

Ethical Challenges in Clinical Research at Both Ends of Life

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This article summarizes the conclusions and discussion from a workshop in Brussels, jointly organized by the European Forum for Good Clinical Practice and the European CRO Federation, looking at how pediatric and geriatric clinical research might learn from each other in dealing with the ethical issues particular to each area. Experience with the Paediatric Regulation, which since 2007 has provided the legal framework in Europe for all research involving children, suggests that the incorporation of geriatric expertise at all lev-

els in the drug discovery process, including ethics committees, would yield considerable benefits. This should be combined with an upward revision of the age ranges that define who is elderly and a public debate about the need for research involving elderly people. Further work on practical guidelines on the ethical conduct of clinical trials in elderly people should be a priority. In both pediatric and geriatric research, the concepts of consent, assent, and dissent require further elaboration.

Key Words

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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 pediatric and geriatric research rarely get to talk to each other. But at a conference on aging organized by the European Forum for Good Clinical Practice (EFGCP) in 2009, the idea came up that researchers in the field could learn much from pediatrics, and vice versa.

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

Hence this unique workshop, organized by the EFGCP and the European Contract Research Organization 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 pediatric and geriatric research. It was followed the next morning by two sessions on the ethical challenges in, respectively, pediatric and geriatric research, before a final session that sought to find lessons to be learned for both fields.

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

EXECUTIVE SUMMARY AND KEY MESSAGES

Research on 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 experi-

ence, but more particularly what geriatrics might learn from pediatrics.

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 pediatric colleagues, with a geriatric regulation, a geriatric committee at the European Medicines Agency (EMA), 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 were the following:

1. Though it is still too early to evaluate the success of the Paediatric Regulation, pediatricians seem to be very positive about its effect on promoting research in children, although the burden on industry is recognized.
2. Further work is required to assess the consistency of decisions on proposals for pediatric investigation.
3. Many of the areas of ethical concern in pediatrics 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 take 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 EMA, possibly via a geriatrics committee and definitely through networking; (b) the raising of the upper age of adulthood, that is, the start of “elderhood,” as laid down by the EMA, 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 pediatric and geriatric clinical trials.

KEYNOTE INTRODUCTIONS

UNSOLVED ETHICAL ISSUES IN PEDIATRIC CLINICAL RESEARCH

Helen Sammons (University of Nottingham, UK), a working pediatrician, 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 centered. 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 labor or shortly after delivery, or in an emergency. In these and other cases, she advised a “dynamic” consent process—going back and reinforcing 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. That is, how acceptable is the “group benefit” argument introduced by the Clinical Trials Directive? Linked with this is the question of whether one might imagine 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 centered.

UNSOLVED ISSUES IN GERIATRIC CLINICAL RESEARCH

For Jean-Pierre Baeyens (International Association of Gerontology and Geriatrics–European Region and European Union Geriatric Medicine Society, Belgium), geriatrics is following in the footsteps of pediatrics, 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. A study in the *New England Journal of Medicine* (1) showed that patients discharged from nongeriatric departments to their homes or to nursing homes were more than three times as likely to die within a year as 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, Baeyens 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 poly-pathology 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 (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: poly pathology, 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.

ETHICAL CHALLENGES IN PEDIATRIC CLINICAL RESEARCH

The chairs of this session were Klaus Rose (EFGCP Children’s Medicines Working Party and Granzer Regulatory Consulting and 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 Smit-Marshall (EUCROF 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 doing a survey looking at the competence, capability, and experience of ethics committees, published in 2010.)

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

As of April 2010, the United States has seen 591 proposed pediatric study requests. The FDA

has also required 383 pediatric studies to be performed. A total of 224 studies have been conducted under the two US acts that cover pediatric research, involving 95,000 patients; and 163 products have received pediatric exclusivity.

In Europe, the EMA’s Paediatric Committee has received 701 validated pediatric applications, covering a total of 1,057 indications, and has adopted opinions on 229 pediatric investigation plans (PIPs).

In 2008 EUCROF conducted a retrospective survey of contract research organizations (CROs), pharmaceutical companies, and ethics committees in 15 European countries to gauge activity in pediatric research. It found a mixed picture, with large differences between countries as regards both the number of pediatric 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% of trials recorded there. 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 pediatric 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 pediatric

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 hematology 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 pediatric 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 pediatric 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 pediatric 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 pediatric studies account for around 5% of the total). But following experience in the United States, 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 (GCP) 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 PEDIATRIC INVESTIGATION PLANS

Any pharmaceutical company developing a medicine that falls within the scope of the Paediatric Regulation needs a 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 authorization in children (with or without a request for a deferral that would permit them to perform the pediatric 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 fulfill its responsibility to ensure that trials are safe and ethical? Nathalie Seigneuret (Human Medicines Special Areas, EMA) used anonymous 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 years; and another open-label study for pulmonary hypertension failed to include a description of the standard of care for the condition.

These cases may reflect the fact that pediatric 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 are appropriate. "Some PIPs received in the early days had no mention of number and volume," Seigneuret said. The committee is also keen to see more and more use of modeling and simulation.

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.

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 minimize pain and distress.

Three years into experience with the regulation, "we have definitely changed the environment. . . . Pediatric 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 center stage, and has highlighted gaps in knowledge, especially of methodology.

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 3 years old (Ethical Considerations on Clinical Trials with the Paediatric Populations, 2008)? Now, she said, is the time to engage in a dialogue among all stakeholders.

Workshop delegates had other questions. Luc Stuit (AFRT [Down Syndrome Patient Organization], France) wanted to know why we export

our trials to developing countries and why research on so many diseases is neglected. That is 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 (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. In many cases, said Seigneuret, 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 pediatric 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 (EFGCP Ethics Working Party, UK) had the impression that "the Paediatric Committee is very good on science but not very good on ethics," and that advice on pediatric 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 proto-

col that is presented to ethics committees. That response prompted Angeliki Siapkara (Medicines and Healthcare Products Regulatory Agency, UK) to call for the Paediatric Committee to find a way around this problem. Seigneur-et indicated that the Paediatric Committee tries to have as much interaction as possible with the EMA's Committee for Medicinal Products for Human Use (CHMP), the body that will recommend, or not, whether marketing authorization should be granted.

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

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

Hugh Davies gave a plea about ethics: "We don't need new guidance. We need to look at what we've got already and redraft it appropriately. There are libraries of guidance. The 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.

ETHICAL CHALLENGES IN GERIATRIC CLINICAL RESEARCH

The chairs of this session were Florian von Raison and Anna Jurczynska (EUCROF Paediatric Working Group and Quantum Experimental, Spain).

PROPOSAL FOR A GUIDELINE ON PERFORMANCE OF CLINICAL TRIALS IN THE ELDERLY POPULATION

There is a regulation for children, but no accepted European guidelines for the ethical conduct of trials with elderly people. Do we need them? asked François Hirsch (INSERM, France).

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 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 than 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 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 nonvulnerable adults, while vulnerable older people remain vulnerable. Meanwhile, many older people lack the information technology skills to access information about trials, while such skills are common among children.

The ethics of clinical research in elderly people are "poorly addressed" in international reg-

ulations, and 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 would have a real impact.

The proposal suggests studying 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 that may be crucial for the elderly). Dedicated civil society organizations, such as patients' organizations, should take part in the ethical debate about when and how to involve the elderly in research.

When looking at a proposed trial, several 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 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 to produce a finished document.

PREDICT: INCREASING THE PARTICIPATION OF THE ELDERLY IN CLINICAL TRIALS

Peter Crome (PREDICT Project, University of Keele, UK) 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 that affect them more the older they get, such as stroke, heart disease, Alzheimer disease, and colorectal cancer.

There are many barriers. On the clinical side, health professionals say pharmaceutical companies are not obliged 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 about the effect of taking part in their own care and about risks as well as about the consent process, and a dislike of randomization—all coupled with a host of practical issues affecting elderly people.

A major factor, said Crome, is exclusion criteria in trials relating to coexisting illnesses and treatments—which are a fact of life for many older people.

PREDICT has several work packages looking at different aspects. Work Package 1 examined the existing literature finding, for example, that 25.5% of clinical trials in cardiovascular disease, including those for devices and educational interventions, have an explicit upper age limit. The work package determined that 45% of exclusions were unjustified. Comorbidity was "an almost universal exclusion criterion," said Crome. Other causes of exclusion: upper age limits; physical or cognitive impair-

ment, or reduced life expectancy; and polypharmacy.

Work Package 2 has been gauging professional opinion. In a questionnaire it conducted of 507 practitioners of all kinds, most 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, predefining 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% agreed that too few elderly people take part in clinical trials, and overall around 60% 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 raft of issues. These range from ensuring that trials are scientifically pertinent to the need for 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 are a diverse population, that they should be valued, that they should be able to make informed decisions about trials—and that they have a right to take part in trials.

Finally, Work Package 4 developed a charter originating in work in the UK with Help the Aged (now part of Age UK), seen as a possible extension of the European Convention on Human Rights. The 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 recognize the values and risks of drug therapy for them; and be invited to participate in clinical trials of their treatment.

It follows 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 caregivers, 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.

In the discussion that followed, Mirela Barbu (Swiss Agency for Therapeutic Products, Switzerland) gave an example of the kind of delays that can occur: trials rejected by ethics committees because the consent form contains the phrase “have been invited to participate.”

Sven Erik Gisvold (chair, Regional Ethics Committee, Norway) asked whether the issue of information for patients is a problem. Crome felt that 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 2 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 toward 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.

Raphael Teichmann (Monipol Contract Research and Medical Consultants, Germany) noted that most trials do not have an upper age limit. So why is it that 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.

A linked issue, perhaps, is that of withdrawal. Anne Vinsnes (Trondheim Regional Ethics Committee, 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, said Rod Mitchell, is cost, or perceptions of cost: patients need to have possible expenses explained clearly.

Others wanted to look at the role of alternatives to clinical trials. “There are many different ways of studying how to treat and manage old people,” said Soeren Rasmussen (Pfizer, US). “You can do noninterventional 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? Ingrid Klingmann (EFGCP and Pharmaplex, Belgium) noted that the subject of the workshop was 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 pediatric trials, but elderly people are very different. . . . While we have very strong representation from patients on the pediatric 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 organization. “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 generalize about older people. All the countries in the PREDICT partnership had lay representation on their working groups, he said. Frank Wells agreed: “The majority of elderly patients can easily be motivated to take part in clinical trials.” Quite so, said Michael Bone (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 then introduced to the workshop a recent (anonymous) research study that initially received unfavorable ethical review from an ethics committee of which he is a member, and invited the workshop to explore the reasoning and discuss its conclusions. The process he described took only a month to complete.

First he ran through the provision of the Clinical Trials Directive dealing with patients incapable of giving consent. “It is worthwhile emphasizing that the patient’s interests and well-being prevail over all other aspects,” said Bone.

The study involved a vulnerable population with Alzheimer disease and Lewy body dementia along with their caregivers, 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 National Health Service 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 disease—SPECT and PET. It involved 100 subjects over the age of 60: 40 with Alzheimer disease, 30 with Lewy body dementia, and 30 controls. Caregivers were not to be scanned.

In addition to scans, questionnaires, and tele-

phone calls to caregivers, there were a number of additional cognitive tests, and a willingness-to-pay tool (to find out whether caregivers or 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 health care team to recruit the patients. Recognizing the possibility of coercion in recruitment, patients and their caregivers 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 lacked 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.

The committee’s opinion was initially unfavorable. “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 the 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 recognized that they had not met the requirements of the Mental Capacity Act and re-

moved the right of the caregiver 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 he or she became ill. But that is neither consent nor assent and is not legally binding. The revised proposal also met the researchers’ legal duty to give feedback to individuals and caregivers 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 caregivers, be piloted, and come back to the committee for approval. It also included the patient information sheet and the consent form.

But there were still issues. The consent form said the researchers 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 the 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 had not spent enough time considering strategies for recognizing 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.

LESSONS TO BE LEARNED

Chairs of the session were Frank Wells (EFGCP) and Soeren Rasmussen (Pfizer, US).

SIMILARITIES AND DIFFERENCES OF THE INFORMED CONSENT PROCESS IN CHILDREN AND THE ELDERLY

What can pediatrics and geriatrics learn from each other about consent? There are three broad issues, said Hugh Davies (National Re-

search Ethics Service, UK): informed consent and competence; developing and failing competence; and the relationship between children, elderly people, and their caregivers (“because, to me, the relationships matter”).

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 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 well-being. If I feel they are making an unwise decision, don’t I have the opportunity to seek to change it?” he said. “In pediatric 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 the capacity to understand, then to weigh up, then to decide. Do elderly people lose these capacities in the same order? He suggested 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.

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.

“Pediatricians 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, that is, consultees. “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.

Sometimes the decision is not as major as it appears, he said. In a randomized controlled

trial of two established treatments of acute asthma that are both seen by all pediatricians as valid, for example, he said, “You’re going to have one or the other anyway. We need to provide support and guidance for those making that decision.”

Difficulties must not be an excuse for inaction. Davies 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 un-researched care.” We need a sensitive approach, he said, but it must also be pragmatic. It must not stop us from moving on to evidence-based care.

ENSURING ADEQUATE EXPERTISE FOR REVIEWING PEDIATRIC AND GERIATRIC TRIALS

The responsibilities of ethics committees are enshrined in law: to protect the rights, safety, and well-being of human subjects. That’s a huge responsibility, but as Petra Knupfer (Baden-Württemberg Ethics Committee, Germany) explained, the law says relatively little about how they achieve or maintain expertise in pediatrics and geriatrics.

Pediatrics fares a little better than geriatrics in the Clinical Trials Directive, with a specific article saying that ethics committees must have pediatric expertise or take advice from pediatrics 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, pediatrics, geriatrics, psychiatry, gynecology, nephrology, and oncology (and the list could go on). But you cannot have all of them, she said, so along with lawyers, a theologian, an ethicist, a statistician, a layperson, 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.”

Then systems must be in place to ensure quality: checklists and standard operating procedures (SOPs). These should also cover the evaluation of different study types 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.”

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 demon-

strate experience and specialization in the relevant indication with the 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. Jean-Marc Husson asked how it works in the UK.

Pretty much the same as Knupfer described, said Hugh Davies, with an induction program for new members focused on the skills involved in critical appraisal.

Davies also gave some further desired characteristics to be enhanced in training: respect, courage, insight, and clarity. 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 pediatric cases and only with pediatricians, and likewise for geriatricians,” she said. 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 favor of a change in the Clinical Trials Directive to mandate the inclusion of a member with geriatrics experience. “If it’s in the law, people will follow. If not, it’s just goodwill and self-discipline,” she said.

A subject much discussed 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 in one country and re-

fused in another. That information should be in the public domain, especially since at the end the medicines may be authorized 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. 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 United States. But he also talked about “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 (E. Hoffmann-La Roche, Basel) asked whether it would help to mandate the registration of ethics committees, as the FDA has recently required in the United States 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 relative standardization 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 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 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 is 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 (EUCROF, Germany) wondered what happens to patients’ 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 have retained their capacity to consent.

OPEN FORUM DISCUSSION

The topic of discussion was what can be learned from the regulatory approach to pediatric drug development to encourage drug development for the elderly. Chairs for the session were Jean-Marc Husson (EFGCP Geriatric Medicines Working Party and Eudipharm, France) and Juergen Schaefer (Paediatric Working Group, EUCROF, and Corneso, Germany).

GERIATRIC POPULATIONS: A NEED FOR A NEW CLINICAL DEVELOPMENT APPROACH FOR MEDICINAL PRODUCTS IN ELDERLY AND ORPHAN POPULATIONS

Around the world the population is aging—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 is 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 a uniform definition of frailty—the EMA’s guidelines call for frail elderly people to be treated as a subgroup, but there is no accepted definition of frailty.

By way of an introduction to the final discussion, Husson outlined the information gaps: 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, there are 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 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 in pediatrics? 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 Plan, links with children’s medicine working groups, a European-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 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 nonadapted tests, said Husson, and 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: a group of geriatricians (the EUGMS, perhaps) at the EMA should 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 we need to decrease the number of medications given to older people.

Husson's cochair, 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 pediatrics? And have the measures in pediatrics really been successful?

There was general agreement among 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 pediatrics 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.

That approach was echoed by Ingrid Klingmann. “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 authorization dossier would make drug development—again—more expensive and time consuming,” she said. The solution is to support a public debate about 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% 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 (Pfizer, US). “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 randomized controlled clinical trial is not the only way to measure success.”

The Paediatric Regulation incentivizes industry, said Amparo Alemany Pozuelo, but we also need to encourage ethics committees and regulators to give fast approval to clinical trials in children—and 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. 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 at least 2 years for anything more than establishing an email list. 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 3 years into implementation of the Paediatric Regulation, and have had only 2 years of agreeing on plans. So it is “far too early to question whether the measures taken in pediatrics have really been successful,” she said, although there has been an increase in studies and registered products. Even so, said Helen Sammons, as a pediatrician she is “delighted” with the regulation—it is the medicines authorized before the regulation came into force that cause the problems, she said.

CONCLUDING REMARKS

The session was chaired by 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 the other hand, delegates learned from Jean-Pierre Baeyens that geriatric patients treated in nongeriatric 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 pediatric 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 DSMBs in pediatric 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 revitalize pediatric 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 on methodological learning about how to improve that situation,” she said. Then there was

Michael Bone’s “very interesting case,” which gave 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 does not work.

As for progress, Klingmann thought that changing the cutoff 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 realization there are similarities but also some differences in pediatric and geriatric clinical research. Important progress has been made in pediatric 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 authorization.” So observational data, including follow-up of a sample of frail elderly people, may be an option in framework of postauthorization commitments as part of the risk management plan.

For the future, we need to work toward systematically requiring the appraisal of exposing elderly people to drugs (as appropriate), and the standardization of findings in the CHMP assessment report and its summary of product characteristics.

REFERENCE

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Martine Dehlinger-Kremer and Ingrid Klingmann report no relevant relationships to disclose. Peter Wrobel has disclosed that he served as a consultant to EPGCP, Brussels.

