contributions to a published study. More specifically,

"An author must take responsibility for at least one component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity." (ICMJE, 2010, p.2)

Authors should also be involved in the drafting of the article, its revision and final approval before publication. The prevalence of gift authorship (based on failure to comply with ICJME criteria) was found to range from 0.5% to 60% of research papers as measured in a selection of peer-reviewed journals and 60% of senior researchers in one university are believed to have benefited from gift authorship (Pignatelli et al., 2005 and Mowatt et al., 2002 in Hodgkinson, 2007; Zaki, 2011).

Gift authorship is linked to issues of honesty, integrity, trustworthiness, possible manipulation and the inappropriate use of power. If the list of authors is not in accordance with the recommendations made by the publishers, it could also be construed as scientific misconduct (Albert and Wager, 2003). In some organisations, junior researchers may find it difficult, if not impossible, not to include the names of senior researchers as authors of their research.

Gift authorship may result in people who are not experts in the topic being considered as such and even being asked to review the work of other researchers. They may also be asked to accomplish other tasks, which are beyond their level of expertise, and be perceived as more skilled than their colleagues which may result in unfair professional advantages (Zaki, 2011). Moreover, the issue is not just about giving credit to the people who actually carried out the research but also of responsibility and accountability for published work (Hodgkinson, 2007). Accepting such gifts may therefore represent a professional risk.

Research ethics committees increasingly recommend involving patients and patient representative groups in research which focuses on issues of relevance to them. The inclusion of such groups as authors on articles may be interpreted as a validation of the related studies. In cases where this is gift authorship, researchers may be benefiting from a perceived sign of approval from those organisations. In other cases, patient groups may be consulted during the study and such consultation may be simply reported in the article or in the acknowledgements section of an article. This can sometimes by misleading as, whilst it may be true that organisations or people with dementia were consulted, their opinions and comments might not necessarily be reported or taken into consideration.

Ghost authorship is perhaps not as widespread as gift authorship. It may involve a professional writer who is paid by a commercial organisation to write an article about research in which the former played no active role. Alternatively, it may involve a person who was heavily involved in the research not being included in the list of authors of a published article about that research. The use of professional authors may conceal a possible conflict of interests or serve to present data in the best possible light but if openly acknowledged may simply improve the quality of articles (Hodgkinson, 2007).

A useful article by Albert and Wager (2003) provides guidance on how to handle authorship disputes. Some of their suggestions are included in our recommendations below.

10.3 Recommendations on the publication and dissemination of research

Researchers should question their findings, consider competing explanations for their findings and take the necessary measures to check the validity or trustworthiness of their conclusions.

All published work should be accompanied by a statement of possible conflicts of interest.

All researchers should be willing and authorised by funders to submit their findings to expert scrutiny if justifiable reasons for such scrutiny are provided.

In order to avoid confusion, researchers should clearly distinguish in published articles and reports between research criteria for Alzheimer's disease and clinical criteria for Alzheimer's disease.

Organisations responsible for the secondary reporting of research findings should strive to be objective and clear in their reporting, providing additional explanations if necessary in order to facilitate understanding of the possible implications of the findings.

Unrealistic or sensationalist reporting should be avoided.

Patient groups and related organisations should challenge sensationalist reporting of dementia research and try to present findings in a more balanced way.

Publishers should be encouraged to publish the results of research which was inconclusive or negative.

Governments should set up an obligatory national registry for clinical trials combined with a database with details of the results of all clinical trials, which should be freely accessible to the general public.

Researchers should follow the requirements of the International Committee of Medical Journal Editors regarding authorship (please see the references section for details).

Researchers should discuss authorship issues right at the start of a project, preferably at a face-to-face meeting and make a written record of any decisions taken.

Researchers should acknowledge contributions from people who do not qualify for authorship but did contribute towards the research project.

People or organisations who were consulted in the course of a study should not be individually named in a published article without their consent.

Local customs and practices which condone gift or ghost authorship should be challenged by researchers.

All listed authors should be given the opportunity to see the final draft of an article before it is submitted for publication and to withdraw their names if they so desire.





Glossary

11 Glossary

Allele

An allele is one member of two or more forms of a gene that is located in a specific position on a specific chromosome. Sometimes, different alleles can lead to distinct traits.

Biomarker

A biomarker, sometimes called a biological marker, is a substance within the body which can be used by researchers as an indicator of normal or abnormal biological processes (which might further indicate the presence or absence of disease or medical problems). Such biomarkers are therefore sometimes objectively measured and evaluated during scientific studies.

Cerebrospinal fluid (CSF)

This is a clear, colourless liquid that circulates throughout the central nervous system. It lies between the brain and the skull and therefore also acts as a kind of shock absorber or cushion, protecting the brain and spinal cord (which are the main parts of the central nervous system) from damage (e.g. in the event of a blow or fall). Another function of CSF is to deliver nutrients and wash away waste materials.

Cohort

A cohort is a group of people who all experienced a certain period of time together during a particular time span. This does not mean that they necessarily knew each other but simply that they lived through that time. A cohort might therefore be people born between particular dates, people aged between 40 and 50, people who lived through the Second World War or people who worked in coal mines between the age of 20 and 40.

Control group

The control group in a clinical trial is the group of participants which does not receive the experimental drug. This does not necessarily mean that they receive nothing or a dummy pill (placebo) as they might receive the standard treatment for their condition. In experimental studies, the control group is not exposed to the experimental intervention. For example, in a study to measure the effects of exercise on memory recall, the control group would not do the exercise but the other group (the experimental group) would.

Double blind placebo controlled

The participant in a clinical trial, his/her relatives and the researchers are all unaware of which participants are receiving the treatment, the placebo or another intervention.

Gatekeeper

In the context of dementia research, a gatekeeper is the term used to describe a person who is in a position to facilitate or block researchers' access to people with dementia who might be willing to take part in a study. An example of a gatekeeper would be the manager of a care home or day care centre.

Hypothesis

The hypothesis is the specific question to which researchers want to find an answer. Hypotheses tend to be phrased in specific ways which include a prediction that there will be a relationship between two or more variables and even what the nature of the relationship will be. This is accompanied by a null hypothesis which basically states that this will not be the case. Statistical analysis establishes which of the two hypotheses is most likely.

Longitudinal studies

Longitudinal studies are studies which involve the same group of people on more than one occasion (usually several times and often over a fairly long period of time).

Placebo

The placebo is an inactive intervention. In clinical trials, this may, for example, be a tablet or an injection which looks just like the one taken by other participants who are not in the placebo group but it does not contain the active ingredient.

Pharmacokinetics

The term pharmacokinetics comes from two Greek words which mean drug and "to do with motion". As a science or study, it is about how drugs move through the body covering, for example, how they are absorbed, at what rate and how they are eliminated from the body.

Pharmacodynamics

Pharmacodynamics is the study of the effects of drugs. The term describes the biological and physiological effect that a drug has on the body, the mechanisms of the drug action and the relationship between the concentration of the drug and its effect.

Pharmacogenomics

"Pharmacogenomics" combines two terms: pharmacology (the science of drugs) and genomics (the study of genes and their functions). It is about how a person's genes affect the way their body responds to drugs. The aim is to eventually develop drugs which are tailored to each person's genetic make-up.

Polypharmacy

Polypharmacy literally means "many drugs" and is the term used to refer to the situation whereby elderly people, in particular, consume a relatively large number of prescription or over-the-counter drugs (i.e. medication, tablets, liquids, medical patches etc.). The number and combination of these drugs may, in some cases, be harmful.

Protocol

A protocol, in the context of research, is a plan which is drawn up by the researchers and contains all the details of what they will do during a particular study and how they will do it. This typically covers the design of the study, the criteria for the choice of participants,

step-by-step details of how the intervention (or review or observation etc.) will be carried out and how the data will be analysed.

Randomised controlled trial

In a randomised controlled trial, people are assigned to different groups (e.g. to the experimental drug group or the placebo group) in a random manner. The principle is similar to tossing a coin but usually this is done with the aid of a computer programme which generates random numbers which can then be used to determine which group each person is assigned to. The main purpose of randomisation is to avoid possible selection bias. It may also be perceived as being fair.

Retrospective studies

Retrospective studies collect data in the present and linked to the past. For example, a retrospective study might involve asking people about their smoking, drug taking or drinking habits at various stages of their lives.

Sample

A sample is a subset of the population. In some studies, particularly quantitative studies, the sample is representative of the population, which means that it shares the same characteristics of the population. This is not always the case or even necessary, particularly, in qualitative studies where selection may be based on other criteria such as theoretical concerns or the desire to obtain a wide range of different responses (e.g. attitudes or perceptions).

Statistical analysis

Statistical analysis is a way of analysing data which permits researchers to state with varying degrees of certainty whether there is a relationship between different variables. Statistical analysis can never prove that a hypothesis is true. It can only provide sufficient evidence to support or refute it.

Variable

Variables are the characteristics or attributes that the researchers are interested in and which typically "vary" in two or more categories (e.g. male/female; mild/moderate/severe or on a continuum of score e.g. satisfaction score rated on a scale of 1-5).



Annex 1: Possible issues to cover in a consent form

12 Annex 1: Possible issues to cover in a consent form

The following list provides examples of some of the main points which should generally be included in a consent form (depending on the type of research and the methods adopted). They are phrased in the form of questions or statements requiring the potential participant to tick or cross boxes marked YES and NO. For some studies, there may be additional issues to consider and some researchers may prefer to have additional consent forms for specific issues (e.g. for video recording or to waive the right to anonymity under certain conditions).

The consent form should contain a reference number and date (e.g. Version 3, 18 March 2011), the title of the study and the name of the chief researcher.

SAMPLE QUESTIONS AND STATEMENTS FOR A CONSENT FORM

1.	Have you received the Participant Information Sheet (reference articipant information sheet) or had it explained to you?	nd da YES		he p NO	
2.	Have you had the opportunity to talk about the study and ask que	estior YES		NO	
3.	Are you satisfied with the answers to any questions you may have	had? YES		NO	
4.	Do you understand that it is your choice to take part in the study?	YES		NO	
5.	Do you understand that refusal to take part in the study or w adversely affect your current or future care and treatment?	ithdr YES		will r NO	
б.	Do you understand that your anonymity and confidentiality wistated in the Participant Information Sheet?	l be YES	•	cted NO	
7.	Do you understand that you will be filmed/photographed/recorstate which, if any] for the purpose of this study?	ded YES		rcher NO	
8.	Do you agree to any images or recordings (as mentioned above) context of this study? [or in future publications if this is the case – res		her to		ify]
9.	Do you agree to information obtained during this study being rep sional or academic journals and reports?	rodu YES		prof NO	
10.	Do you agree to any of the data from this study (e.g. informatio images) being used for future research? YES (without restri YES (on the following conditions)	ction) □;	NO	□;
11.	I would be pleased to be consulted about the interpretation of study.	the r YES		of t	

12.	In the event of my future incapacity or d collected to be used in the study.	eath, I wou	ld like data tha	t has alread YES 🗖	dy been NO 🗖
13.	In the event of my future incapacity, I v study (if still possible and valuable to the Only if the person mentioned hereafter the necessary information to make a dec	e researche consents to	rs). o this after hav	YES □;	NO □;
14.	I understand that if during the course of illegal or unethical or which causes has bound to report it to the proper authori	m to anot	· ·		
15.	I understand that I can withdraw from that any time without having to explain w	-	refuse to take	part in any YES	activity
16.	I authorise the researchers to inform my this study.	general pra	actitioner that NO 🗖 (to incl	-	
17.	Based on my responses to the above que	estions, I co	nsent to taking	part in thi	is study. NO 🗖
18.	Numbers of statements or questions that	t I have nei	ither ticked no	crossed:	
Nar	ne: Date:		Signature:		





Annex 2: Possible issues to cover in a Participant information sheet

13 Annex 2: Possible issues to cover in a Participant information sheet

The Participant Information Sheet should provide the relevant information that a person would need in order to make an informed decision about whether or not to take part in the proposed study. The content of the information will differ greatly depending on the type of study being carried out and especially with regard to possible burdens and risks linked to taking part in the study. Participant Information Sheets for clinical trials, for example, would contain considerable detail about the kinds of tests to be carried out, the risk of side effects and various medical issues. Observational studies might provide more detail about the manner and extent to which participants will be observed as well as limits to such observation. Nevertheless, as with the consent form, there are likely to be several common issues. These include:

- · The title and reference number of the study.
- · The name of the chief researcher.
- How the study has been organised and funded, including any commercial partnerships.
- The purpose of the Participant Information Sheet.
- · What giving "informed consent" means.
- · What the study is about and why it is being carried out.
- · Clarification that the aim of research is not to benefit individual participants.
- · Why the person has been chosen.
- · What will happen to participants and how this might affect their daily lives.
- That the person would be able to withdraw without having to explain why at any time.
- · Whether there are any costs involved and if so, whether they will be reimbursed.
- · Whether there are any potential benefits to taking part.
- · Whether there are any risks or burdens linked to taking part.
- · Whether taking part in the study will be kept confidential.
- Whether the person's identity and personal information will be anonymised.
- · How details and data will be anonymised.
- · How the data will be handled and analysed.
- · Whom to contact in case of complaint.
- How the scientific quality of the study has been evaluated.
- Details of any ethical approval which has been obtained for the study.

- What the person should do if s/he has further questions.
- What the person should do if interested in participating.

Possible additional information for medical research:

- What side effects are possible and if so, how will they be handled?
- Whether participants have other treatment choices.
- Whether participants will have to pay for the medication or care they receive as part of the study.
- Whether samples of human tissue or blood will be taken.
- Whether genetic information will be collected.
- How various samples and genetic information will be handled.
- Whether participants (or their treating doctor) will be informed of any additional important medical information of relevance to their health in the course of the study.
- Whether participants will be entitled to receive details of personal data resulting from the study or obtained during the study once it has ended.





Annex 3: Issues that researchers and committees might consider

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In some countries, there is as yet no national system for the ethical appraisal of research proposals, although some studies may be required to obtain ethical approval from universities or other institutions. It may also be the case that ethical approval is obligatory for certain types of study (e.g. clinical trials) but not for others (e.g. psycho-social studies, observational studies or survey-based studies). Alzheimer Europe has stated in its recommendations that all researchers should consider the ethical issues linked to their study and seek, whenever possible, ethical approval from a recognised body.

Where this is not possible due to the absence of appropriate reviewing bodies, researchers are nevertheless encouraged to consider ethical issues related to their study. Individuals or organisations funding research are encouraged to consider whether such issues have been adequately addressed before proposing funding. The following examples are intended to guide both. The term "participant" will be used to refer to people who are approached with a view to their participation in a study, even if they eventually decide not to participate.

The aim of this list is to encourage researchers and funders to consider ethical issues linked to dementia research. The aim is not to hinder good quality research or to dampen the enthusiasm of researchers interested in conducting valuable research in the field of dementia. For this reason, the list could be helpful to researchers who are not familiar with these issues in the preparation of their research proposals and in deciding on the design of their studies.

An excellent document also exists in French, published by the Fondation Médéric Alzheimer (FMA), which provides an ethical framework for reflection (http://www.fondation-mederic-alzheimer.org). It is targeted at researchers carrying out dementia research in the social sciences but it is also used by FMA to guide its own research and to evaluate research proposals submitted by external researchers.

The study in general

Have details of the main ethical and design issues been adequately considered?

What is the scientific justification for the study?

Does the research team have the necessary skills and expertise? [If not, how could they obtain these e.g. through training in methodological issues?]

What is the original contribution of this study? [need to avoid unnecessary duplication/redundancy of studies]

What is the potential social value of the study?

How have/will people with dementia, carers and patient organisations be involved in the various stages of the study (e.g. design of the study, data collection, data analysis, interpretation and dissemination of the results)?

Recruitment

What are the criteria for including and excluding participants?

What are the reasons for the exclusion of specific groups (e.g. older people or people from ethnic minority groups)?

How will participants be approached and by whom?

Will access to participants involve negotiating with other people (e.g. nurses, social workers or carers)?

If so, how will researchers ensure that this does not lead to the unfair exclusion or coercion of some people?

Will participants receive any payment or other incentives? If so, please give details.

Will the chief researchers or others involved in the study receive any payment or other incentives for any aspects of the study (e.g. for recruitment, conducting the study etc.)

Protecting the wellbeing of participants

What are the potential risks and burdens to participants and how will they be minimised or overcome?

Has the researcher considered any risks to him/herself or to others involved in conducting the study and if so, how would s/he deal with them, should they occur?

Does the researcher already have an adequate understanding of dementia?

If not, how could the researcher familiarise him/herself with dementia?

Has the researcher sought the support of carers in studies involving people with dementia? [This must be done with tact and not if the person with dementia clearly objects to the carer being consulted or involved.]

Is the study likely to bring up issues that are sensitive, embarrassing or upsetting and if so, how does the researcher intend to deal with this?

Does the researcher have insurance against possible harm to research participants?

Anonymity and confidentiality

How will participants, samples or records be obtained?

Will the researcher be obtaining personal information from participants?

Will measures be taken to ensure that consent forms or other documents containing personal information are stored separately from the data obtained from them?

Will data be anonymised and if so, how?

Who will have access to data?

How will data or samples be stored? Please include precise details of any storage of data on computerised or digital equipment.

How long will data be stored?

How will data eventually be disposed of?

Does the study have the potential to result in the disclosure of illegal acts or misdemeanours? If so, how does the researcher plan to handle this?

Consent and capacity

In what way will informed consent be obtained and from whom?

Does the researcher (or somebody in the research team) have the necessary expertise and know-how to obtain informed consent from a person with dementia? If not, how could this be organised?

In what way and for how long will proof of informed consent be stored?

Will the researcher seek the assent of participants who lack the capacity to give informed consent and if so, how?

What steps have been taken to ensure that informed consent has been given freely and that participants do not feel under any kind of pressure to participate?

How will the researcher ensure that participants have fully understood the information they were given?

If the participant loses the capacity to consent to the study during the study (even if s/he had the capacity to consent at the start of the study), will s/he be kept in the study and what will happen to data already collected?

Dissemination of the results

What means will the researcher use to disseminate the results of the study (e.g. presentations at conferences, articles in peer reviewed journals, publications etc.)?



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Design: binsfeld corporate

Layout: Docs

Print: Imprimerie Centrale © Alzheimer Europe 2011 ISBN: 978-2-9599755-8-5