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## WORKSHOP REPORT

EFGCP Geriatric Medicines Working Party Workshop on  
“The challenge of an ageing population for  
medical research:  
Is Europe ready to cope?”

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*Organised by the*

**European Forum for Good Clinical Practice**

## The challenge of an ageing population for medical research: Is Europe ready to cope?

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'Is Europe ready to cope with the challenge of an aging population for medical research?' On the 19<sup>th</sup> and 20<sup>th</sup> November 2009 the Geriatric Medicines Working Party of the European Forum for Good Clinical Practice brought together in Brussels around fifty experts from the fields of clinical research, academia, regulatory affairs, ethics, and the pharmaceutical industry for a Workshop to debate this question.

Opening the Workshop **Jean-Marc Husson**, co-founder of the Geriatric Medicines Working Party and member of the EFGCP Board, welcomed delegates to the meeting and set the scene for the two days discussion.

The world population is aging and in Western Europe it is projected that over 'one third' of the population will be over the age of 65 years by the mid century. This is expected to have a major impact not only on medical research but also the use of medicines within the European Union.

Many clinical studies have traditionally had age cut-offs thus limiting their applicability to the older population. First-in-man studies are nearly always carried out in young fit male volunteers with completely different pharmacokinetic (PK) and pharmacodynamic (PD) characteristics from in the older, predominantly female population. Together with the fact that many older people suffer multiple morbidities and increasingly consume multiple medicaments these question the credibility of many clinical trial results with their narrow inclusion and extensive exclusion criteria.

In addition, the aging process produces its own specific pathological states and diseases which can only be studied in the older population, and the lack of research data in this population has been of increasing public concern. At the same time, however, it is recognised that the older participant may be particularly vulnerable in a number of ways which may preclude autonomy and dignity thus limiting inclusion in clinical trials and access to the benefits of medical research.

For all of these reasons the current approach to drug development, with little recognition of the extent this aging population will have on medical research in general and clinical trials in particular, is being questioned. Jean-Marc Husson hoped, therefore, that the Workshop would be of interest, offer guidance to investigators, and set the agenda for funding bodies, ethics committees, the pharmaceutical industry and regulators alike, in order to facilitate and promulgate high quality ethical clinical research and drug development for this increasingly important population across the whole of the European Union.

## Plenary session 1

Jean-Marc Husson then gave a particular welcome to the first speaker **Beatrice Lucaroni**, Project Officer within the European Commission 7<sup>th</sup> Framework Programme for Human Development and Aging.

Health is a major theme of the FP7 'Cooperation' programme with an overall budget of €6.1 billion. Within this the objective of health research is to improve the health of European citizens and boost the competitiveness of health-related industries and businesses, as well as address global health issues.

Beatrice Lucaroni outlined the structure and content of the 'Health theme' with priorities primarily structured on the three pillars of 'Biotechnology, generic tools and technologies for human health'; 'Translating research for human health'; and, 'Optimising the delivery of health care to European citizens'. Bridging these pillars were a number of cross-cutting issues including child health, health of the ageing population and gender-related health. She went on to describe the funding schemes together with the processes of submission and evaluation within the Health theme.

For the Workshop, relevant activity falls within the 'second' pillar of 'Translating research for human health' and the cross cutting issues where health of the ageing population had been highlighted. The current (4<sup>th</sup>) call for proposals had recently closed for two-stage calls and was about to close for single-stage calls and both had included important and relevant topics. These included 'Integrative systems biology and comparative genomics for studying human ageing'; 'Markers of cellular senescence for human ageing' (both two-stage calls); and, 'Frailty and its implications in modern society' (a single-stage call). It was highlighted that all submissions would be expected to identify, discuss and take into account relevant ethical issues including informed consent, data protection and privacy.

As a project example Beatrice Lucaroni outlined those topics which had been within the 1<sup>st</sup> call (2007) singling out a project concerned with the 'increasing participation of the elderly in clinical trials'. The PREDICT project, which started in February 2008, received a grant 'to investigate reasons for the exclusion of the elderly in clinical trials and to provide solutions for this problem'. This project, coordinated by the Medical Economics and Research Centre in Sheffield (UK), is made up of five 'work packages' which are being conducted by a multi-disciplinary team of experts in geriatrics, gerontology and social medicine.

Work Package (WP) 1 involves a systematic review of the literature to assess both the extent of exclusion of older people from clinical trials and what might be done to remedy this situation. There will also be a review of ongoing clinical trials to assess the exclusion of older people, and thus give a more current picture. WP2 will investigate why older people are under-represented in clinical trials and what can be done to improve their participation, through exploring the views of health professionals and ethicists using structured questionnaires; whilst WP3 will explore the perceptions of older patients and carers using a focus group methodology. WP4 will then be used to develop a Charter for the rights of older people in clinical trials and WP5 will disseminate and implement the findings of PREDICT through publications for health professionals and lay people, meetings, the internet and the media.

The findings were clear that exclusion of older people from clinical trials on age grounds alone was unjustified and that their under-representation was causing difficulties for both prescribers and patients. The focus groups showed an awareness of the need for research specifically on older people but suggested that only those capable of giving informed consent should be invited to participate. The full research findings will be presented together with the launch of the Charter for rights of older people in clinical trials at an international meeting in London on February 1<sup>st</sup>, 2010.

'European regulations and medicines for geriatric patients' was the subject of the paper by **Jean-Pierre Baeyens**. He introduced the European Medicines Agency (EMA) which was set up in 1995 with funding from the European Union and the pharmaceutical industry, as well as indirect subsidy from member states, in an attempt to harmonize (but not replace) the work of existing national medicine regulatory bodies. EMA operates as a decentralized scientific agency (as opposed to a regulatory authority) of the EU, with head-quarters in London, and is responsible for the protection and promotion of human and animal health through the evaluation and supervision of medicines. It has a legal responsibility for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmaco-vigilance of medicinal products, and providing the Member States and the institutions of the EU the best-possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use referred to it in accordance with the provisions of EU legislation.

EMA operates a number of committees each of which has a number of working groups. Of current relevance is the Committee for Medicinal Products for Human Use (CHMP) and the Working Group with Healthcare Professionals (the Healthcare Professionals' Working Group - HCP WG). The latter, together with the 'patients and consumers working party' both have geriatrician (EU Geriatric Medicine Society - EUGMS) and patient (AGE – the European older people's platform) representatives for the older population. Although there remains a need for EMA to have a parallel committee to that for paediatrics there is an increasing recognition of the needs of the older persons and the EMA website does at least now have a specific section for this population.

In 2006 EMA received a request from the EC for CHMP to provide an opinion on the adequacy of guidance on older people regarding medicinal products. The outcome was recommendations which included discussing the opportunity for updating ICH E7, and to seeking to define 'elderly', 'frailty' and adequate age cut-off points. ICH (the International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use) is a project that brings together the regulatory authorities of Europe, Japan and the United States, together with experts from the pharmaceutical industry, to discuss scientific and technical aspects of product registration. In 1993 ICH had proposed guideline E7, 'studies in support of special populations: geriatrics'. This tripartite guideline had noted that for drugs with significant use in older people, the inclusion in clinical trials of a minimum of 100 patients aged 65 years or older 'would usually allow detection of clinically important differences' in drug responses compared with younger patients.

More recent discussion, including input from the CHMP report, has led to the publication in October 2008 of an ICH concept paper whose main recommendations are 'to discuss the number and age distribution of expected elderly participants in a given indication development and the criteria on which these figures are based'; 'to plan a development approach that will ensure exposure of a sufficient number of elderly and very elderly patients, with appropriate testing to adequately characterise the safety in that population'; and, 'to describe specific elements in clinical studies that will be evaluated in the assessment of the risks and benefits of the drug in the elderly, including in the context of common co-morbidities and concomitant therapies'.

Jean-Pierre Baeyens then went on to discuss the definition of geriatric medicine (based on that published by the Geriatric Medicine Society of Malta in 2008) and proposals for an operational definition of the geriatric patient for clinical trials. These could be set out under five headings:

1. Age: that the geriatric population should be defined as over 80 years, and not 65 years as in the current ICH E7 document.
2. Gender: that, with specific exceptions, the majority of recruited persons should be female.

3. **Functionality:** that in a 'trial' group there should be a good representation of 'frail' older persons. The proposal was that this should be based on the SOF-index (study of osteoporotic fractures) comprising loss of weight, impossibility to get up from a chair without using the arms, and lack of 'energy'.
4. **Polypharmacy:** that the group of subjects has to take a mean of three medicines a day.
5. **Exclusion criteria:** that any exclusion criterion has to have clear and detailed argument to support it.

In conclusion although the European authorities had agreed to consider the older person as a specific group and agreed with the evidence to include very old, frail patients with co-morbidities there remained a need for a formal geriatric medicine committee within EMEA and this should be pursued.

The final paper in the first plenary session was delivered by **Joël Ankri** on 'epidemiology and older people in the EU'. Recognising that aging was a world-wide phenomenon the changes underlying this and some of its implications were discussed under the three headings of 'demographic change', 'epidemiologic change' and 'health care change'.

Whilst the proportion of older people varies considerably in different regions of the world that in Europe is one of the highest with 25% of the population age 65 years and over, and this is predicted to rise to over 50% by 2050. Within this the proportion of the population over the age of 80 years is predicted to rise from 3.4% in 2000 to nearly 12% by 2050. These changes have, over the years, resulted from reductions in infant mortality and a subsequent decline in mortality for older adults. At the same time there has been a decrease in fertility although this may be on the rebound in Europe. The result is that the ratio of persons aged 15-64 years to persons of 65 years and over has fallen, with the implication that the overall demand for care will increasingly have to shift from the young to the 'elderly'.

Considering the epidemiologic change this could be looked at in relation to either the common medical conditions in the older population or in respect of disability and frailty. It is clear that during the past 100 years the overall pattern of mortality rates from individual diseases differs widely, from an increase for heart disease to a decrease from infectious disease. However, for many of the common problems – cardio-vascular disease, cancer, dementia (etc) – the prevalence increases with age such that survival curves show an increasing gap between disease free survival and total survival, with the greater proportion of older people showing higher levels of disability and handicap. The Disability-adjusted or Healthy Life Expectancy (HLE) – the number of years a newborn can expect to live in good health – is a useful measure of health to compare populations and it differs substantially from country to country.

There are notable differences between the disease patterns of adulthood and old age. In the latter there are co-morbidities, multiple causes of ill health, more chronic/progressive disease. In addition the therapeutic goals are focused more on restoring function/palliation whilst prevention is geared to prevent functional decline and disability. It is certain that many of the common conditions in older people impact on their functional ability and there are a number of models which aim to 'show' the disablement process – for example the accelerated aging model and the continuum model. In all cases, however, there are known risk factors and these may be medical, psychological or social. The main characteristics of disability in older persons are that there is a hierarchy of functional loss (early loss of complex activities; late loss in basic self-care); its prevalence and severity increase with age; there is a gender difference (females live longer but are more often disabled); and that non-medical factors (e.g. housing, low income, availability of caregiver) play an important role. The main medical causes of disability in this age group are the musculo-skeletal diseases, cardio-vascular disease, neuro-

psychiatric diseases and hearing and visual impairment. Whilst it is difficult to study, and there are wide differences between countries, the estimates of disability range up to 20% in the over 65 year age group.

This aging population and the higher prevalence of disability and chronic disease, with attendant dependency, in this older age group lead to the third 'health care' change where there becomes a greater need for future planning and realignment of national priorities to deliver improved quality of healthcare. There is a shift in organization from that centred around the hospital to specialized, 'structures' integrating the home, residential care and long term care facilities, and hospitals into a single co-ordinated unit.

## Plenary session 2

The second plenary session introduced an ethical dimension to the Workshop with a paper by **Michael Bone** on the potential for abuse of the older research participant. Abuse was defined as 'a single or repeated act or lack of appropriate actions occurring within any relationship where there is an expectation of trust which causes harm or distress'. It can take many forms – physical, emotional, verbal, sexual; intimidation or manipulation; intrusion into psyche; social, economic, intellectual, spiritual – and may affect all levels society, all cultures, all ages and both men and women: but in each case the overall purpose is control. The effect of abuse may be physical, resulting in injury, pain, suffering or discomfort; it may be psychological, associated with negative perceptions of self-worth, emotional suffering, or aberrant thoughts or behaviours; or it may result in social harm, affecting relationships or interactions with others.

In the context of (medical) research although there is a common respect for individuals and the principle of 'do no harm' there is, nevertheless, an inherent conflict between the role of the physician and the role of the researcher which can, albeit inadvertently, give rise to abuse. A number of case examples were described to illustrate potential situations where abuse might occur.

In clinical trial units complex studies may impose on participants in relation to commitment, with overnight stays and invasive test procedures, and lifestyle restrictions, both of which can provide the potential for abuse as the researcher 'quests for knowledge'. Research in the home setting may create potentially unsafe/threatening situations (an older female with a younger male researcher); therapeutic misconception; or exaggerated role conflict where the researcher may overlook incidental discovery of neglect or exploitation. Research in nursing homes may give rise to abuse through undue influences on recruitment and participation secondary to the influence of instilled trust engendered through the dependent relationship between carer and client.

The researcher must be sensitive to the needs of the older population. One safeguard to abuse arising through research is the independent review by research ethics committees whose role is to protect the dignity, rights, safety and well-being of research participants. The potential for abuse can be mitigated by close attention to the recruitment process, adherence to a proper provision of information and the consent process, and these would undergo specific scrutiny by an ethics committee. The role of care providers in nursing and residential homes would be discussed both in terms of their support (consent) for the research but also their possible involvement in the research itself. Researchers must, however, be alert to the potential for abuse by third parties, for example, the carers themselves. The issue of coercion with undue influence on the older person to participate in the research by virtue of their 'vulnerability' would be of particular concern.

In all cases there must be disclosure with understanding, and this is seen as being of especially important in research involving the older person. Although most older people are 'cognitively intact' the researcher must ensure that the information provided has been understood and they should have appropriate procedures in place to ensure that this is the case. Conversely researchers should recognise that dementia *per se* is not congruent on decisional incapacity. Although the research ethics committee has a part to play it is important that the researcher is in a position to minimise and prevent abuse, not only at the design stage of the research but also throughout the study itself. There should be awareness by those conducting research of ethical issues that might arise and this should result from a relevant education and training programme.

There should be an overall concern where research is to be conducted in older persons that there is proper respect and care being shown; that physical needs are recognised; that dignity and privacy are being protected; that there is a proper assessment of abilities; and that the rights both to participate freely without coercion and to withdraw from the research at any time are fully recognised.

'Some challenges in undertaking longitudinal research with older people' was the title of the paper by **Anthea Tinker**. Both challenges from researching older people and from conducting longitudinal studies need to be recognised.

The first consideration is the definition of an older person which, unlike in many instances where an arbitrary choice may suffice, usually needs to be made taking into account the research objectives. The danger of generalising across all older people, no matter how defined, is neither practical nor ethical. Neither should there be an automatic presumption that older people are vulnerable and therefore cannot take part in research; 'age or frailty alone is not a reason for doubting a person's capacity'. However, there are particular problems in the older population both in respect of a greater variation in biological characteristics and, where there is cognitive impairment, from an ethical perspective, ensuring informed consent. The lack of research on older (especially very old) people is practically and ethically unacceptable, particularly where the results of studies in younger populations are then extrapolated to older people. This is especially important where it relates to the use of drugs, where uncertainties over the risks and benefits of treatment in older people may lead either to delays in bringing new treatment or in minimising possible adverse reactions.

Longitudinal studies are increasingly being recognised as essential in gaining an understanding of the ageing process in older people, particularly as life expectancy and the proportion of older people in the population continues to increase. However, participation rates in such studies have been decreasing and research has shown that drop-out is greater among older participants. Although it is important to retain participants in longitudinal research studies there are ethical issues over how far they should be encouraged/persuaded to remain in the study and not drop out.

A research study has been conducted to address the question as to 'What factors encourage older people to remain as participants, or discourages them from continuing to participate in health related longitudinal or panel studies?' The study involved a literature review, a secondary analysis of existing data, and the collection of new data through focus groups and telephone interviews.

Overall the findings suggest that the people who are most likely to drop out are older, have cognitive impairment and poor functioning, live alone, have lower socio-economic status, and are women, unmarried, less educated and engage in fewer social activities. There are also practical reasons, including the study being too time consuming or contact too frequent, and the questionnaires being too difficult, humiliating and/ or repetitive. Where medical tests are involved these, are sometimes felt to be tiring and there is a dislike of certain things such as blood samples and cognitive tests. Some people felt

that these tests were unnecessary as they were being seen elsewhere by, for example, their GP. Long and difficult journeys were also seen as being a problem.

The main reasons why older people continue to take part in such studies is that they liked to receive the medical results and an explanation of them; home visits were also popular as was the prestige of the study/publicity featured. Many older people felt that they were 'giving something back to society'.

As to what might encourage older people to continue to participate in longitudinal studies then the medical tests were a main factor with some suggestion that other tests, relevant to their age group, could be introduced. Other factors included the provision of information (newsletters, feedback on the study, personal response to queries, meetings, study website and personal gestures, e.g. birthday cards); emphasising the importance of the study through, for example, media coverage; and incentives. There were also more practical issues in respect of the conduct of the study such as the offer of home visits or the use of headphones for deaf people; making the experience as pleasant as possible (comfortable surroundings, helpful staff, good refreshments); and, shorter questionnaires which could be completed on-line.

This research would indicate that it is worthwhile investigators concentrating on those most likely to drop out such as older, single women who are not well off and not well educated. Longitudinal studies are facing serious problems of drop out and the study has shed light on the issues involved and how these might be addressed.

### Breakout Groups

Workshop participants divided into two groups for parallel sessions and the resultant discussions were reported back to the plenary group.

**Group 1** discussed the two issues of 'Informed consent for older people in medical research. How to improve understanding and communication'; and, 'Decision-making capacity measurement. Its importance and use in medical research'.

The group was chaired by **Michael Bone** and facilitated by **Laurence Hugonot-Diener** with **Marianne Maman** acting as rapporteur.

The length and complexity of the information sheet/consent form were recognised as a real problem but it was also recognised that this was to a large extent legally driven. The problem was confounded by the time which is required and necessary to ensure that the information component of the process is properly communicated and understood through opportunities for face-to-face discussion with research team. The possibilities for 'group' communication and the use of alternative media, such as video, were among the additional/alternative options discussed. The consent process should be tailored to the target population and the potential advantages of including members of the study population in defining the most appropriate method for obtaining informed consent were debated. It was considered important that the 'burdens' through obtaining consent did not out-weigh the 'benefits' of the research.

Michael Bone introduced the Newcastle 85+ checklist which had been designed for investigators to ensure that there was continuing informed consent throughout any study. This raised further questions over the practicalities of this approach in respect of the time commitments required and whilst there was no consensus it was broadly thought that the use of such an instrument would best be considered on a case to case basis. It may have a place where there was a likelihood of fluctuating capacity but there was also a concern that it might increase 'stress' in study participants.

Laurence Hugonot-Diener discussed the capabilities that the research subject must demonstrate to show capacity for decision making. This must follow an assessment of the ability to communicate. There were a number of tools available for assessing clinical trial informed consent comprehension but all had limitations. It was considered that the UCSD task force decision tree would be a good starting point and a ten question 'brief assessment of capacity to consent scoring scale' which had been developed was presented. Whilst an objective assessment tool would be valuable there were questions over the administration and validity of such a tool in all situations and, as with the previous discussion, the group could not reach a consensus in the time available on its validity and usefulness.

In reporting back to the meeting **Marianne Maman** summarized relevant points from the group discussion. Capacity and cognitive status are related but not identical. Decision-making capacity is a clinical determination that evaluates the persons capacity to understand the information relevant to the decision, appreciate the situation, weigh up the information, retain it, make a choice, and then to communicate the decision. Decision-making capacity is thus specific to the situation and circumstances in which it is made and, in the current context, the research protocol; it can fluctuate over time. If there is any doubt, investigators should briefly assess the understanding of research participants. However, when inconclusive a more formal assessment of capacity should be considered, ideally by someone outside the research team. Although standardized and validated instruments exist they ideally should be tailored to the protocol, these would require specific training and may be time consuming. As a result, shorter versions exist and are currently being evaluated.

To ensure that consent forms genuinely fulfil their objectives, they should be written in a way that is understandable to the patient population concerned, avoiding technical and legal jargon. Sentences should be short, simple and layout should use white space border and large fonts. The use of very succinct consent forms may be useful, but could, according to one discussant, be challenging to implement in some countries. The research team should consider including supplemental materials to support complex information or to explain procedures. Video would be one possibility whilst positive experiences were also reported using dynamic diagrams and interactive computerized presentation. The process for the provision of information is important and enough time should be provided to the older people who may have a short attention span or who can be more easily distracted. To make best use of everybody's time, including that of the investigator, it may be worth bringing in groups of research participants to explain the important aspects of the research, provide them with any update including new information, and possibly re-consent them if deemed necessary.

**Group 2** discussed 'Clinical studies including older people. How to improve recruitment and retention' and 'Patient advocacy groups: What are the expectations and visions toward medical research in older people?'

The group was chaired by **Jean-Pierre Baeyens** and facilitated by **Jean-Marc Husson** with **Cees Smit** acting as rapporteur.

Initial discussion centred on the two different approaches to the testing of pharmaceuticals, the regulatory approach with a controlled pre-marketing scientific-study or the more practice-based, post-marketing approach. Both approaches have their advantages and disadvantages and both raise different issues in respect of the recruitment and retention of participants. The group discussion broadened in considering these issues to a review of definitions, study endpoints and the health care policies for the older person, all of which were considered to have an impact on the best approach in any given situation.

The retention of research subjects was also considered to be related to compliance centring on the practical issues of formulation and dosage of the study drug. Many older people found swallowing medication, particularly tablets, difficult. Crushing pills and some packaging (blister packaging) did not serve to make the difficulties any easier. These problems may lead to study drugs being thrown away rather than taken, particularly where subjects were living on their own at home.

In discussing the role of patient and patient advocacy groups it was recognised that these may have a valuable part to play in defining the most appropriate outcome measure for studies, particularly in the context of those subjective end-points reflecting quality-of-life measures. There was, however, the qualification that the membership of these patient groups should reflect and be representative of the geriatric population or perhaps, in some cases, of the population who were the target of the pharmaceutical under investigation.

Both break-out groups had a wide-ranging discussion and although no consensus was reached on any of the matters raised there were many points on which participants could reflect and take away to consider further in their day to day work.

### Plenary session 3

This session began with a forum discussion on 'ethical considerations: a proposal for older people in medical research' by **Jean-Marie Vétel** and **François Hirsch**.

Jean-Marie Vétel opened the discussion by making the point that although it has been argued that studies should not be performed in the older population when they can be performed in younger adults it would be wrong, and amount to discrimination, if this meant that older persons were automatically being classed as vulnerable. Protection against the risks of research should not lead to denying older people the benefits of research. 'Elderly' people are, however, not only old adults who should be included in population studies; there will also be a need to conduct specific trials in this group that cannot be performed only in younger adults. In all cases it does, however, need to be recognised that there is a 'high' prevalence of dementia in the older population and that this represents the most vulnerable of all geriatric groups and therefore necessitates even more careful review.

The question as to the definition of a 'geriatric population' is important and although this is often based on chronological age, over 65 years, it has to be recognised that there are different geriatric 'groups' – quasi-adult, old adult, elderly legally incompetent – and that these correlate poorly with aging. In relation to the specific study objectives trials may be performed across the different groups, with consequences for ethical aspects of their conduct.

There is therefore a need for clinical trials involving older people to improve their well-being and the treatment available to them. Differences in pharmacokinetics and pharmacodynamics, and in adverse reactions are common in 'elderly' people compared to adults and the choice of subsets of the geriatric population to be included should be made on the basis of the likely target population for the medicine being tested, the possibility of extrapolation, and the scientific validity of such an approach.

From the ethical perspective it is important to follow the ethical principles of 'respect for persons', beneficence (doing good and avoiding harm), and justice. The role of the ethics committee was discussed alongside guidelines outlining issues for consideration and how these might 'translate' to the older population. For example, frequently (but not always) older people are unable to provide informed consent (in the legal sense) but it remains important that their assent should be sought using age appropriate information. This lack of legal ability to consent has implications on the design, analysis and

the choice of comparators used in trials. Working through the ethical principles and guidelines it was concluded that the ethics committee, must have geriatric expertise and take advice in clinical, ethical and psychosocial problems in the field of geriatrics in order to balance the benefits and risks of research in the older person. Not only should there be a proper scientific review in relation to the inclusion of older people but the ethics committee's geriatric expertise should be available when reviewing the initial protocol as well as any subsequent substantial amendments. Ethics committees specialising in geriatrics could be considered for the evaluation of trial protocols that are complex or in serious geriatric diseases.

The guidelines discussed by Jean-Marie Vétel were revealed as being essentially those of the EMEA (European Medicines Agency) guidelines for young persons in which reference to 'children' had been substituted by 'older person'. Few general texts exist on ethics and clinical research in the elderly whilst these do exist for children. With the same ethical principles applying across both age ranges this should support the need for specific protections being defined for research in the older population. Official specific geriatric texts are needed to have a real impact on research practice.

This argument for specific guidance was developed by François Hirsch who pointed up some differences between children and older persons – whilst all children are considered vulnerable only some older people are vulnerable; vulnerable children do not (necessarily) become vulnerable adults whereas vulnerable older people remain vulnerable; and few children experience difficulties in respect of 'information, communication and technology' (ICTs) whereas many older people do. Despite these differences there is a lot to be learned from the ethical considerations for children published by EMEA and this highlights the need to have geriatric-targeted legal tools (international regulatory documents and conventions) for there to be any real impact. These should be developed alongside recognition of the importance of having geriatric expertise on ethics committees and active participation in the ethics debate of the research by Civil Society Organisations (CSOs).

**Richard Rowson** then presented the 'ethical aspects of medical research and older people from a philosophical perspective'. He began by identifying the core values essential to sound and valid medical research. Firstly valid research should have 'integrity' – it should proceed by sound reasoning and transparent analysis of data, with no hidden agenda or unacknowledged factors taken into account; secondly it should have autonomy – it should be an independent evidence-based process, not influenced by other considerations. Thirdly the research must be justified in terms of minimising harm (that is doing no gratuitous or unnecessary harm) and maximising benefits. Finally for researchers to have integrity they must apply these three values to the way they treat participants; participants should be treated differently from each other only if required by acknowledged aspects of research, or by relevant differences between them. This results in treating participants fairly and justly.

These four core values for the conduct of research processes, including the treatment of participants, can be summarised as: *Fairness* – treating fairly and justly; *Autonomy* – respecting informed views; *Integrity* – integrating statements and actions; and, *Results* – maximising benefits, minimising harm. Within this *FAIR* framework it is important to recognise that no one value has absolute priority over another and that the values are culturally impartial in that they are not affiliated to any particular culture, although they do occur in most religious and secular traditions. However, even though the ethical grounding of medical research should be culturally impartial, the conduct of research must take into account cultural sensitivities of individual participants.

The implications of these *FAIR* values were considered in the context of research in older persons. To treat participants fairly we should not only *value* their interests equally but also give equal *care* to ensuring the well-being of them all. There is often a tendency among researchers to consider that the

interests of older people are less important than those of younger people and this can be a particular problem if researchers are only used to carrying out research with younger people, or when they are dealing with research participants of varying age. Older people may be seen as less productive members of society, or outdated. In the design, conduct and follow-up of research it is necessary to take into account likely differences between participants, so that some are not put under more stress than others. We treat participants justly when we don't stereotype them, but treat them as individuals.

Autonomy reflects an individual's understanding their situation and making decisions freely without coercion. To respect participants' autonomy they should be equipped to make informed decisions about what they do and how they are treated. Older people should be given information about a research project which is as full as they can cope with and in a language, or form, that they will understand. Where older people may be heavily dependent on care from professionals for their day-to-day existence it is particularly important to ensure that they do not feel in any way pressured to join research projects. They should also understand that they can withdraw from study participation at any time without having to give a reason.

Integrity requires researchers to integrate their actions with their stated values and to ensure honesty and clarity when informing participants about such matters as the aims and objectives of the research; the risks and realistic expectations of benefits, and the limits of confidentiality and anonymity.

When seeking the best results then in respect of harms researchers should be aware that comparatively minor inconveniences may loom large in the lives of older people. They should also consider whether taking part would be likely to cause tensions among family and friends or fellow residents in old people's homes, since there can be very strong jealousies and resentments among older people. There is also the need to ask the question as to whether the benefits of the research can justify causing any harm? Older people often have enough problems trying to achieve a good quality of life, so any research which adds to those problems must be likely to produce exceptional benefits to justify asking them to take part. These benefits may be couched in terms of maximising the value of the research findings to others or of having direct benefit to those involved – researchers should not, however, make assumptions as to what older people would regard as a benefit.

Finally there is the balance of responsibilities between the ethics committee and the researchers themselves. If there is an articulated and acknowledged general ethical framework, such as the *FAIR* framework, in which people in the research community have received some training, it can increase ethical ownership, competence and accountability of researchers. If ethics committees can trust researchers to make decisions in circumstances as they arise, then the ethics committees do not have to try to anticipate everything that might happen and so do not then have to impose so many conditions and restrictions on the researchers. This in turn can reduce the possibility of antagonism between researchers and ethics committees and the more researchers are trusted to exercise professional autonomy, the more their self-esteem and moral responsibility may increase.

The final paper in this session was a presentation by **Anette Hylan Ranhoff** on 'how to run medical research in older people with delirium: an example of patients with hip fracture'. Norway has the highest incidence of hip fractures in the world, 10,000 per year / 4.7 million population. Hip fracture patients are old (mean age 83 years), 75% are women and most have fallen indoors. Delirium is characterized by impaired consciousness and cognition, rapid development and a fluctuating course. In a study of hip fracture patients (aged 65+ years) the prevalence of preoperative delirium was 21%, while postoperative incidence was 36%. Delirium in the older hospital patients is a potentially preventable and treatable problem, but the fact that it is often poorly recognized contributes to a poor outcome. In older patients with hip fracture delirium is associated with increased mortality, length of stay and

institutionalization and research is needed to better understand risk factors, how to prevent and treat delirium, and the pathophysiology and consequences of delirium.

The common problems of researching older patients with delirium are seen to relate to informed consent; patient communication and collaboration in interviews, tests and examinations; and the nature of delirium itself with acute onset, fluctuating course and variation of symptoms and subtypes.

The ethical issues relate to obtaining informed consent in a population in whom there is a high prevalence of impaired mental capacity – either due to the nature of delirium itself or due to the fact that individuals with dementia and severe illness are those most at risk. There is thus a conflict between a need to protect vulnerable individuals and the priority need for research in a neglected condition. It is therefore necessary to achieve an ethical balance between respecting autonomy through obtaining adequate informed consent and avoiding sample bias.

It has been suggested that 'Stringent testing of capacity may exclude patients with delirium from studies, thus rendering findings less generalisable. A different method is necessary to achieve an ethical balance between respecting autonomy through obtaining adequate informed consent and avoiding sample bias'. The proposal has been that recruitment rates are higher where, rather than a formal test of capacity (in line with legal guidelines) followed by a request for consent (or assent from a proxy), there is a combined capacity/consent process.

A number of studies were presented which set out to understand the pathophysiology of delirium through the study of regional brain perfusion. However, even with a combined capacity/consent process the number of subjects presenting with delirium who were able to complete the necessary test methodology was very small. None of these studies were conclusive although many of the older patients with delirium had a demonstrable disturbed cerebral blood perfusion. However, some older patients with delirium had normal cerebral perfusion and more than 50% of older patients without delirium and dementia were shown to have disturbed cerebral perfusion. It remains unknown how representative the study population was.

Delirium research could potentially deliver important benefits for patients and is urgently required. Such research involves the recruitment of patients who have impaired capacity to consent, and the current research regulations are unnecessarily stringent and may impede good-quality delirium research. There is in particular the danger that they lead to the recruitment of unrepresentative study populations. Changes to the regulations have been suggested extending the use of the existing European Union procedures for registered medical practitioner proxy consent. There is no doubt that research on older patients with delirium can be extremely difficult to run because the fluctuating course of delirium and patients reduced ability to communicate and collaborate. Methods and resources to meet these challenges must be sought.

#### Plenary session 4

The final session of the Workshop began by returning to the theme of regulation for pharmaceuticals with a paper by **Kristina Dunder** on 'proposed changes in E7 relevant to safety reporting for the elderly: the regulatory authorities' perspective'.

The EU has a single market for pharmaceuticals with the head office for the regulatory activities at the European Medicines Agency (EMA) in London. This agency coordinates a large number of experts and regulators in the different member states. Within the EMA, the Committee for Human Medicinal Products (CHMP) is responsible for the assessment of marketing applications,

variations and post-marketing safety issues and include one or two members from each EU state. This committee also provides scientific advice to the pharmaceutical industry and issues regulatory guidelines. For certain areas, these guidelines are based on guidance issued by the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which is an organisation consisting of representatives from both regulatory agencies and the pharmaceutical industry in USA, Japan and Europe.

The ICH E7 guideline (Note for Guidance on Studies in Support of Special Populations; Geriatrics) was adopted in 1993. In this document, elderly are defined as patients aged 65 and older and it is stated that a minimum of 100 patients would usually allow detection of clinically important differences between elderly and younger patients. Older patients should either be included in Phase II/III studies or studies conducted exclusively in geriatric patients.

In 2006, The EMEA received a request from the EU Commission to provide for an opinion on the adequacy of guidance on the elderly regarding medicinal products for human use. As a result the EMEA performed a review of existing European guidance documents as well as a survey of a sample of recent European Marketing Authorisations. Overall, there was a reasonable fulfilment of ICH E7 requirements both concerning the guidance documents and the applications. However, some areas of improvements were identified and it was recommended to discuss the need for an update of the ICH E7 guideline.

In September 2008, the ICH steering committee endorsed a concept paper for the creation of a new question and answer (Q&A) document as a complement to the ICH E7 guideline. The main recommendations that should be specified to Applicants were: To discuss the number and age distribution of expected elderly participants in a given indication and the criteria on which these figures are based; to plan a development approach that will ensure exposure of a sufficient number of elderly and very elderly patients, with appropriate testing to adequately characterise the safety in that population; and, to describe specific elements in clinical studies that will be evaluated in the assessment of the risks and benefits of the drug in the elderly, including common co-morbidities and concomitant therapies. Other identified points that could be included were the usefulness of specific endpoints in the elderly population and questions concerning the evaluation of pharmacokinetics.

A working group with representatives from all the organizations participating in the ICH was implemented and a draft Q&A document was released for consultation in October 2009. This document consists of 6 questions covering the issues identified in the concept paper.

1. Q: Why do we need an adequate representation of geriatric patients in the clinical database?

A: There is an increasing prevalence of the geriatric population (elderly and very elderly). Age-related physiological changes could affect the PK and PD of the drug and so influence drug response. Co-morbidities and concomitant therapies could interact with the investigational drug and make them more prone to adverse effects. Not all potential differences can be predicted from non-geriatric populations.

2. Q: What should be taken into account when estimating an adequate representation of geriatric patients to be included in the clinical database?

A: The study population should be representative of the target patient population. It might be appropriate to include more than 100 geriatric patients in the Phase II and III database. Data should be presented for patients aged 65 to 74 and for the very elderly patients aged 75 and older.

3. Q: Are there any special patient populations or characteristics that are particularly important to address in the planning of the clinical development program?

A: Geriatric patients often have co-morbidities and concomitant medications that could interact with the new drug and make them more prone to undesirable effects and interactions. Therefore, to assess the safety and efficacy of a drug in these complex patients, the inclusion/exclusion criteria of a study should, allow their participation.

4. Q: What should be considered for the clinical development program to adequately characterize the safety and efficacy of a drug for a marketing application?

A: In general it is preferable to include both non-geriatric and geriatric patients in the same study(ies), which can facilitate observation of age-related differences. This information would ordinarily be expected in a marketing application. Every effort should be made to include geriatric patients with concomitant therapies and co-morbidities in the premarketing clinical development program. In some cases, enrolment of these patients can be challenging and it could be appropriate to collect data post marketing.

5. Q: Are there concerns related to the data specific to the geriatric population that could be considered in the planning of the clinical studies?

A: Depending on the mechanism of action of the drug and/or the characteristics of the disease, certain specific adverse events should be looked for in the geriatric population and these would include effects on cognitive function, urinary incontinence or retention, weight loss, sarcopenia, and effects on balance and falls.

6. Q: In light of recent advances in the field of pharmacokinetics and assessment of drug-drug interactions since the ICH E7 guideline was established, what studies should be considered when developing a drug that will be used in geriatric patients?

A: The pharmacokinetics in geriatric patients (including the very elderly) should be evaluated to identify age-related differences that are not explained by other factors such as reduced renal function or weight differences. Population pharmacokinetic analysis could provide the requested data if a sufficient number of patients in different age ranges (including patients >65 and >75 years) are included in the clinical trials. A specific pharmacokinetic study comparing non-geriatric and geriatric subjects in the same study could achieve the same goals.

The consultation period is 3 months and, depending on the number of comments, the Q&A may be finalized at the next ICH meeting in June 2010.

**Solange Corriol-Rohou** in her paper on 'ICH E7: update and implications for industry' further reviewed the background to the ICH E7 guideline and discussed the development of the Q&A document. The complexity and length of the overall process, involving not only the ICH parties but also observers who could be very vocal, were highlighted. The six questions within the Q&A were reviewed. The new features appear to be quite challenging and there would need to be a close interaction with the regulatory authorities to appropriately generate data relevant to the use of any new drug in the elderly. Whether this data would need to be generated within any Marketing Authorization Application (MAA) or New Drug Authorization (NDA) or as a post-approval commitment in Europe, in the US or Japan, it is clear that more than 100 geriatric patients will now be required; that data should be presented for patients aged 65 to 74 years as well as for the very elderly patients aged 75 years and over; that every effort should be made to include geriatric patients with concomitant therapies and co-morbidities

as soon as possible in the clinical development program; that certain adverse events specific to the elderly population would need to be looked for; and that consideration should be given to generate appropriate PK data.

All of these would undoubtedly impact on industry and present additional challenges on top of those of the existing EU paediatric regulations. However, being conscious of the requirement, set out in the Q&A document, to ensure that the 'special' needs of the older person are taken into consideration when developing, registering and using new medicines should obviate the need for any additional specific regulation. The pharmaceutical industry will now have to give a particular consideration to the requirements detailed in this ICH Q&A document when developing any new drug, and more specifically those being developed for use in the older population. If there is a medical indication for a study in older persons then it will need to be decided, depending on the product and its mechanism of action, whether the data should be collected prior to MAA/NDA or as a post-marketing commitment. But this is a question which will have to be discussed upfront with the Authorities.

The final Workshop paper 'health economic outcomes for older people in Europe: what are the winning strategies for countries and Europe to prepare for the future?' was delivered by **Fausto Felli**. With the proportion of the population over the age of 65 years increasing it is crucial that people grow older in good health. Healthy life-years must be maximised. The Green Paper on the European Workforce for Health states that 'Health promotion and disease prevention are not only important in their own right, but can significantly reduce future demand for treatment and care services. The public health workforce throughout the EU must be properly skilled and have sufficient capacity to be able to carry out these activities effectively, and this needs to be built into training and recruitment plans.' This requires a rebalancing of budgets and an integrated programme to work towards 'health production'.

There are many studies which show that attention to lifestyle promotes health and longevity. For example researchers in the US had followed a group of over 2,000 men for about 25 years beginning in their early 70s. They found that the men who lived the longest had some things in common: they avoided smoking, didn't become obese or diabetic, controlled their blood pressure, and remained physically active, exercising two to four times per week. These men had greater than a 54 percent chance of living into their 90s. There are also studies which demonstrate the benefits of a lifestyle change on those who have developed an ill health. The effectiveness of such lifestyle changes are not in question, the issue is how to apply them on a large scale.

It would seem important to involve all levels of decision-making in creating an integrated approach to the problem of the ageing population. The EU and the Member States should provide support to the regional and local authorities to help them find sustainable solutions to offer services that are adapted to health promotion and the needs of older people. The goal must be to reduce the relative costs and impact of ill health in relation to future population aging.

There are a number of large scale studies underway, particularly in Italy, where through networking and communication public health budgets are being directed towards programmes to 'produce health' on a large scale. These programmes are ongoing and their evaluation remains, however the vision of a pan-European health system, in which 'chronic health' is a priority, must be our objective for the future.

## Discussions

Whilst each paper presented throughout the Workshop was followed by a question and answer session seeking clarification and specific points of fact from speakers each of the plenary sessions was followed by a panel discussion in which both specific questions and broader issues for debate were raised by participants.

Where possible, in this report, I have tried to incorporate the clarification and points of discussion in the summary presentation provided of each paper. Inevitably, however, there were recurring issues and topics which have not been specifically reported and below I present a number of questions and discussion points which I recorded as being of particular note.

- There was a tacit agreement through discussion that use of the word 'elderly' could show a lack of respect to the older person in that this countermanded the fundamental right of older persons to be treated with respect (UN, 1995). In this report I have therefore minimised use of the word 'elderly' excepting where context demands it.
- The relevance age *per se* in the definition of the older person for the purpose of clinical trials. It was generally agreed that definition based on age only was not enough and some participants went as far as saying that age was almost irrelevant. Where age was considered relevant then there was little agreement as to the age specific categorization for the definition.
- Age itself is not a problem in drug testing in the older person, the problems are co-morbidities and poly-pharmacy, which are often set as exclusion criteria. The need for a better management of poly-pharmacy was seen as being as important as the need to research drugs in older persons.
- In which 'Phase' of new drug development should older persons be included. Should the focus be pre- or post-marketing. What are the ethical issues relating to off-label prescription in the older person.
- There was a continuing debate over the need for Regulation for the older person (paralleling that for paediatrics) as opposed to guidelines and recommendations. This discussion continues through the proposed action to follow the Workshop.
- Aging is associated with negative perceptions and there is little interest in 'healthy aging'. Financial grants for medical research are generally given for study in the 'general population' (with a consequence that the older persons are excluded) and where they are directed to the older population this is primarily for research into specific disease states rather than for study of the 'disabling process' itself. Research in the older person needs to be holistic.
- There was a suggestion as to the possible use of advance directives, taken alongside obtaining consent, as a way to maintain older persons in a (longitudinal) research study. This would obviate the need to withdraw volunteers if they were to lose capacity.
- Would one get a representative sample if recruiting only in care homes? Should research be conducted outside of care/nursing homes because of the power relationships which exist in these institutions? Or should research only be conducted in residential settings because of compliance issues? The general view was that all sources for recruitment should be included.
- There was a strong call for the need to have specialized research ethics committees where the particular issues relevant to research in the older person could be properly understood and taken into account.

## Wrap-up and Closing remarks

**Florian von Raison**, co-chair of the Geriatrics Working Party of the EFGCP, summarised the issues which had been brought out during the Workshop. There are clear ethical concerns, not the least of which revolves around informed consent, which require continuing discussion and consensus, as the study of the older population becomes increasingly important and relevant to pharmaceutical development. It was unanimously agreed that there is overwhelming need to improve the availability of data in clinical trials coming from older people. In particular data is needed from 'frail' people as well as those with a more robust health. Specific endpoints need to be defined or adapted for older people and age relevant diseases. Finally, but by no means the least important, there is a continuing debate to be had over the need for regulation as opposed to guidelines and recommendations.

It was proposed that the next step should be to progress the guideline proposed by Jean-Marie Vétel in his presentation and circulate this to participants for their endorsement. If such a document could be agreed then this could be used as the basis for engagement and further discussion with the Regulators. In the meantime colleagues should further consider the ICH E7 Q&A and respond to this consultation before the imminent deadline.

In conclusion **Jean-Marc Husson** acknowledged the challenges which still remain but thanked participants for a successful Workshop which had demonstrated that Europe is moving towards the position of being able to cope with an aging population in the context of medical research.

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