Meeting Report

EFGCP-EUCROF Joint Workshop on

Ethical Challenges in Clinical Research at Both Ends of Life

Common Lessons to be learnt from Paediatric & Geriatric Clinical Development

Crowne Plaza, Antwerp, Belgium

27 & 28 April 2010

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ETHICAL CHALLENGES IN CLINICAL RESEARCH AT BOTH ENDS OF LIFE

Report of the EFGCP–EUCROF Joint Workshop on

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1: Introduction and workshop structure

Childhood and old age – Shakespeare's "second childhood" – are both very different and very similar. Neither stage in life is capable of being defined simply, neither is physiologically uniform, both populations can be considered as vulnerable, and both raise complex problems of treatment, especially (but not solely) ethical issues.

Working at different ends of the spectrum of life, professionals involved in paediatric and geriatric research rarely get to talk to each other. But at a conference on ageing organised by the European Forum for Good Clinical Practice (EFGCP) in 2009, the idea came up that researchers in the field could learn much from paediatrics, and vice versa.

In particular, there was debate about the opinion that experiences in applying the Paediatric Regulation might spur the realisation of similar legislation – currently completely absent – to kick-start research activity in the field of geriatrics.

Hence this unique workshop, organised by the EFGCP and the European CRO Federation (EUCROF) – a coming together of more than 50 specialists from across Europe working in various aspects of both worlds, which took place over two days in Antwerp, Belgium.

The workshop began with a scene-setting of the principal unsolved issues in paediatric and geriatric research. It was followed the next morning by two sessions on the ethical challenges in, respectively, paediatric and geriatric research, before a final session that sought to find lessons to be learnt for both fields.

This report seeks to draw out the main lines of thought and discussion, rather than provide a blow-by-blow account. The presentations and programme are all available on the EFGCP and EUCROF websites, www.efgcp.eu and www.eucrof.eu.

2: Executive summary and key messages

Research into children within the European Union now takes place in the framework of the Paediatric Regulation, which came into force in 2007 with the aim of ensuring better drug treatment for children. Before that, they were seen as an "orphan" population, largely neglected in the process of drug development.

There is another orphan population: the elderly. The workshop examined what might be learned, in both fields, from each other's experience, but more particularly what geriatrics might learn from paediatrics.

Discussion was both wide-ranging and specific. The meeting covered issues of consent, assent and dissent, as well as more particularly considering whether geriatric researchers should tread the path followed by their paediatric colleagues, with a Geriatric Regulation, a Geriatric Committee at the European Medicines Agency, a legal requirement to produce a Geriatric Investigation Plan for all drug trials, and so on; it considered a case study; and it drew a number of conclusions.

The key messages to emerge:

1 Though it is still too early to evaluate the success of the Paediatric Regulation, paediatricians seem to be very positive about its effect on promoting research in children, although the burden on industry is recognised.

2 Further work is required to assess the consistency of decisions on proposals for paediatric investigation.

3 Many of the areas of ethical concern in paediatrics are shared in geriatrics, although in one important respect they are diametrically opposite: children tend

to gain capacity to understand the implications of taking part in research; adults, as they grow older, tend to lose it.

4 Nonetheless, it would be wrong to start from an assumption that older people necessarily lack capacity to consent to taking part in research.

5 Instead of pushing now for the adoption of a Geriatric Regulation to mirror the Paediatric Regulation, efforts should focus on three areas:

   a. The creation of geriatric expertise at the European Medicines Agency, possibly via a Geriatric Committee and definitely through networking.

   b. The raising of the "normal" upper age of adulthood, i.e. the start of "elderhood", as laid down by the European Medicines Agency, from 65 to 75.

   c. A public debate about the need for research in elderly people.

6 The further elaboration of practical guidelines on the ethical conduct of clinical trials in elderly people produced by the EFGCP's Geriatric Medicines Working Party should be a priority, and involve the broad research and ethical community.

7 Ethics committees should have a member or members with geriatric expertise, and standard operating procedures that include training (and should be subject to audit and inspection).

8 There is a strong need to develop further the concepts of consent, assent and dissent in paediatric and geriatric clinical trials.

3: Keynote introductions

Unsolved ethical issues in paediatric clinical research – Helen Sammons, University of Nottingham, UK.

Helen Sammons from the University of Nottingham, UK, a working paediatrician, researcher and clinical pharmacologist who also sits on an ethics committee, started with the most fundamental question of all: Is research needed in children? Yes, she said, but only when the research cannot be conducted in adults. Indeed, it might be unethical not to conduct research in children.

Children are not small adults. Their physiology is different – and different at different stages of childhood – and drugs work differently in them. Frequently children also need treatment to be delivered in different ways; medicines need to be palatable, for example. Adolescents are "a completely different species again", she said.

Research with children, though, is fraught with problems, notably of methodology and consent. Studies have to be child-centred. For example, it is not viable to take multiple

blood samples from small children and babies; placebo should be used only where there is no established therapeutic option.

Sammons took a detailed look at issues around informed consent (normally from the parent) and assent (from the child) – a theme that ran like a thread throughout the workshop. Researchers often have to seek consent in stressful situations, such as during labour or shortly after delivery, or in an emergency. In these and other cases, she advised a "dynamic" consent process – going back and re-informing consent as the study progresses.

Seeking assent from children raises, sharply, the same questions met in adults. How much can children understand? To what extent are they capable of making a decision? Sammons cited research on what children understand, and on the extent to which parents or clinicians think children should be involved in research. The results show a lack of unanimity. For example, a third of US and Canadian clinicians surveyed thought drugs could be tested in healthy children, but a majority disagreed.

A difficult issue – and one that came up throughout the workshop – is whether research in children should take place only when there is a possible direct benefit to the child, i.e., how acceptable is the "group benefit" argument introduced by the Clinical Trials Directive . Linked with this is the question of whether one might imagine there are conditions beside vaccine studies in which healthy children could be enrolled in research.

For Sammons, a number of the ethical issues remain unsolved. These include several questions around consent and assent, such as the age at which assent should be sought from a child, when it is appropriate to seek it, and how to record it. "With children we can't give blanket age ranges for consent, but we need to give them their voice," she said. Methodology, too, should be child-centred.

Unsolved issues in geriatric clinical research – Jean-Pierre Baeyens, International Association of Gerontology and Geriatrics – European Region (IAGG–ER) and European Union Geriatric Medicine Society, Belgium

For Jean-Pierre Baeyens, geriatrics is following in the footsteps of paediatrics, only 30 to 40 years later. Both fields look at the whole person rather than being focused on a particular organ.

What is old? Age alone is not a helpful indicator. "You can be very old at 60 or relatively young at 80," said Baeyens. As a group, geriatric patients are older, they often have multiple illnesses ("polypathology") and poor homeostasis, a tendency to inactivity and various psychosocial problems. Linked to polypathology, they also tend to come to hospital with "a whole basket of medicines" – and this "polymedication" has been a problem for over a century.

As with children, diagnosis is complicated. Often, said Baeyens, you learn nothing from the patient. Hence the need for a "really comprehensive" geriatric assessment, which can only be done by a proper geriatric department in a general hospital with the required multidisciplinary teams. Shockingly, a study in the *New England Journal of Medicine* showed that patients discharged from non-geriatric departments to their homes or to nursing homes were more than three times as likely to die within a year than those discharged from geriatric departments.

Age apart, one area where older people might differ from children is in their priorities. For younger people it is "longevity at any price". But older people place higher value on their quality of life and ability to live autonomously. And that means that clinical research in older people requires different endpoints. Indeed, he said, "I am more and more convinced that we need separate trials for geriatric patients."

As with children, the exclusion of older people from clinical trials raises ethical issues in itself. Like children, very old patients react to medicine differently from other adults, so clinical trials without them may not yield helpful information. The result is that many medicines for geriatric patients are prescribed "off-label", with little idea of efficacy, dosage or adverse effects. And yet many ethics committees still refuse to accept older people in clinical trials – because of "paternalism", said Baeyens.

Including geriatric patients in clinical trials also raises a raft of issues. Some are issues that differ from those encountered with children: getting multidisciplinary teams to accept the treatment, and the problems raised by polypathology and polypharmacy.

Others are similar: issues of information and consent, either by the patient or by the patient's family. Baeyens had some clear principles to offer here: treat all older patients as adults, and start with the idea that every person has the "presumption of capacity" unless proved otherwise. "Individuals have to be supported to make their own decisions. You have to help them, but not influence them," he said, adding, "Just because someone makes an unwise decision doesn't mean they don't have the capacity to make a decision. We can all make mistakes."

Above all, anything done for or on behalf of someone who lacks capacity must be in their best interests and "least restrictive of their basic human rights and freedoms".

Baeyens ended – prompted by a question from Francesca Cerreta of the European Medicines Agency (EMA) – with a sketch of the desired composition of a clinical trial for geriatric patients. "We need to have information for the group of patients who have the typology of the older patient: polypathology, poor homeostasis and many problems," he said. That means starting with a mean age of 80 or 85, but at that age there are four times as many women as men.

4: Ethical challenges in paediatric clinical research

Chairs: Klaus Rose, EFGCP Children's Medicines Working Party and Granzer Regulatory Consulting & Services, Germany, and Amparo Alemany Pozuelo, Paediatric Working Group, EUCROF and Trial Form Support Spain, Spain.

Impact of the Paediatric Regulation on the clinical trial environment – Philippa Smith-Marshall, EUCROF Paediatric Working Group and PharmaNet, the Netherlands

Philippa Smit-Marshall from EUCROF's Paediatric Working Group and PharmaNet, the Netherlands, took the workshop through a quick overview of Europe's Paediatric Regulation and work done by EUCROF to assess progress in clinical research. (EUCROF is currently doing a survey looking at the competence, capability and experience of ethics committees; it will be published later this year.)

The US and the European Union both have legal instruments that seek to encourage the development of treatments for children. Japan allows paediatric data from other countries to be part of submissions for marketing approval, and is working on paediatric legislation.

As of April this year, the US has seen 591 proposed paediatric study requests made. The FDA has also required 383 paediatric studies to be performed. A total of 224 studies have been conducted under the two US acts that cover paediatric research, involving 95,000 patients; and 163 products have received paediatric exclusivity.

In Europe, the European Medicine Agency's Paediatric Committee has received 701 validated applications for paediatric applications, covering a total of 1,057 indications, and has adopted opinions on 229 Paediatric Investigation Plans (PIPs).

In 2008 EUCROF conducted a retrospective survey of clinical research organisations (CROs), pharmaceutical companies and ethics committees in 15 European countries to gauge activity in paediatric research. It found a mixed picture, with large differences between countries as regards both the number of paediatric trials as a proportion of all trials and as regards other activities, such as networks, working groups and conferences.

The survey also looked at the ClinicalTrials.gov database, finding European participation in between 10 and 20 per cent of trials recorded there – "quite high", said Smit-Marshall. Most studies were being conducted in children younger than either 3 or 9 years, rather than in adolescents.

The main conclusion was that there were fairly few paediatric trials and little other activity, and that the impact of the Regulation had yet to be felt. A follow-up survey, which finished in February 2009, aimed to dig deeper, concentrating on more recent studies and seeking to tease out the problems that researchers had encountered.

CROs, companies, ethics committees and investigators in 11 countries were approached, but only 39 responses were received. It seems that concerns over

confidentiality of information may lie behind the level of response (that, at least, was what some respondents said, although as Nathalie Seigneuret from the EMA said, the explanation is odd, since none of the information is confidential). Still, within these limitations, there were interesting results.

What does the landscape look like? Few respondents had experience of Phase 1 paediatric trials, more in Phase 2 and good levels of experience in Phase 3, tailing off a little in Phase 4. Infectious diseases and oncology topped the list of indications, followed by haematology and diabetes. Most respondents had been involved in less than five studies, with "quite a high proportion" of less than two weeks' duration.

Respondents saw the main hurdles for clinical research as insufficient or inadequate information about paediatric clinical studies, and felt studies in their own countries were being held back by issues around recruitment, legislation and administration, cost, difficulties in obtaining ethics committee approval and consent from parents…and a low level of interest from potential sponsors. Nearly three-quarters said that dedicated paediatric workshops and seminars were attractive sources of information.

Smit-Marshall said that the results, although limited by the response rate, showed a "clear lack of experience in many aspects of paediatric research", with respondents seeking external support, and looking for more education and sharing of experience.

Overall, she said, clinical research in children is expected to increase from its present level (EMA statistics indicate that paediatric studies account for around 5 per cent of the total). But following experience in the US they will also become more complex, take longer, and cost more, leading to a drive to find patients in other countries. A new landscape is emerging, one of limited populations, competition for patients, and a need for the timely completion of studies – coupled with new Japanese regulations, for example, allowing data to be accepted from China and Korea.

Meanwhile, global compliance with Good Clinical Practice has improved, and legal and regulatory frameworks in developing countries are becoming "much more robust", said Smit-Marshall, who rejected a suggestion that companies and CROs might be "exploiting" those countries.

With more activity, the gaps in sponsors', CROs' and ethics committees' capabilities are likely to decrease. A new survey in 2010 and 2011 will seek to determine how that is going.

Ethical aspects of the Paediatric Investigation Plans – Nathalie Seigneuret, Human Medicines Special Areas, European Medicines Agency (EMA)

Any pharmaceutical company developing a medicine that falls within the scope of the Paediatric Regulation needs a Paediatric Investigation Plan (PIP). Companies must submit the PIP to the EMA's Paediatric Committee to show a plan that will generate the data to support a marketing authorisation in children, (with or without a request for a

deferral that would permit them to perform the paediatric research later). Otherwise they must go to the Paediatric Committee to ask for a waiver on the three grounds laid out in the Regulation.

How does the Paediatric Committee fulfil its responsibility to ensure that trials are safe and ethical? Nathalie Seigneuret from the EMA used anonymised examples of PIP applications: a pharmacokinetics study in asthma would have required taking 7.5 ml of blood 17 times from patients aged between 6 and 11; and another open-label study for pulmonary hypertension failed to include a description of the standard care for the condition.

These cases may reflect the fact that paediatric expertise is often absent when a company prepares a plan. Seigneuret insisted that ethics and science go hand in hand, and there are aspects to be considered which will ensure that the clinical trial is designed appropriately to ensure the protection of children. To help companies to consider these aspects systematically, the EMA has produced forms outlining the design of the proposed study to be filled in at the time the PIP is submitted. These cover areas such as the main inclusion and exclusion criteria, where the study will be performed, why it is relevant, the standard of care, and issues of diagnosis. The process forces companies to think from the start about whether there might be a need for rescue treatment, what it would be, and whether stopping rules are needed (and if so, what). Other aspects include whether a Drug Safety Monitoring Board (DSMB) is needed.

When it receives a PIP, the Paediatric Committee will look closely to ensure that the methodology is correct, in particular whether the number and volume of samples is appropriate. “Some PIPs received in the early days had no mention of number and volume,” she said. The Committee is also keen to see “more and more” use of modelling and simulation. “The use of placebo versus comparator is a topic in itself,” she said.

Seigneuret said that the statistical approach was “definitely important and often overlooked in the plan”. Again, the aim here is to limit the number of children included, but at the same time to ensure that the study will answer the question. The Committee has set up a working group on how to extrapolate results from adults to children. She also reported “extensive knowledge gaps” in terms of markers and the validation of scales and endpoints.

A review of 20 opinions from the Paediatric Committee adopted in 2009 found that in 19 out of the 20 the opinion asks for a DSMB. Other changes called for, though less frequently, include requests for a staggered approach to study the pharmacokinetics or measures to minimise pain and distress.

Three years into experience with the Regulation, “we have definitely changed the environment…Paediatric development is now part of the normal consideration of the development of a medicinal product,” said Seigneuret. The Paediatric Regulation has brought greater transparency and reinforced the need for trials whose scientific quality

is high, put ethical considerations centre stage, and has highlighted gaps in knowledge, especially of methodology. “There is no excuse for poor science,” she said.

But a number of questions remain, or have been thrown up by the process. “Has the Paediatric Committee been consistent?” wondered Seigneuret. “Is having a DSMB for most studies justified, and a real protection measure?” The Paediatric Committee is pushing for new methodology, but are the licensing bodies ready for it? Should there be a revision of its ethical guidance, now three years old (Ethical Considerations on Clinical Trials with the Paediatric Populations, 2008)? Now, she said, is the time to engage in a dialogue between all stakeholders.

Workshop delegates had other questions for Seigneuret. Luc Stuit from the AFRT, France’s Downs Syndrome Patient Organisation, wanted to know why we export our trials to developing countries, and why research on so many diseases is neglected. That’s slightly beyond the scope of the Paediatric Regulation, replied Seigneuret, adding that it is “not the role of the Paediatric Committee to inspect all the sites and decide where to hold a trial, although it will look at whether this would have an impact on the standard of care, choice of comparator or relevance of the data to the EU population”. For Marianne Maman from Novartis, Switzerland, studies are needed in developing countries, though we should be careful about sample size and having GCP-trained investigators. The West should contribute to capacity building in developing countries, she said.

Stuit also asked why the Paediatric Committee did not oblige trials to compare new drugs with standard treatment. That has happened, said Seigneuret, but in many cases it is hard to use comparators because so few products are currently licensed for use in children.

Finally Stuit asked why we should accept “low-cost methodology for paediatric investigations”. “We don’t ask how much the study will cost,” replied Seigneuret, adding that the Committee’s role is to ensure that the methodology is used correctly. Maman wanted more from the Paediatric Committee in terms of methodologies. “Many of us would agree that there is a need, if the Regulation is a success, to expand on methodologies. The Paediatric Committee is in an excellent position to reach out to stakeholders to develop operational guidance, she said.

Frank Wells from the EFGCP’s Ethics Working Party had the impression that “the Paediatric Committee is very good on science but not very good on ethics”, and that advice on paediatric studies to ethics committees is not getting through to them. “Do you think the 20 studies you surveyed were hindered by inappropriate action of the ethics committees that looked at them subsequently?” he asked.

The answer: “Once we give an opinion we don’t necessarily have the feedback from the company or ethics committee.” The EMA does not know, either, whether the opinion of the Paediatric Committee is attached to the protocol that is presented to ethics committees. That response prompted Angeliki Siapkara from the UK Medicines and

Healthcare products Regulatory Agency (MHRA) to call for the Paediatric Committee to find a way round this problem. Seigneuret indicated that the Paediatric Committee tries to have as much interaction with the EMA's Committee for Medicinal Products for Human Use (CHMP), the body that will recommend, or not, whether marketing authorisation should be granted.

Florian von Raison from the EFGCP's Geriatric Medicines Working Party and Merck-Serono asked whether a survey is being planned of the acceptance of paediatric research among the lay public. (No, was the answer.)

The Paediatric Committee does have a representative for patient organisations, but Rod Mitchell from the European Genetic Alliance Network made a plea for patient representatives to be introduced into all aspects of the paediatric clinical trials process. "It is time to open the doors. We do understand confidentiality, we do have integrity," he said.

Hugh Davies, from the UK National Research Ethics Service, gave a plea about ethics: "We don't need new guidance. We need to look at what we've got already and re-draft it appropriately. There are libraries of guidance. Problem for ethics committees is they don't know the prominence, authority and hierarchy of this advice." The National Research Ethics Service has experience in this and would be happy to share it, he said.

5: Ethical challenges in geriatric clinical research

Chairs: Florian von Raison, EFGCP Geriatric Medicines Working Party and Merck-Serono, and Anna Jurcyzynska, EUCROF Paediatric Working Group and Quantum Experimental, Spain

Proposal for a guideline on performance of clinical trials in the elderly population – François Hirsch, INSERM, France

It says something about the relative progress in clinical trials for children and elderly people that there is Paediatric Regulation on the one hand, but no accepted European guidelines for the ethical conduct of trials with elderly people. Do we need them, asked François Hirsch? But the question was rhetorical: he was there to present the rationale for and outline of a draft EFGCP Geriatric Medicines Working Party proposal on precisely that.

Elderly people are by no means all the same, and cannot be defined by an age range. Some are adult, some are somewhat slower than younger adults, and some suffer from a degree of mental deterioration (and of those some may have legal representation, and some may not be capable of giving consent themselves to take part in a trial).

In principle, trials should only be performed in elderly people when they cannot be done with younger adults, said Hirsch. In such cases, the groups to be studied must be

chosen carefully – even more carefully with vulnerable patients such as those with dementia. "But older people should not be denied the benefits of research," said Hirsch.

The rationale is clear: we need trials with elderly people to improve the treatment available to them; because old people show different pharmacokinetics and pharmacodynamics, and have different adverse drug reactions from younger adults; because treatments for elderly people need to be tested before being used; and because some conditions are specific to elderly people.

The general ethical principles that should apply stem from three fundamental rights, "three pillars" as Hirsch called them: autonomy (of the individual); beneficence (do good and avoid harm); and justice (a fair distribution of the burden and benefits of research).

Key differences between children and older people emerge straight away. All children are considered vulnerable, whereas only some older people are considered vulnerable; no children can give legal consent, while only some older people cannot consent; and vulnerable children become non-vulnerable adults, while vulnerable older people remain vulnerable. Meanwhile, many older people lack the IT skills to access information about trials, while IT skills are well shared among children.

Not only are the ethics of clinical research in elderly people "poorly addressed" in international regulation, ethics committees often lack relevant expertise. So, elderly people should be considered as an orphan population, suggested Hirsch, as was the case with children. The important question is whether legal instruments targeted at geriatric research would have a real impact.

The proposal suggests studying only drugs that target conditions seen only in the elderly, and drugs that have markedly different actions dependent on age.

The proposal calls on ethics committees to welcome geriatric expertise and to take advice on clinical, ethical and psychosocial problems in geriatrics, both when assessing study proposals and when reviewing follow-up, especially beyond the end of the study (a period which may be crucial for the elderly). Dedicated civil society organisations, such as patients' organisations, should take part in the ethical debate about when and how to involve the elderly in research.

When looking at a proposed trial, a number of points need to be examined:

- Trials should not be replicated unnecessarily in the elderly.
- The inclusion of elderly people must be shown to be necessary to meet the trial's objectives.
- Age-relevant formulations must be appropriate.
- The initial hypothesis must be based on relevant publications and experimental work.
- The quality of the trial must be such as to yield pertinent results.

- Potential risks that might affect older but not younger people; reporting on Suspected Unexpected Serious Adverse Reactions (SUSARs) needs to take account of reactions that might vary in severity from those seen in younger people.
- The safety report should look specifically at adverse reactions in elderly people.

With those conclusions as a basis, the EFGCP is recommending that a future European instrument on clinical trials, such as revised legislation on clinical trials, should include special provisions for older people.

That raises the question of specific ethical considerations. "We need some documents and guidance on ethical considerations for clinical trials with the geriatric population," said Hirsch. Work has already started, he said, though the draft prepared has no official status yet. As Frank Wells added, the EFGCP's Ethics Working Party and Geriatric Medicines Working Party will work together to produce a finished document (which will be in a different format from the draft circulated at the workshop).

PREDICT: Increasing the PaRticipation of the ElDerly in Clinical Trials – Peter Crome, PREDICT Project. University of Keele, UK

Peter Crome presented the PREDICT study, funded by the European Union, which is looking at involving more elderly people in clinical research in a collaboration across nine European countries (see www.predicteu.org).

Crome laid out a background of failure to include older people in trials that overwhelmingly affect them, and indeed which affect them more the older they get, such as stroke, heart disease, Alzheimer's disease and colorectal cancer.

There are many barriers. On the clinical side, health professionals say there is no obligation for pharmaceutical companies to include elderly people in trials; and there are concerns about the implications for a treatment of a patient taking part in a trial. One solution would be to include geriatric specialists on research ethics committees. For patients there are concerns around the effect of taking part on their own care and about risks as well as about the consent process, and a dislike of randomisation – all coupled with a host of practical issues affecting elderly people.

There is, he said, consistent under-representation of older people in trials of treatments in a range of conditions. A major factor is exclusion criteria in trials relating to co-existing illnesses and treatments – which are a fact of life for many older people.

PREDICT has several working parties looking at different aspects. Work Package 1 examined the existing literature: it has found, for example, that 25.5 per cent of clinical trials in cardiovascular disease, including those for devices and educational interventions, have an explicit upper age limit. The working party looked at the exclusions and determined that 45 per cent of them were unjustified. Comorbidity was "an almost universal exclusion criterion", said Crome. Other causes of exclusion: upper

age limits; physical or cognitive impairment, or reduced life expectancy; and polypharmacy.

Work Package 2 has been gauging professional opinion. In a study it conducted involving a questionnaire of 507 practitioners of all kinds, it was generally felt that even with no specified upper age limit older people and those with comorbidity would not be recruited into clinical trials. Suggested solutions included making the inclusion of older people legally obligatory, pre-defining specific numbers of older people in trials, and providing some financial incentives.

One particularly telling result: when asked whether they think the present arrangements are satisfactory, geriatricians were the most dissatisfied – and pharmaceutical representatives the most satisfied. More than 80 per cent of those asked agreed that too few elderly people take part in clinical trials, and overall around 60 per cent felt that national and EU regulations need changing to encourage participation.

What do patients want? Work Package 3 worked with focus groups of patients, and has come up with a whole raft of issues. These range from ensuring that trials are scientifically pertinent, the importance of clear information, the importance of the consent process and of the absence of compulsion, the need to encourage older people to take part, safety and quality of life. The key issues are that the elderly represent a diverse population, that they should be valued, that they should be able to take informed decisions about trials – and that they have a right to take part in trials.

Finally, Work Package 4 developed a charter that originated in work in the UK with Help the Aged (now part of Age UK), envisaged as a possible extension of the European Convention on Human Rights. The charter's basic principles are that older people should expect to: be offered medications that might benefit them; be informed about medicines in a way that helps them make treatment choices; decline treatments if they wish to, without affecting other care; be treated by doctors who recognise the values and risks of drug therapy for them; and be invited to participate in clinical trials of their treatment.

It follows from this that older people have the right to access evidence-based treatments – properly evaluated and shown to be effective in people of their age. They should also be informed about and invited to take part in clinical trials. (The ICH E7 guideline says that the more older people are likely to be affected by the results of a trial the more they should be included – "but we know it doesn't happen," said Crome.)

Trials should be as practical as possible for older people. That means thinking about how to get information across, including large print, involving family or carers, and training researchers in how to communicate with elderly people. And the outcome measures should be relevant to older people. One thing that came across "very strongly", said Crome, was that people should be able to withdraw from clinical trials without detriment to other treatments and to their overall care.

The next step is to translate these principles into practical suggestions. The PREDICT partnership is disseminating the charter and seeking support both nationally and on a pan-European basis, said Crome.

In the discussion that followed, Mirela Barbu from the Swiss Agency for Therapeutic Products gave an example of the kind of delays that can occur: she said she had seen trials rejected by ethics committees because the consent form contains the phrase "have been invited to participate".

Sven Erik Gisvold, chair of a Norwegian regional ethics committee, raised the issue of information for patients. Is this a problem, he asked? Crome felt it was a general problem in trials, not a specific one for geriatric medicine. "No matter how much information you give someone and how clearly you give it, if you go and ask them two months later what they have consented to they will not be able to tell you precisely. That applies to everyone. That's one reason you have an ethics committee providing independent review," he said.

One issue that often crops up in discussing ethics across Europe is the possible impact of differences between western and eastern Europe. François Hirsch wanted to know whether the survey had found different attitudes towards recruiting older patients. Yes, said Crome, there were some. But he said he was "very reluctant" to read too much into differences between the focus groups because they had been selected in different ways. There will be differences between countries, he said, but it's not just between ex-Communist countries and others: "Spanish people in their mid 80s would have gone through very different life experiences than people in, say, the Netherlands, which might affect their views."

Raphael Teichmann from Monipol Contract Research & Medical Consultants, Germany, noted that most trials do not have an upper age limit. So how come older people don't take part in trials? For Crome there are two factors: comorbidity (most people over 80 have more than one disease), but also ageism. That's why the charter makes suggestions about mandating numbers or percentages of older people in a trial.

What might be a linked issue is that of withdrawal. Anne Vinsnes from the regional ethics committee at Trondheim, Norway, noted that older people may be sufficiently alert to consent to a study, but deteriorate a few months later such that proxies will say they cannot remain in the study. Crome agreed that concern about dropout, with all the costs and work involved, is a reason for exclusion. Another reason, raised by Rod Mitchell, is that of costs, or perceptions of costs: patients need to have the issue of expenses explained clearly.

Others wanted to look at the role of alternatives to clinical trials. Soeren Rasmussen from Pfizer, USA. "There are many different ways of studying how to treat and manage old people," he said. "We are not just talking about clinical trials – you can do non-interventional trials, historical studies, registry studies… to me GCP is good clinical practice and not necessarily good research practice." Nathalie Seigneuret agreed: we

should use cohort or registry studies much more, she said, rather than specifically clinical trials.

So, what to do about the situation? Ingrid Klingmann from the EFGCP and Pharmaplex, Belgium, noted that the subject of the workshop was about the ethical aspects of trials, "but we have to go further" – to the overall methodology. "We have spent a lot of effort improving the methodology for paediatric trials, but elderly people are very different…While we have very strong representation from patients on the paediatric side we have very little from the elderly in general." Very old people cannot or do not make the effort to be involved in a patient organisation. "How can we develop the methodology that we need systematically in a relatively short period of time?" she asked.

Crome responded by saying that it is hard to generalise about older people. In his experience, some enjoy the camaraderie of being involved in a clinical trial. All the countries in the PREDICT partnership had lay representation on their working groups, he said. Frank Wells agreed with him: "The majority of elderly patients can easily be motivated to take part in clinical trials." Quite so said Michael Bone from the UK Association of Research Ethics Committees and the EFGCP: "If you respect your patients and develop a partnership with them, you don't have any problems in recruiting them, and they do enjoy that search for the truth."

Discussion: Complex Considerations for Ethics Committees on a Trial in a Vulnerable Population – Michael Bone, AREC, AAPEC, EFGCP, UK

Michael Bone then introduced to the workshop a recent (anonymised) research study that initially received unfavourable ethical review from an ethics committee of which he is a member, and invited the workshop to explore the reasoning and discuss its conclusions.

First he ran through the provision of the Clinical Trials Directive dealing with patients incapable of giving consent. Trials with such patients may only go ahead if they are approved by a patient's legal representative (which may be revoked at any time); if the incapacitated person has been given information about the trial and its risks according to their capacity to understand it; if there are explicit provisions about respecting the wishes of "incapacitated" people not to take part in or to withdraw from a trial; and if no incentives or financial inducements to take part are offered (apart from compensation for costs incurred).

That, then, is the background against which the study was assessed by an ethics committee. "It is worthwhile emphasising that the patient's interests and wellbeing prevail over all other aspects," said Bone. The process he described took only a month to complete.

The study involved a vulnerable population with Alzheimer's disease and Lewy body dementia, along with their carers. It was an academic study by a leading research group in gerontology whose chief investigator was a professor with "an impressive research

pedigree". It was fully funded, and had obtained NHS indemnity. Its aim: to compare the clinical utility, patient preference and cost benefit of two different brain scanning techniques in the evaluation and diagnosis of Alzheimer's disease – SPECT or PET. It involved 100 subjects over the age of 60: 40 with Alzheimer's disease, 30 with Lewy body dementia and 30 controls. Carers were not to be scanned.

In addition to scans, questionnaires and telephone calls to carers, there were a number of additional cognitive tests, and a willingness-to-pay tool (to find out whether carers/patients would be willing to pay for scans).

The trial team were "very honest that there was no benefit to the patient", said Bone. They planned on approaching members of the healthcare team to recruit the patients. Recognising the possibility of coercion in recruitment, patients and their carers had a week to reflect on whether to be recruited, and voluntariness and right of withdrawal were included.

So far so good, perhaps. But the proposal didn't include copies of assessment tools, patient information sheets or consent forms. Furthermore, they were planning to investigate patients unable to consent for themselves and to use identifiable patient data, but failed to address these issues in their research protocol.

From the point of view of patient safety and protection, time spent, radioactivity exposure, the ethics committee "didn't really have any concerns", said Bone. But the committee's opinion was initially unfavourable.

"We thought it was an important study, the doses justified, and it would be an important contribution to furthering our knowledge about accurate diagnosis with a relatively non-invasive technique," reported Bone. "But we thought there was insufficient justification for the inclusion of those lacking capacity, and not enough work on how to assess that capacity."

In particular, there was no strategy for dealing with those patients who might develop incapacity during the study. Additionally, the committee felt one of the cognitive tests (the MMSE) was insufficient – as a tool it is accredited for memory tests, but not to gauge capacity for consent. It raised concerns about willingness-to-pay tool (which could create unnecessary anxiety), and some additional assessments that were "perhaps onerous in this population".

On top of this, the committee doubted that the requirements of UK legislation (the Mental Capacity Act) had been met, and wanted to see the patient information sheet and the consent form. It also had concerns about what plans the researchers had for informing the patients of the results.

A month later the researchers came back. They recognised that they had not met the requirements of the Mental Capacity Act, and removed the right of the carer to consent – which is not allowed under UK law. Physicians have the right to instigate treatment for patients under their care, and for this have developed the role of the "consultee", someone who would indicate what they feel the individual's approach might have been

before they became ill. But that is neither consent nor assent, and is not legally binding. The revised proposal also met the researchers' legal duty to feed back to individuals and carers and what they have done, and the right of an individual to withdraw at any time and by any means.

The new submission introduced a capacity assessment tool and deleted the MMSE test. The willingness-to-pay tool would now go only to carers, be piloted, and come back to the committee for approval. It also included the patient information sheet and the consent form.

But there will still issues. The consent form said they would keep data for 10 years. "Was it proportional? Did they need that length of time?" The form also asked permission to use data for other studies without being clear under what conditions. The committee also thought the advanced directive was too rigid, and that role of consultee should only be as a guide. Capacity assessment still needed some work – it was "too global and not specific to the aspect that they were seeking consent for". The committee thought the trialists hadn't spent enough time considering strategies for recognising and dealing with distress. And now it said that perhaps the questionnaires were too basic.

Those issues were finally resolved, and the trial was approved at the beginning of January 2010.

6: Lessons to be learnt

Chairs: Frank Wells, EFGCP, and Soeren Rasmussen, Pfizer, USA

Similarities and differences of the informed consent process in children and old people – Hugh Davies, National Research Ethics Service, UK

When it comes to consent, what can paediatrics and geriatrics learn from each other? There are three broad issues, said Hugh Davies: informed consent and competence; developing and failing competence; and ("because, to me, the relationships matter") the relationship between children, elderly people and their carers.

Davies explored five issues around consent and competence, or capacity. First, everyone has the right to make their own decisions, but how do we apply that to children and the elderly? The tendency, legally, is to start from the point of view that children lack the capacity to consent. "Perhaps with the elderly it is the opposite, that we assume they have capacity much longer than they actually have." Conversely, Davies thought that the "burden of proof" is put onto the child: "I'm not certain how much we listen to their evidence, and in legal terms we don't; the consent is with the parent."

A second ethical principle is that we should give "all practicable help" before treating anyone as lacking competence. But do we? "I don't think that's actually the case with

children," he said. Equally, perhaps, we can be guilty of "talking down" to elderly people.

For Davies another problematic principle – raised earlier in the workshop – is that just because people make an unwise decision does not mean they lack capacity. "The idea denies me as a physician any opportunity to affect their wellbeing. If I feel they are making an unwise decision, don't I have the opportunity to seek to change it?" he said. "In paediatric practice we would strain very hard to get round a child who made an unwise decision. With elderly people would we make those efforts?"

A fourth principle is beneficence – that everything should be done in the best interests of the patient. Davies thought we were good at applying that to children, but wondered whether the same applied to elderly people.

His fifth principle was that anything done for someone lacking capacity should be the least restrictive of their basic rights and freedoms. "I am not sure that applies to children," he said.

His next topic was about developing and failing competence. Here there are many similarities between children and elderly people, because although the vast majority of elderly people will be able to give consent, "if we are serious we will have to research elderly patients from giving consent until death". The question is, how quickly do children gain capacity, and how quickly do elderly people lose it?

Children, said Davies, first develop capacity to understand, then to weigh up, then to decide. Do elderly people lose them in the same order? He suggested that it would be worth looking at examples in the children's literature in relation to assent, consent and dissent.

Relationships matter, but they can be a difficult area. "We accept the responsibility of parenthood, by and large, but we hope we never have to get asked for consent for a child to take part in a clinical trial. Do we accept that responsibility when we get older and have elderly parents?" he asked. And how does that work when there are, say, three siblings trying to decide together what their mother's best interests are, or what her will might have been?

When it comes to competency and consent, said Davies, there is broad agreement that the principles apply to both children and the elderly – but there are differences. "We are more cautious with children, and within that you have to look at the relationships," he said. We need to know more about the competencies and how they are gained and lost in children and in adults. Davies called for work to develop the concepts of consent, assent and dissent in these age groups and to "remodel" the provision of information to meet these concepts.

"Paediatricians hate the information sheets they are given. They want short ones. Unfortunately, they would be illegal. The model I am suggesting frees them up: information specifically for a child can be much more focused on what you think the child needs," he said.

Davies defended the "parental" as opposed to "paternal" approach, saying it applies broadly. Being serious about research in the elderly will require professionals to be more confident and comfortable when they turn to the new surrogate "parents", i.e. consultees. "If the elderly are to benefit from research, we will need people to understand that we will need to obtain consent from others rather than the subjects themselves," he said. "But we need to be sensitive to the responsibility we are placing on these people. It may have consequences."

So Davies stressed that making a decision must not be compulsory: "If someone doesn't want to make a decision they should not be forced to." And sometimes the decision is not as major as it might be seen to be, he said. In a randomised controlled trial of two established treatments of acute asthma that are both seen by all paediatricians as valid, for example, the only risk of research is being hit by the coin you toss to decide which treatment to go for. "You're going to have one or the other anyway. We need to provide support and guidance for those making that decision," he said.

Finally, there is one common issue between research in children and the elderly: difficulties must not be an excuse for inaction. Davies too was worried about the elderly becoming "therapeutic orphans, like children". So he cautioned clinicians, while continuing to debate informed consent in children and the elderly, to "keep the ethicists like me on a lead and tell them there is far more danger from unresearched care". We need a sensitive approach, he said, but it must also be pragmatic. It must not stop us moving on to evidence-based care.

How can ethics committees ensure they have adequate expertise for the review of paediatric and geriatric trials? A need for training and capacity building – Petra Knupfer, Baden-Württemberg Ethics Committee, Germany

The responsibilities of ethics committees are enshrined in law: to protect the rights, safety and wellbeing of human subjects. That's a huge responsibility, but as Petra Knupfer explained, the law says relatively little about how they achieve or maintain expertise in paediatrics and geriatrics.

Paediatrics fares a little better than geriatrics in the Clinical Trials Directive, with a specific article saying that ethics committees must have paediatric expertise or take advice from paediatrics experts. There is nothing in the Directive specifically about geriatrics, though there is a mention of expertise in relation to the "incapacitated adult".

The starting point, said Knupfer, is a recognition that both children and elderly people are heterogeneous groups, requiring multidisciplinary ethics committees. These committees must be familiar with the medical field, the study population, directives and national laws, and international guidelines. "They can't just come into a committee and start to give opinions," she said. "They need education, training and experience."

So committees need a balance of experts. Knupfer proposed, in order of priority, clinical pharmacology, internal medicine, cardiology, paediatrics, geriatrics, psychiatry,

gynaecology, nephrology and oncology (and the list could go on). But you can't have all of them, she said, so along with lawyers, a theologist, and ethicist, a statistician and a lay person, and one or two substitutes per member, ethics committees need a team of fast-working consultants who can respond to tight deadlines.

The next step is training, both initial training and regular courses. Substitute members must be involved as well, said Knupfer: "Committees must have the same quality of opinion independent of who is there." That includes training for consultants, too.

Then there must be systems in place to ensure quality: checklists and standard operating procedures (SOPs). These should also cover the evaluation of different study types (for example, concentrating on studies in healthy volunteers, first-in-human trials, minors and elderly people) and training for investigators, and should include guidelines and samples for the process of informed consent. Knupfer also recommended that SOPs should make it possible to demand discipline from honorary members: "A member who comes to a meeting without preparation is useless, even if that person is a distinguished professor." But committees should not be weighed down by bureaucracy. Checklists and SOPs should "be as short as possible", she said.

Knupfer listed a number of issues with which committee members have to be familiar – what is legally permissible or impermissible, whether there is direct benefit for the trial subjects, what the risk/benefit ratio is, and definitions of minimal burden and minimal risk. The committees also have to ensure that the investigators will monitor safety continuously during the trial.

Committees must be able to check how the informed consent process – both written and oral – will operate, and that there is adequate information and provision for assent for children, adolescents and incapacitated adults. "Oral consent we can control the least, but it requires time, knowledge, responsibility and experienced investigators," said Knupfer.

And they must evaluate the investigators. But how? CVs and other documents that demonstrate experience and specialisation in the relevant indication with relevant age group sometimes say more than mere certificates, said Knupfer, and committees must check that.

"We only see what we know," she warned, "so investigators as well as committee members need training and experience from the beginning."

The presentation sparked a lively discussion. Frank Wells said Knupfer's stress on training was notable, but she described it as "woefully inadequate" in Europe. How does it work in the UK, asked Jean-Marc Husson from the EFGCP Geriatric Medicines Working Party.

Pretty much the same as Knupfer described, said Hugh Davies, with an induction programme for new members focused on the skills involved in critical appraisal. Wells added that within his committee new members have a mentor for the first two or three meetings.

Davies also gave some further desired characteristics to be enhanced in training: respect, courage, insight and clarity. "They need to be nice people," he said. For an ethicist, he was more relaxed about ethics training itself. "I'm not too bothered about ethics training. Get the basics right and the ethics follow." He also mentioned topic-specific training, and training for the chair of the committee.

Like others, Davies stressed the multidisciplinary side. "I'm very keen on mixed-audience training," he said. "Ethics committees are there to promote ethical research. That means getting everyone together…those who train together should work better together."

Knupfer was explicit about the need for multidisciplinary committees. "I think it is wrong to make committees only for paediatric cases and only with paediatricians, and likewise for geriatricians," she said. That would be "too narrow". An interdisciplinary group, with people bringing in their different experience, offers the best protection for patient safety, she said.

Responding to a question from Ingrid Klingmann, she said she was in favour of a change in the Clinical Trials Directive to mandate the inclusion of a member with geriatrics experience. "Yes. If it's in the law, people will follow. If not, it's just good will and self-discipline," she said. She was in favour of "real harmonisation": the authorities are trying to harmonise the way they work, so why not ethics committees?

A subject that raised a fair amount of discussion was the variability in the performance, or at least in the opinions, of ethics committees. "You want to know why a study has been accepted on one country and refused in another. That information should be in the public domain, especially since at the end the medicines may be authorised throughout the whole of the EU," said Nathalie Seigneuret. "One of the objectives of the Paediatric Regulation is to promote research in Europe. So if we want to promote clinical trials in Europe but cannot perform them in some countries, there is a contradiction to be addressed."

Davies agreed that decisions should be transparent. "If we are placing great pressure on researchers to register their research and their trials, then there should be pressure on us as ethics committees to do likewise," he said. But as Wells noted, although the EudraCT database will list the status of a proposed trial and whether it has ethical approval, it will not give the committee's reasoning.

Ethics committees love their independence, said Knupfer, so self-discipline will not work without pressure from a Directive to audit and certify ethics committees. That's what happens in the UK, said Davies, and as a result, perhaps, decisions are more standard than in the US. But he also said that there was "justifiable and unjustifiable" inconsistency. "There are times when ethics is a matter of opinion," he said; the important thing is to know whether committees are being consistent (and to have a fair appeals process).

Adolf Häuser from F. Hoffmann-La Roche, Basel, asked whether it would help to mandate the registration of ethics committees, as the FDA has recently required in the US with the Institutional Review Boards (IRBs). Knupfer doubted this: "We [in Baden-Württemberg] are registered, but that's it. It doesn't mean you are more or less competent." Soeren Rasmussen reminded the workshop that the US registration is "far from an accreditation process". In the UK, said Davies, the standardisation (relative to the US's variability) is due not to registration but to audit and accreditation – "but it does require resources, and not all countries have the ability to implement it". Wells agreed: for him the IRBs are "incredibly variable", and that audit is what maintains a uniform standard.

François Hirsch noted that the workshop had earlier identified loss of patients during research as a major problem with trials involving elderly people. "Should committees focus on this aspect of the protocol?" he asked. That was not a big problem for Hugh Davies. "Elderly people will lose capacity, they will die. That's not research design, it's God's design."

The simple answer is to anticipate dropout with adequate numbers. (And in the UK research proposals are expected to have undergone scientific review before they are submitted for ethics committee approval.) Knupfer agreed, adding that the problem is not unique to geriatric trials: it's the same in oncology. And as Marianne Maman said, it is possible to offer advance directives as part of the trial's protocol.

Dagmar Chase from EUCROF wondered what happens to patient's data when they become incapacitated. Do we lose them? That should be covered by the Patient Information Sheet, said Wells. In German drug law, said Knupfer, the data are kept even if the patient drops out. Equally, though, investigators must check whether patients remain with their capacity to consent.

7: Open forum discussion – What can be learned from the regulatory approach to paediatric drug development for the encouragement for drug development for the elderly? Chairs: Jean-Marc Husson, EFGCP Geriatric Medicines Working Party and Eudipharm, France, and Juergen Schaefer, Paediatric Working Group, EUCROF & Corneso, Germany

Geriatric populations: a need for a new clinical development approach for medicinal products in the elderly, and orphan population – Jean-Marc Husson

Around the world the population is ageing – with women living much longer than men. We need a new way of doing things, said Jean-Marc Husson, starting with definitions of age. The EMA currently reckons that "elderhood" starts at 65. That's too early, said Husson, and we need to be thinking about 70 or 75, the age at which drug metabolism becomes notably different. We also need to have a uniform definition of

frailty – the EMA's guidelines call for frail elderly people to be treated as a sub-group, but there is no accepted definition of frailty.

By way of an introduction to the final discussion, Husson outlined the information gaps. We need proper data about effective dose ranges in acute and long-term use, starting doses, side effect profiles, the potential for accumulation in the body, the risk of drug–drug interactions, and about potential drug–disease interactions.

Alongside this, we have to deal with at least five types of problems in elderly people: ethical concerns, the demands of regulators, the impact on society, health (including drug use), and risk management to avoid incorrect prescription and treatment.

A number of initiatives are already under way seeking to address many of these issues, including the EFGCP proposal outlined earlier by François Hirsch as well as moves by the EMA and the European Union Geriatric Medicine Society (EUGMS). The question is, should developments in geriatric medicine mirror those that have taken place in paediatrics? Yes, said Husson – but without a Geriatric Regulation.

Husson called for the EMA to set up a Geriatric Committee (or at least a Geriatric Medicine Working Party). He also wanted to see a non-mandatory Geriatric Investigation (a GIP to sit alongside the PIP?), links with children's medicines working groups, a Europe-wide geriatrics network and links with national agencies (Japan and the US, as well as in Europe).

The tools used to evaluate geriatric medicines should be specifically designed or adapted for the population. That means being aware of the role of ethnic factors in the acceptability of data from trials conducted outside Europe. Exclude unfeasible or non-adapted tests, said Husson, use only geriatrically validated scales (including linguistic scales) and clinically relevant tests. And pay attention to drug formulations.

These considerations led Husson to three broad conclusions: there should be a group of geriatricians (the EUGMS, perhaps) at the EMA to evaluate medicines for elderly people; more regulatory clinical trials should be held in all types of geriatric populations in the EU, but without a new Regulation; and that we need to decrease the number of medications given to older people.

Husson's co-chair Juergen Schaefer added his own questions to the mix. Given that we need more regulatory trials in elderly people, how do we get there? What can we learn from paediatrics? And have the measures taken in paediatrics really been successful?

There was general agreement among workshop delegates – though not unanimity – that a Geriatric Regulation was not the right thing to go for now. Peter Crome said that if good practice works better than a new law, then that is what he would go for. "We want to work on an incremental basis which states what the problem is and suggests that all stages of the drug development process see changes," he said.

Florian von Raison was also wary of a Geriatric Regulation. The introduction of PIPs in paediatrics was "a huge effort for stakeholders", he said, requiring "a lot of energy,

resources and money". Companies developing drugs are under enough financial pressure, and would not welcome "another burden", he said: "We need something to kick off the process without the heavy regulation of the PIP."

That approach was echoed by Ingrid Klingmann. "Usually I am an optimist, but I have strong doubts whether extending the current paradigm of drug development to an older age group will improve the overall drug development process. Requesting mandatory trials with older people for the marketing authorisation dossier would make drug development – again – more expensive and time-consuming," she said. The solution is to support a public debate about the geriatric research. "Unless we raise this public debate we won't be able to motivate the researchers," she said. Hugh Davies, too, spoke of the need for education – "Academia and industry should top-slice 5 per cent of their funds to educate the public that research is good for our health," he proclaimed.

Regulations have "a terribly important part to play", said Jack Waters from Pfizer, US. "They help ensure integrity and protect public health. But they are only a part of the development of medicines and devices." Medicines are tested with exclusions, so you never know from a trial if drug x can be taken with drug y – but that is how they are used in practice. "Start gathering observational data of our regular clinical practice," he said, so that we can understand what can be used and what cannot. "There are rich seams of data to be mined. The randomised controlled clinical trial is not the only way to measure success."

The Paediatric Regulation incentivises industry, said Amparo Alemany Pozuelo from EUCROF, but we also need to encourage ethics committees and regulators to give fast approval to clinical trials in children – a need that we would envisage for studies in older people as well.

If not a Regulation, should there be a Geriatric Committee as there is a Paediatric Committee? Certainly, said Crome, geriatricians are "very keen" to see one established and are urging the European Commission to set one up. "Some increased involvement from geriatricians somewhere down the line is required," he said. But "we are not going to start immediately with a full-blown committee," said Francesca Cerreta from the EMA. First identify the needs and benefits, she said. In any case, there will be no funding for anything more than establishing an email list for at least two years. She foresaw an exploratory phase – "as happened with other committees" – and a scientific advisory group.

Another voice from the EMA, Nathalie Seigneuret, urged realism, pointing out that we are only three years into implementation of the Paediatric Regulation, and have had only two years of agreeing plans. So it's "far too early to question whether the measures taken in paediatrics have really been successful," she said, although there has been an increase in studies and registered products. Even so, said Helen Sammons, as a paediatrician she is "delighted" with the Regulation – it's the medicines authorised before the Regulation came into force that cause the problems, she said.

8: Concluding remarks: Ingrid Klingmann, EFGCP, and Martine Dehlinger-Kremer, EUCROF PWG and Omnicare Clinical Research, Germany

The outcome of the workshop was "more than I dared to expect", said Ingrid Klingmann. Her first recommendation: go through the slides again – there are so many good ideas, recommendations and experiences, she said.

Her highlights included Helen Sammons talking about expectations for clinical trials in healthy children: "There is lots of potential but we have not managed to make the most ethical and best scientific use of that," said Klingmann. On other hand, delegates learnt from Jean-Pierre Baeyens that geriatric patients treated in non-geriatric departments have much greater risks. "So we need more geriatric trials so that geriatric patients have the opportunity to improve their quality of life," she said. That requires thinking much more about endpoints in geriatric clinical trials.

The EUCROF survey presented by Philippa Smit-Marshall showed that the number of clinical trials in children is still small. "I accept that we are still at the beginning," said Klingmann, "but our knowledge of optimal paediatric clinical trials is still not good enough, and we have not had a methodologically efficient way of benefiting from all the experience as quickly as possible."

Klingmann referred to Nathalie Seigneuret's presentation, and the question she raised of Drug Safety Monitoring Boards in paediatric trials. "What are the criteria, do we always need them or are they just another burden to industry?" she asked. Seigneuret had also raised the issue of whether we need to strengthen or revitalise paediatric guidance. Certainly, we need a systematic evaluation of what we have experienced, said Klingmann.

She highlighted, too, Marianne Maman's suggestion that EMA develop operational guidelines for decisions on comparator drugs in geriatric trials, to ensure capacity building in trials.

Klingmann welcomed the presentation from François Hirsch on proposed guidance presented for geriatric clinical trials. "It is a very important and valuable document," she said. "A very good basis, but it needs to be worked on." The EFGCP Geriatric Medicines and Ethics Working Parties should take this forward, she said, inviting all workshop delegates to be involved in the process. She was also pleased to learn from Peter Crome what PREDICT was all about: "A good start into methodological learning about how to improve that situation," she said. Then there was Michael Bone's "very interesting case", which gave an insight into how solutions are reached.

Hugh Davies's presentation on comparisons between trials in children and elderly patients indicated the need to develop the concepts of assent and dissent in geriatric populations, she said. Petra Knupfer also talked about need to define capacity to consent. The UK idea of the "consultee" is a possibility, said Klingmann, but in many legal systems it doesn't work.

As for progress, Klingmann thought that changing the cut-off for adult clinical trials to 75 instead of 65 is "on its way". With the idea of a Geriatric Committee now with the EMA, the discussion about the need for geriatric trials must be "much more active", she said.

For Martine Dehlinger-Kremer, a major outcome is the realisation there are similarities but also some differences in paediatric and geriatric clinical research. Important progress has been made in paediatric research since the Regulation came into force in 2007, and the experience gained will "certainly help" to develop guidance or regulations for geriatrics, she said.

But Dehlinger-Kremer noted that the requirements of elderly people may lead to "multiple, long and expensive studies, which may not always be feasible before authorisation". So observational data, including follow up of a sample of frail elderly people, may be an option in framework of post-authorisation commitments as part of the risk management plan.

For the future, we need to work towards systematically requiring the appraisal of exposing elderly people to drugs (as appropriate), and the standardisation of findings in the CHMP assessment report and its Summary of Product Characteristics (SPC).

Appendix: Abbreviations and initials used

AAPEC Appointing Authority for Phase 1 Ethics Committees (UK)

AREC Association of Research Ethics Committees (UK)

CHMP Committee on Human Medicinal Products (EMA)

CRO Clinical Research Organisation

DSMB Drug Safety Monitoring Board

EFGCP European Forum for Good Clinical Practice

EMA European Medicines Agency

EUCROF European CRO Federation

EUGMS European Union Geriatric Medicine Society

FDA Food and Drug Administration (US)

IAGG-ER International Association of Gerontology and Geriatrics – European Region.

ICH International Conference on Harmonisation (World Health Organisation)

ICREL Impact on Clinical Research of European Legislation (EU-funded project)

IRB Institutional Review Board (US)

MHRA Medicines and Healthcare products Regulatory Agency (UK)

MMSE Mini-Mental State Examination

PET Positron Emission Tomography

PIP Paediatric Investigation Plan

PREDICT increasing the *Pa*R*t*icipation of the *El*D*e*rly *I*n *C*linical *T*rials (EU-funded project)

SOP Standard Operating Procedure

SPC Summary of Product Characteristics

SPECT Single-Photon Emission Computer Tomography

SUSAR Suspected Unexpected Severe Adverse Reaction

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