The GMWP’s Geriatric Medicines Working Party (GMWP) has published ethical guidelines on medical research for and with older people. The guidelines, the fruit of more than three years of intensive work, can be found on the EFGCP website, www.efgcp.eu, and a shorter version was published in the May edition of The Journal of Nutrition, Health and Aging.

This document is based on several workshops organised by the EFGCP GMWP. Three years ago, it invited Jean-Marie Vetel and François Hirsch to present a first draft based on the European Medicines Agency paediatrics guideline, with the aim of fostering ethical research in this neglected area.

The overall principles and key elements of this guidance were further discussed and revised by the GMWP in the following years and presented at the European Medicines Agency’s workshop on Medicines for Older People, held in London in March 2012.
Following public consultation, the GMWP received many thoughtful comments from academia, investigators, regulators, patients advocacy groups and the pharmaceutical industry, and met twice to review and incorporate as many comments as possible into the final text. The group has shared the text with all those who had contributed or reviewed the draft to inform them and seek their permission to mention their names.

“Older people experience a higher incidence of disease-related morbidities, take more medicines with multiple medication regimes and account for more adverse drug related events than their younger counterparts,” says the guidance. “Thus, it is important to conduct more research and clinical trials in this patient population to further the understanding and management of their conditions and treatment. Medicines used by older people should be of high quality, appropriately researched and evaluated throughout their life cycles. The population included should be representative of the future consumers of the tested drugs.”

The guidance covers definitions of both geriatric and vulnerable patients, informed consent from older and vulnerable participants, and the role of ethics committees in ensuring that research is adapted to yield appropriate outcomes for the elderly population.

The working party hopes that its guidance will be taken up by regulators and others to become firm official guidelines – thus contributing to improving the quality of clinical research in this population.

Laurence Hugonot, Co-Chairman, Geriatric Medicines Working Party

Twenty years of commitment to GCP and to the organisation of successful events leave their mark. Over time, our image had become outdated and “rigid” – and not representative of what EFGCP really is: an organisation that get things moving!

This is why, without radically changing everything, we decided to refresh our logo to convey a younger, more modern and dynamic image. Our colours are brighter, our typography is softer. The whole logotype has been “cleaned” for a bigger impact. But our mission and values remain unchanged.

And, as we are conscious that a good communication doesn’t come without cost, we have invested in the so-called “permanent media” – free and visibility-bearing, they are designed to be all around us: letterheads, business cards, PowerPoint, brochures, and the website.

Our new website will soon see the light. We have tried to build our website so as to keep our members at the heart of the strategy, offering them an access to new functionalities for more interaction between them as well as with the Board and the EFGCP Working Parties.

Putting all this in place has been an enormous team effort, and one that we hope will equip the EFGCP to go forward into the future.

Pascale Leblon

For details of all meetings, see www.efgcp.eu, or email secretariat@efgcp.eu

Forthcoming events

EFGCP conferences

7th DIA/EFGCP/EMA Paediatrics Medicines for Children Conference
24 & 25 September, Hilton London Docklands Riverside Hotel, London, UK

EFGCP Regional Workshop on Turkey – a clinical role model for Europe
Autumn 2013 (date to be confirmed), Istanbul, Turkey. Jointly organised by the University of Istanbul and the EFGCP

EFGCP Workshop on Indemnity schemes for clinical trials: a societal obligation?
November 2013 (date to be confirmed), Brussels, Belgium.

EFGCP Annual Conference 2014 on Benefits and risks of research: How do we redress the imbalance?
28 & 29 January 2014, Brussels, Belgium
Stuttgart hosts expert training for RECs

The European Forum for Good Clinical Practice held its fourth workshop on training for research ethics committees (RECs) in Stuttgart on Wednesday 20th March 2013, generously hosted by the Bezirksärztekammer Baden-Württemberg. Its aims were to develop the report from the third workshop, provide delegates with access to experts experienced in training, practical examples of training and an opportunity to contribute to a training syllabus for ethics committees. Training on proposed EU regulations on Clinical Trials of Medicinal Products was also included on the agenda. 19 representatives from 11 countries attended.

Procedural differences emerged early in the day, but once they were identified it was possible to establish shared principles and build a common structure for ethics committee training that accommodated and respected these differences.

For new REC members training needs to address the question “What is it like to be a committee member and what do I need to now?” Any programme must be founded on the understanding that the task of RECs is a practical one, to evaluate and deliver an opinion on research proposals submitted to them. It must be pragmatic, providing instruction in knowledge, skills and personal attributes that help REC members review research competently and consistently – to do their job. It must go beyond simple “ethical knowledge”.

The most important voices must be those of new members but we should include contributions from experienced members, REC officers as well as those charged with oversight of ethical review systems. It was recognised that any induction programme would be just a start. Learning continues after any formal early courses so REC meetings need to be uncritical arenas in which new members’ confidence is enhanced. Chairs, officers, experienced and expert members need to support new members who shouldn’t be expected to have detailed knowledge when they start.

When considering members’ and RECs’ training needs we need to consider realistically what we expect of the new member and what we expect of the committee as a whole. The former’s needs might be deemed “basic” skills, the latter “the advanced skills” more likely to be met by more experienced members. Members need to share, to pool, their knowledge, not exploit it and “wear their experience or expertise lightly”.

We need to consider assessment from the inception of any analysis. “Assessment drives learning”; it always has and probably always will. Consequently any design must incorporate, or offer the participants opportunities for fair and valid (self) assessment. How this might be mandated or monitored would be a local decision.

Finally it was recognised that nothing can replace the expert teacher and the trainer needs training and for new members a mentor such as a fellow committee members, asked to support them in early meetings, can play a vital role.

For a full report of the workshop, including details of the four “quadrants” addressed during the day, please email secretariat@efgcp.eu. Hugh Davies

Interactive training for inspections

Following the success of its one-day course in London on 19 November 2012 on training for inspections, EFGCP’s Audit Working Party is now offering the course to individuals and organisations such as universities and hospitals.

The interactive course is aimed at clinical trial centre staff such as investigators, co-investigators, study nurses and coordinators and anyone involved in the conduct of clinical trials of any phase and design, sponsored by commercial or academic institutions.

Inspections are no longer linked to a submission by a sponsor to health authorities to obtain a marketing authorisation – in today’s inspection landscape inspections can occur at any time with and without a particular event to trigger them. Especially in Europe, health authorities conduct inspections as part of their routine oversight activity.

So clinical staff need to understand what is required during an inspection, and how to prepare for and follow-up on an inspection. It is also important to understand and apply new trends such as the concept of a risk-based approach that is becoming the reference for inspectors.

For a sample agenda and details of how to apply for a course, email secretariat@efgcp.eu.
Barely two years ago the idea of EUPATI was a mere gleam in the eye, an idea floated in discussion in the PatientPartner project. Patients, so the idea went, need training and education to enable them to play a full part in the medicines research and development (R&D) process. The notion was simple and, once stated, obvious. But equally obvious, and immediately understood, was that to bring this simple idea to reality would be inherently and perhaps impossibly complex.

The Rome conference, held just 14 months after the launch of EUPATI, showed just how far the idea had developed. More than 180 delegates from 28 countries were there to hear about the plans under way for three clear areas of training and education: a certificate level course that by 2017 will produce 100 patient experts drawn from across Europe; less detailed online education for 10,000 patient representatives; and an Internet library with information for anyone with an interest in medicines R&D – hundreds of thousands of people, perhaps millions.

Delegates heard a series of presentations outlining the vision of the project and a number of talks from people around Europe who have been implementing innovative practices in patient partnership.

‘Window of opportunity’

The atmosphere was positive, and for good reason. As several speakers said, there is now a “window of opportunity” for effective patient involvement in medicines R&D. All stakeholders understand the huge benefits that can flow to them, from early research discussions, to better trial designs, more meaningful patient involvement in HTA and regulatory processes, and ultimately a quicker stream of properly tested and adapted innovative medicines.

But along with the opportunity comes the threat that there may be too few properly trained patients to take advantage of the seats that it is hoped will be available at the tables where trials are designed and scrutinised, and where decisions on access will be made.

So the Patients’ Academy is more than a desirable aim: it is both crucial and urgent. And as delegates heard, a number of hard decisions have had to be made to move the project forward. Lacking the resources to replicate the project in every EU country and every EU language, EUPATI has had to restrict itself in order to make the Patients’ Academy a practical possibility.

The certificate-level course will be English only; online education and the Internet library will be developed in the seven most frequently spoken languages in Europe – English, German, Spanish, Polish, French, Italian and Russian (widely spoken by older people in central and eastern Europe). The lynchpin of the project, the National Platforms which will do the work in their own countries, will be established in 12 countries only.

There were few illusions about the scale of the task. More work is needed on presenting the projects aims and its value also to lay patients. The broad outlines of the content of courses and material have been established, but finding the right way of teaching them will prove more of a challenge – as will selecting 100 people from across Europe. Even translation into the chosen languages poses problems when, for example, there just isn’t a term for “randomisation” in some languages. The audience learned why ethical oversight and transparency are fundamental to the EUPATI project and how these concepts are applied in practice. So-called “soft” communications skills are also crucial if partnerships between patients, researchers, industry and regulators are to be as fruitful as possible.

An overarching concern is sustainability. The project is funded by the European Commission’s Innovative Medicines Initiative, but only to 2017. By then the European Patients’ Academy must have established sufficient roots to carry on, along with ways of ensuring that the courses and information it offers continue to be relevant and up-to-date. But going by the conference in Rome, that seems to be a challenge that many will relish.

A full report of the conference is available at www.patientsacademy.eu.
A history of the European Forum for Good Clinical Practice

Jean-Pierre Tassignon and Olga Kubar present a review of the activities and leadership of the EFGCP, going back over two decades.

This is a review of the first 20 years of the European Forum for Good Clinical Practice (EFGCP). The EFGCP is a not-for-profit think tank open to all stakeholders in clinical research. Members are natural as well as legal persons who wish to debate and conduct research in the interface between science and ethics concerning the practice of clinical research.

In the late 1980s, just before the EFGCP was created, clinical research was internationalising at great speed. The newly formed clinical contract research organisations (CROs) of the early 1980s were developing into multinationals. Headquartered mostly in the USA, where clinical research was – and still is today – the most prolific, the largest pharmaceutical companies and CROs were busy trying to accommodate an increasing number of clinical trials of increasing sample sizes, and they needed more clinical sites every year. Europe experienced an overflow of translatic trials.

The AIDS epidemic accelerated the internationalisation of the clinical research industry. As the mega-trials required to test the efficacy and safety of zidovudine, the first active drug in this indication, forced the efficacy and safety of zidovudine, the first active drug in this indication, forced the clinical research establishment in emergent countries up to speed with Good Clinical Practice (GCP) was critical, as well as momentous.

In 1991, Europe was planning to create the European Medicines Agency. It was time for closer cooperation among all those participating countries. Bringing the clinical research establishment in emergent countries up to speed with Good Clinical Practice (GCP) was critical, as well as momentous.

In Brussels, Prof. Joseph J. Hoet was Vice-Chairman of the European Ethics Review Committee (EERC), the first multinational ethics committee in Europe. It was the ethics committee to review transnational clinical trial protocols and it enjoyed a de facto reciprocity status with the ethics review systems of various Member States.

Parallel to his research and teaching responsibilities at the Catholic University of Louvain, Prof. Hoet was also President of the International Diabetes Federation (IDF), headquartered in Brussels. The IDF is an umbrella organisation of 200 national diabetes associations in over 160 countries. From this unique position and his innumerable trips to all countries in the world, Prof. Hoet understood clearly that the clinical research community was globalising very quickly under the pressure of patient associations fighting for new safer and more effective drugs. Globalisation of clinical research would only survive if all stakeholders would adopt one set of quality standards.

Dr. Jean-Pierre Tassignon, also based in Brussels, was Executive Vice President of the largest clinical CRO in Europe at the time (G.H. Besselaar Associates, Inc., Princeton, USA, now part of Covance, Inc.), running many multinational clinical trials in all age groups and indications with many experimental drugs, in particular the first new biotech wonder-drugs erythropoietin and granulocyte-colony stimulating factor (rhG-CSF). Given the size of its clinical operations and network of offices in Europe, this CRO was the principal customer of the EERC, meeting quasi monthly.

The two started brainstorming about the need for a neutral place where professional organisations involved in clinical trials, including from the regulatory authorities and even patient associations, would meet and debate how to translate our moral, scientific and technical responsibilities into daily practice in so many countries. An invitation letter was co-signed proposing to establish the EFGCP. Representatives from 25 organisations involved in clinical research in Europe met at a hotel at Brussels airport in November 1991.

This assembly of pharmaceutical companies, CROs, IT companies, the EERC, the United Kingdom Medical Research Council and the Wellcome Foundation, nominated a Foundation Working Group under the chairmanship of...
Alfred Pauls, Head of Information Systems at Schering AG. After intense consultations and meetings in 1992, encouraged by the result of a needs assessment in a multistakeholder conference at the European Parliament, the EFGCP held its constitutional assembly in May 1993, hosted by the European Organisation for Research and Treatment of Cancer (EORTC).

**Overall achievement**

In just over 20 years, the EFGCP has created productive working parties, which, together with its board, have organised an impressive number of 150 open, multidisciplinary meetings for all stakeholders of clinical research, in Europe and well beyond. It has produced many authoritative position papers.

The board kept for itself the organisation of an annual conference, the publication of the EFGCP News and the running of the EFGCP as an organisation, which since 2005 has had permanent staff in offices located in the European district of Brussels. The first annual conference was organised in 1993.

Between 2009 and 2011, the EFGCP transferred its annual conference outside Brussels; however, feedback from EFGCP members and financial considerations led to the board’s decision to hold the annual conferences principally in Brussels. Identification of problems and solution finding by collaboration of all stakeholder groups in working parties was essential to the working model of the EFGCP.

Some working parties were dismantled after having completed their missions, but most are still very active, in particular the Ethics, the Education and the Audit Working Parties, which were created in 1993, as well as the more recently established Children’s Medicines and Geriatric Medicines Working Parties. The most recent EFGCP-EGAN (European Genetics Alliance Network) co-led Patients’ Roadmap to Treatment Working Party reflects the absolute necessity of including patient representatives into a very close partnership with clinical research professionals.

The working parties produce a constant flow of position papers, guidelines, international workshops, large conferences and training courses concerning hot issues in their respective specialties. A Science and Ethics Council chaired by Prof. Françoise Meunier, Director General of the EORTC, gives general direction to the working parties.

While deliberately focusing the activities on Europe, the EFGCP was gradually able to reach out to partner organisations on all continents. The EFGCP promoted the development of GCP in the CIS, India, China, Africa and Latin America. Of course, given their closeness to Europe, most efforts were concentrated on the CIS countries. Activities ranged from setting up conferences locally to sending delegates to lecture at national events, or hosting delegations visiting the EFGCP in Brussels.

With its neutral, multilateral setup, the EFGCP became involved in joint projects under the EU Framework Programmes (FP). The EFGCP was awarded FP grants in six projects and Innovative Medicines Initiative (IMI) grants in two.

Figure 1 above illustrates the amplification of meetings driven by the EFGCP, usually in partnership with other organisations in Europe and well beyond.

Dr. David Langford was the first elected chair in 1993. Wellcome plc promoted him to Medical Director Europe in the following year, and he stepped down after having given a very strong impulse to the newly born EFGCP: the first Annual Conference, the first issue of EFGCP News, the first working parties nominated. His successor was Gérard Marsat, Director of Regulatory Compliance – GCP at SmithKlineBeecham in the UK. He chaired the EFGCP until 1998.

This is the period during which the EFGCP’s Working Parties became very active and published EFGCP’s first consensus papers and guidelines like “Minimal standards for research ethics committees”, became an associate member of World Health Organisation’s CIOMS (Council for International Organisations for Medical Sciences), and embarked on an intense cooperation with the newly formed Forum for Ethics Committees in the CIS (FECCIS).

Already in 1991, a postgraduate course in pharmaceutical medicine was being set up at the Free University of Brussels, called PHARMED, and many members of the EFGCP became lecturers on the course. To this day, this partnership has held firmly.

From 1994, the EFGCP invited representatives from patient associations to attend its events as lecturers, session chairs and facilitators of breakout groups.

In 1991, the Soviet Union transformed into the Russian Federation, opening up a vast region stretching from Eastern Europe to Central Asia and Siberia for clinical research activities. On the borders of Russia, the Nordic Council on Medicines, which federates the interests of Sweden, Norway, Denmark and Finland, plus the Baltic States, perceived the opportunity, and called upon the EFGCP to help train investigators and members of the newly formed Ethics Committees in Russia and the Baltic States in the new GCP standards.

Dr Roger Bickerstaffe, at the time Vice-President Pharmaceutical Communications, Solvay Pharmaceuticals, was EFGCP chair during this period. Figure 1 indicates that, in this period, the EFGCP kicked off as a strong organiser of international meetings. It hired its first staff, and this gave it the power needed to project its expertise to all corners of the world.

In 2000, Prof. Olga Kubar, at the time chairperson of FECCIS and based at the Pasteur Institute in St Petersburg, Russia, joined the EFGCP Board to mark the importance of the contribution of CIS countries to European clinical research. The countries of Europe plus Russia and the CIS countries host a population of 1 billion.

The WHO was also very much concerned with capacity building in emergent countries, i.e. countries adopting clinical trials under the new international standards in clinical research. The EFGCP delegated lecturers at training events in Africa, Latin America and Asia.

The fine-tuning of the new position regarding the use of placebos in clinical trials written in the revised World Medical Association Declaration of Helsinki of 2002 required EFGCP action.

In the EU, the new Clinical Trials Directive (CTD) of 2001 would change the way clinical trials were regulated. The EFGCP entered into a closer cooperation with the European institutions and addressed matters related to the actual implementation of the CTD, starting from 2004, the year the CTD became applicable in the whole of the Union, including ten new Member States mainly in Central Europe.

In 2003, the EFGCP added a new dimension to its pool of interests as it joined EuroSOCAP (European Standards on Confidentiality and Privacy in Healthcare Among Vulnerable Patient Populations), a consortium seeking EU funding under the Framework Programme.

Hence, the EFGCP reached the full scope of activities in 2004, including the first successes in obtaining EU Framework Programme grants.

The EFGCP enters the Ivy League of EU-funded consortia (2005-to date)

Dr Jean-Pierre Tassignon, President of Crossover Clinical Research Infrastructures AG, became chairman in 2005 and was succeeded in 2010 by Dr Ingrid Klingmann, President of Pharmaplex bvba.

In this period, the EFGCP kept pace with the vigorous trend set at the end of the previous period. The EFGCP was particularly successful in joining or leading EU-funded consortia. A very important FP7-funded project was ICREL, led by the EFGCP, which measured the impact of the Clinical Trials Directive on clinical research in Europe. As a consequence of the project results the consortium initiated the “Roadmap Initiative for Clinical Research in Europe”, leading to a series of workshops on areas of particular concerns in the current legislation. Their outcome strongly influenced the European Commission’s current draft proposal for a Clinical Trial Regulation.

Another important project was the FP7-funded “PatientPartner” project, set up to identify strategies on enabling patients to become true partners in medicines development. This developed the concepts taken up by the IMI project EUPATI (European Patients’ Academy on Therapeutic Innovation), in which the EFGCP also plays a leading role. Since 2010 the EFGCP has been involved in the IMI-PharmaTrain project, with Klingmann being the Deputy Coordinator and Leader of the Work Package on Ethics. An important outcome of this project is not only the harmonisation and advancing of master courses in pharmaceutical medicine but also the development of a concept for comprehensive and harmonised investigator training in Europe. Financial audits by the European Commission in some of the projects underscored the trustworthiness of the EFGCP as a programme partner and Project Coordinator.

The efficiency of the EFGCP increased tremendously after it entered its own offices in the European district of Brussels in 2005. Staff increased gradually to three FTEs. The
EFGCP website received a facelift in 2007, and is currently being refreshed with new functionalities.

Initially, only individual members were recruited as members of the EFGCP. They came mainly from the pharmaceutical industry, contract research organisations, ethics committees, regulatory authorities, academia, healthcare institutions and investigator networks, suppliers of IT systems and equipment, and any other professional groups involved in clinical research. From 2008, corporations, healthcare institutions, associations of participants in clinical research and patient advocates were admitted as members as well.

Partnerships with patient and patient-led organisations intensified. Between 2007 and 2011, the EFGCP was able to host the secretariat of the European Platform for Patient Organisations, Science and Industry (EPPOSI) in Brussels. Regarding the CIS, this period is characterized by training organised by FECCIS with delegates from the EFGCP in Russia, the Ukraine, Kazakhstan, Azerbaijan, Kyrgyzstan, Armenia and Moldova. These meetings were always supported by the local ministry of health, the medicines agency, the national ethics committee and academia. Ties were also strengthened in Asia, especially with China, India and Thailand. It is worthwhile to single out the co-foundation of the Indian Forum for Good Clinical Practice and the visit to Brussels in 2005 of a delegation from the Chinese State Food and Drug Agency and the Shanghai Municipal FDA to discuss systems of ethics review in Europe, visit Phase I units and meet with the EMA.

The Ethics Working Party published The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe and Beyond, coordinated, regularly updated and expanded by Dr. Frank Wells, comparing the ethics review processes in the various European countries and beyond, which became one of EFGCP’s star publications. With his leading involvement in a global initiative for research integrity, Wells enabled the EFGCP’s Ethics Working Party to have ongoing involvement in this highly relevant area on an international basis.

The EFGCP’s Audit Working Party has developed a number of highly appreciated guidelines such as The Role of the Quality Assurance Unit. In close collaboration with the EMA, the Children’s Medicines and the Ethics Working Parties supported the development of the EMA’s guideline on ethical consideration in paediatric trials, and recently the Geriatric Medicines Working Party completed their guidelines on ethical considerations in geriatric trials.

Since 2010 training of all stakeholders in clinical research became an increasingly important activity for the EFGCP. The 2011 annual conference was dedicated to this topic, and a very successful training course, “GCP for the experienced investigator”, is regularly held at the EORTC, different European university hospitals and clinical trial sites. An “Inspection Preparation” training course was recently developed by the Audit Working Party, and further training programmes as well as a professionalisation of the training function is currently under development by the Education Working Party. The elaboration of a systematic approach to training of ethics committee members by the Ethics Working Party has been ongoing since 2007.

Concluding remarks

The EFGCP has always stressed the importance of personal commitment of its members in the working parties, on the board and on the Science and Ethics Council. It is within the EFGCP structure that multistakeholder consensus ripens and is pragmatically formulated.

It is vital to continue to reach out to partner organisations outside the EFGCP and to open up the discussion to as many stakeholders as possible. A successful example is the ongoing collaboration with DIA in organising the Annual Paediatric Conference.

In this way, the EFGCP fulfills its mission of helping all stakeholders in clinical research to cope with their respective responsibilities when they engage in research on human beings.

Clinical research is becoming increasingly complicated and fraught with risks. By and large, it is practised for the advancement of medicine and in the public interest. We trust the EFGCP will continue to arrange for all stakeholders to consult each other incessantly about the way each is supposed to discharge his responsibilities in the framework of the clinical trial protocol for the protection of each consenting participant.

Jean-Pierre Tassignon is a former Chairman of the EFGCP; Olga Kubar is a member of the EFGCP Board. Members of the EFGCP Board, Chairs of Working Parties and EFGCP delegates to other bodies, along with senior managers, are available at www.efgcp.eu.
Randomised clinical trials are still the best way of establishing the efficacy of any kind of treatment on a basis of evidence, regardless of the technology or type of treatment, said Silvio Garattini. Where there is true uncertainty, any other kind of trial will be dangerous and may expose patients to avoidable risk but, on the other hand, deciding not to treat can deprive patients of possible benefits. However, he said, clinical trials are ill. And like for any illness, it is important to establish how to diagnose the sickness, and then see how it can be prevented or treated.

The diagnosis of any disease is based on recognition of specific symptoms. Here we are dealing with a multifactorial illness. The first symptom is the abuse of placebo. According to the Helsinki Declaration, the efficacy of a new drug must be challenged against the best available treatment and not helped by favourable research conditions, such as comparison with a placebo.

Placebo comparisons

Garattini led off with a couple of examples, one being a trial for a new drug, fingolimod, to treat multiple sclerosis. Given that we know there are drugs available, like interferon beta 1a and 1b or glatiramer, that have been shown to reduce relapses by about a third, one would expect them to be used as a comparator for any new multiple sclerosis drugs – but not so. Fingolimod was compared against placebo (as were drugs in other trials mentioned by Garattini – cladribine, natalizumab, dirucotide, teriflunomide, laquinimod. “I submit to you that the patients given placebo have been damaged,” he said. “I calculated a total of 591 relapses which would have been avoided with a proper comparator.”

A second symptom of illness is the use of non-inferiority trials. In these trials, investigators test the null hypothesis that a new drug is worse than an active control. When they can reject the null hypothesis, they accept the opposite and conclude that the new drug is not inferior. Usually in order to establish non-inferiority you set the “delta”, the margin within which you agree that a new drug is no worse than the control, said Garattini. Enlarge the delta, and everything becomes non-inferior.

“Are there specific reasons for allowing a non-inferiority approach?” he asked. “It seems illogical to use such a design. One reason advanced is that not all patients respond to a given treatment, so another treatment is better than nothing. But in reality the proper design is to select patients who are not sensitive to a given drug and to see if the new drug is effective.” In such cases it is appropriate to use a placebo. Furthermore, clinical trials are designed to establish beneficial effects – while the adverse reactions become evident under clinical practice.

One justification given for non-inferiority trials is that they may enable an investigator to show whether drug adherence improves. But Garattini said that if this were the case, then “better compliance should lead to better results, not a ‘not worse’ outcome”.

Other justifications put forward for these trials include testing for non-inferior efficacy when accompanied by greater safety. This would be reasonable, said Garattini, if the safety issues at stake have comparable clinical importance. But in such cases, it is better to test the superiority of two treatments, rather than use a placebo. Furthermore, clinical trials are designed to establish beneficial effects
while the adverse reactions are more likely to become evident under clinical practice.

Before 1999 there was just one non-inferiority trial a year. After 2007 that rose to more than 100, said Garattini, adding, “The quality of these trials is usually not very good.” Specifically, only 24 per cent explained how the non-inferiority margin was selected. And there have been many other criticisms in the literature.

Garattini’s third symptom was the use of surrogate endpoints. These are thought to be a simple way of looking at something important, he said. “But this is not always the case. Drugs don’t act on a single target, they have lots of actions, and some may counteract their benefit on a surrogate endpoint.” He gave a striking example, rimonabant, an anti-obesity drug that was accepted on the basis of a number of surrogate endpoints. But when studies were done on “hard outcomes” such as death or strokes or myocardial infarction there was no difference from a placebo, and it had many side effects – which is why it was withdrawn.

Similarly, the drug nesiritide was approved in 2001 for heart failure on the basis of surrogate endpoints. Ten years later, a large study published in the New England Journal of Medicine found that drug did not affect mortality or the need for hospital readmission, and that it increased hypotension.

**Prevention**

“How can we stop these things happening,” asked Garattini. The first step is to do systematic reviews or meta-analysis – to challenge the question asked in the study before doing it. The second way is to register protocols so observers can establish the relation between the protocol registered and what is later reported in a publication. His third way is to give access to raw data – which is “unfortunately quite uncommon”, he said.

Also important, and we don’t talk too much about it, is that more preclinical work is often needed, said Garattini, adding that many drugs go into clinical use without any real evidence of efficacy in preclinical trials. “Most of the anti-tumour drugs that go to clinical trials today have relatively little effect in animals. We know that the rates of response are insignificant when carried over to the clinical level.” Often there is no confirmation in several animal species, no comparison with existing drugs, no realistic doses and treatment schedules, and inadequate toxicological testing. He complained that opposition to the use of animals can hamper thorough animal studies.

**Treatment**

This sickness in clinical trials requires “quick-acting therapy”. First, we should introduce the requirement of added value: new drugs must add to what is already available.

Next, we have to fix the misuse of placebo. And here, said Garattini, we have a problem with the Helsinki Declaration on the ethics of human experimentation. The first part of Article 32, stating that placebo may be used where there is no proven intervention, is very clear. The problem comes in the second part, which has been altered to say that placebo can be used when it does not subject the patient to any risk of serious or irreversible harm – which is too open, he said, noting that the European clinical research network ECRIN has proposed amendments to the Declaration deleting “serious or irreversible”.

Third, non-inferiority trials should not be considered an option by the scientific community, which he said bears heavy responsibility in this, and should not be accepted as a basis for marketing authorisation by regulators.

Fourth, Garattini called the use of surrogate endpoints for drug approval “unethical”, especially when there are already products approved after trials involving hard endpoints – for example, new statins, anti-diabetics and anti-hypertensives.

So we need a change in European legislation. ‘Today a drug can be approved if it shows quality, efficacy and safety. But we need to add three more words; “therapeutic added value”, said Garattini. “If we don’t have that we will have continued use of placebo and many useless me-too drugs”.

Another key part of the treatment must be the “abolition of confidentiality”. Reasons for secrecy are mostly put forward by industry: to remunerate development costs; to avoid disclosing data that could give competitors an advantage; and because any lowering of profits could in the end reduce investment in research.

Against this, Garattini advanced the reasons for transparency. Most trials include public money, he noted, and patients take part free of charge. More than that, in most European countries the drug market is prosperous because it is guaranteed by national health services. “Secrecy may be justifiable in relation to the production of the active principles,” he said, “but there is no real reason for confidentiality for preclinical and clinical findings.”

Garattini’s final prescription is the promotion of independent randomised clinical trials. He cited American professor Marc Rodwin, who said that drug manufacturers’ pursuit of profit compromises their impartial assessment of their drugs’ benefits and risks, and that biased evaluation can corrupt public knowledge of drugs, leading to unsafe and/or ineffective drugs and hampering rational prescribing by physicians. “It is a very strong statement,” said Garattini. “But it’s realistic.” Unfortunately, independent academically driven clinical trials have “too many bureaucratic requirements”, which have raised their costs and driven down their numbers.

“We need therefore to introduce a new element in the clinical trials necessary to get approval for a new drug,” concluded Garattini. “One proposal is that we need two pivotal trials to support marketing authorisation: one sponsor-driven, one independent. I hope such proposals will be supported in the future.”
As EFGCP Chairman Ingrid Klingmann said when opening this year’s annual conference, the Forum has a track record of picking up topics not approached by anyone else in a similar way. In the past, that has made for landmark conferences that have led to major initiatives in the field. So how would this year’s meeting fare, with its concentration on technology’s impacts on clinical research?

The topic drew around 100 people to the Belgian Academy of Sciences at the end of January. As Klingmann promised, it was not supposed to be a “techy” conference, but it’s also true that many or even most of the delegates were unsure at the outset about what the topic actually meant — in terms of both ethical and operational considerations.

By the end, though, delegates had been presented with a rich array of possibilities, successes, failures and challenges. Above all, as Hugh Davies from the NHS Health Research Authority, United Kingdom, said in his overall summing up, the new electronic landscape is here, a reality. The status quo is no longer an option. There are e-successes and e-failures, he said, and it’s our job to research it as a healthcare intervention. In this, we may need to “restrain the enthusiast”, he warned — and that may not make us popular.

The conference began with two sessions laying out the scope of e-health. Also called, variously, mHealth, connected health and cybermedicine, e-health focuses on the use of information and communications to inform decisions and actions by professional staff and by the public at large.

Discussion was kicked off by Jeremy Wyatt, professor of health informatics at the University of Leeds, United Kingdom. He picked out three challenges for clinical research. The first two were perhaps more expected: the need to study e-health as an intervention; and the ways in which e-health might support clinical research. His last challenge, though, opened up entirely new prospects — citizen science, or patients using the new methods to conduct their research.

Presentations given at the conference may be seen by delegates and EFGCP members at www.efgcp.eu
own clinical research.

Wyatt took delegates through a variety of positive and less positive experiences with e-health. In one, patients in the Netherlands had uploaded their own photographs of their own (non-pigmented) skin conditions along with filling in a form. A randomised trial then looked to see whether this reduced the need for outpatient referrals. And indeed, it turned out that nearly a third of visits to dermatology clinics could have been avoided. On the other hand, an NHS Direct attempt to use instant messaging to triage queries from deaf people turned out to be time-consuming and marred by a high rate of false positives, and the project was abandoned.

Among the range of interactive and plainer “vanilla” websites, Wyatt looked at a trial of “persuasive technology” – using computers to change what we think and do – in relation to organ transplant. One site sought to encourage people to sign up to donate their organs; a second site was much plainer (and with an intentionally broken link). Yet the trial recorded the same sign-up rate for organ donation in the “persuasive” and control groups. The reason, Wyatt speculated, might be that “serious people use other sources as well to help their decision-making”.

So all is not necessarily rosy in this brave new world. Worryingly, the impact of telehealth on mortality in heart failure appears to vary enormously, with some trials showing increased mortality. Clearly, more research is needed here. Wyatt warned, too, that the Internet had been shown to involve a whole catalogue of adverse effects over the years.

Moving to the challenge of using new technologies to support standard clinical research, Wyatt picked out a range of possibilities. These included online recruitment, online consent, emailed SMS reminders, remote monitoring, online adverse reaction reports, and so on. But he warned, too, of potential confounders in using e-health to capture data.

**Changes on the way**

His third challenge, health citizen science, graphically illustrated the scale of the changes on the way. Over a quarter of Americans, he said, have tracked their own health data online, and there are now a “huge number” of health social networking sites. One of these, PatientsLikeMe, has already conducted a trial into the use of lithium in patients with ALS (motor neurone disease). The trial – “one of the first examples of a really genuine citizen study in which patients decided on and designed the study” – showed no difference in progression, and prompted later randomised clinical trials.

In the new world, said Wyatt, a group of people could meet up via Facebook, decide on a question, define their own eligibility criteria, randomise themselves, obtain drugs from online pharmacies, measure and record end-points, collaborate on data analysis and publish online. Where does that leave Good Clinical Practice, he asked?

Citizen science has “real pros and cons”, he said. On the plus side, it promises faster, wider reach in recruitment, enthusiasm and real patient-related outcome measures. The results are likely to be rapid and focused, and to be adopted quickly. It is also less expensive, and can ask new questions.

But there are some cons. These include, for example, reliability, bias and the risk of
Will the regulation be fit for e-purpose?

While the real world of research is accelerating the use of new technologies, policy makers are finalising the details of the European Commission’s proposed Clinical Trial Regulation. That regulation will come into effect towards the end of the current decade, and as Nick Sykes from Pfizer said, will have to support clinical research in Europe into the late 2020s or even 2030s. Will it be fit for purpose – for e-purpose, that is?

Sykes was not sure. Certainly, the proposed Regulation “doesn’t actually stop us doing the sorts of trials we are thinking about,” he said. But on the other hand, “it could be a lot more supportive.” The proposed Regulation places a “huge emphasis” on pragmatic interpretation by regulators and ethics committees, he noted – and his real concern was that there is simply no consistent approach to pragmatism among regulators and ethics committees across Europe.

Moving to detail, Sykes identified potential problems with just about every fundamental aspect of a clinical trial – starting with investigators and subjects. If, for example, treating physicians are more closely involved with a trial (by taking blood pressure readings and uploading them into a trial database), have they now become investigators and will they now all require checking as investigators. Pragmatism would – or should – suggest no, but non-pragmatic views might prevail.

Likewise, what about trials that involve patients becoming more active, doing their own monitoring and uploading their own data? Or using Facebook for patients to run their own trials? Would they start to be treated as investigators? Would they need to see the protocol as well? Sykes queried whether the current definition of a research “subject” is fit for e-purpose.

Sykes also wondered whether reviewers might seek to limit the role of patients on the grounds that the data they contribute might be of variable reliability – or seek extensive validation for input tools such as iPhones. And would all the patients understand the need to capture all relevant safety data? (On the other hand, safety reporting may actually be enhanced if data are being entered electronically in real time.)

Then take the situation of an investigator sitting in Brussels, using the Internet to recruit patients from all over Europe via Skype. What approval is needed, and where – where the investigator is sitting, or where the patients are? “Europe is not ready yet for pan-European approval,” he said.

Sykes referred to Pfizer’s US-based virtual trial. The company considered holding it in Europe, but backed off. “One regulator said we couldn’t do it because informed consent needs to be done as close to face-to-face as possible,” he said. He acknowledged that doing consent by Skype, for example, might not reveal any off-camera coercion. There are potential workarounds, such as involving the treating physician, but they are not without their own problems.

After indicating other problematic areas (such as manufacturing requirements), Sykes put forward his solution. Rather than make wholesale changes to the proposal – there are too many unknowns at the moment – he called for a provision for regular review to ensure that the Regulation continues to support new approaches to clinical trials. The Commission was initially reluctant to do this, but recently Sykes professed to having seen a “glimmer of hope”.

contamination. But there is “real potential for us the triallist community to engage with patient-led studies to overcome some of these problems,” said Wyatt, calling on clinical researchers to help people to incorporate the literature and theory into their questions.

In the short period for discussion, two questions emerged. First, John Warden from Hull York Medical School, United Kingdom, raised concerns about obtaining consent online. It is right to raise this as an issue, said Wyatt, and the conference returned to the topic later several times, both in workshop discussion and in plenary sessions.

Second, Michael Bretschneider from UCB Biosciences, Germany, asked how to prevent citizen scientists from doing harm with their own trials. One of the founding principles of the Internet, said Wyatt, is that we don’t censor it: “We would have to argue quite hard and long to say we should stop patient-initiated studies.” He added, “We would arguably suggest monitoring and advice, but clearly those trials don’t need to be registered and can’t be regulated.”

Next up was Miguel Orri from Pfizer, which has conducted clinical trials over the Internet. For Orri, the key issue is to use e-health to enable what he calls the “engaged patient” – one who takes an active part in their health and clinical research. Hinting at the possibilities, he talked about an app from Philips that uses a computer’s webcam to image the colour of a patient’s face and, through that, to determine pulse rate. Patients, he said, are doing lots of things online: “We want to benefit from that, do it in a more organised way, and do it in clinical trials.”

For physicians, e-health opens up the possibility of handing over the “heavy lifting” to investigators in specialised trial »
centres, leaving them time to provide effective support. He even suggested full-time investigators, which would lead not just to economies of scale but also more meaningful and profitable work for the investigators.

The more you engage patients, said Orri, the more they are willing – and the better your data. And though there are risks with electronic tools, there are benefits as well: you know when data are filled in, and the quality is better. “You also get real-time safety data – you don’t have to wait for the doctor to come back for their next visit, and then for the monitor to come in after that.”

As Pfizer sees it, the most annoying thing in trials is when patients drop out. It happens frequently, and it is expensive and bad for data. The hope here is that engaged patients are more likely not to drop out.

Orri explained how in a trial on overactive bladders Pfizer recruited patients over the Web, consented them remotely, then sent them a mobile phone and the study drug. It was, he said, the first US FDA-approved trial to be run completely remotely.

“The only thing I regret is that I didn’t write down the number of times I was told ‘You can’t do that,’” said Orri. And he claimed that doing informed consent remotely, aided by a video, written material and a test, can be a “vast improvement” on traditional face-to-face approaches.

But the trial was not without its hurdles. Pfizer had a “good system” for verifying the identity of patients, but they found it off-putting. “We made the system so complicated that we made it almost impossible for the patient to go in, and we didn’t recruit enough,” he said. “We had over 45,000 patients on the website, but we only completed eighteen.”

Patients – enabled or overpowered?

Then it was time for the view from a patient – delivered in gripping manner by Jan Geissler, from Patvocates and EUPATI. “Usually I don’t talk too much about myself, but I will today,” he said. “The reason I am standing here today is because of the Internet.”

Geissler has been an e-patient for twelve years, since he was diagnosed with leukaemia. He described how he was told he had to have a bone marrow transplant, went on the Internet, learned about a new drug coming up, and emailed a doctor in Germany. “Half an hour later I got a reply and information about a new Phase 2 trial.” Today that therapy is the gold standard for the condition.

Whatever reservations there might be about the Internet, life without it is far from perfect. Geissler quoted figures showing that the average patient–doctor consultation in Germany lasts just 9.1 minutes. Combine that with the language barrier posed by medical and legal terminology, and getting information to patients becomes almost a “mission impossible”. For Geissler, the Internet is the solution.

Doctors say their patients are not on the Internet. But that’s a myth, said Geissler, citing a Eurobarometer study of 15 countries showing that almost all patients have access to online information, the elderly often via friends and relatives. Many doctors, too, use Wiki and YouTube.

What Geissler called “Googled health” is a reality, with unblinding of randomised trials on the Internet a reality ten years ago. People don’t want to wait until they die before they find out which arm of a trial they are on.

“You can’t keep a walled garden around medical information. You can’t ensure that only quality controlled information gets on a website,” said Geissler. “The only way to deal with bad information is to get good information online.” No, he said: the e-patient is empowered, not overwhelmed. And the empowered patient is the most underutilised resource in healthcare.

In the second plenary session, delegates got down to some of the basics of e-health in clinical trials: remote recruitment of patients and remote consenting, as well as a look at the infrastructure required in the new models. It began with remote recruitment, and
make a charge for referring patients, but will only refer if patients explicitly opt in to that service. Patients are referred to the sponsor blinded; if the sponsor wants the patient, the information then goes unbanged to the trial investigator.

TrialReach faces ethical issues every day, said Graiver. These include the transparency of the business model – making clear to patients the differences between a commercial and a non-commercial model. Other issues relate to control over data, reliability of the service, and privacy.

“It’s a delicate situation, interacting with patients providing sensitive information going to sponsors and investigators,” admitted Graiver. “And we do it for profit.” He stressed that TrialReach does not recruit patients, nor enrol them. “We help connect patients with trials. If we got paid for enrolling patients that would be a little more tricky, ethically,” he said.

The company neither gives medical advice nor endorses or recommends trials. It aims to provide clear information. “We never tell or even suggest to patients that by participating in a trial they will get any benefit or receive any medication,” said Graiver.

TrialReach’s experience with ethics committees is “not always a happy one”, said Graiver, citing different responses from different ethics committees receiving identical submissions. “In general there is some mistrust between traditional ethics committees and new technologies. And it’s mutual. We need more time to strengthen the ties.”

The company always advises sponsors to include information about specific payments, where they exist, “because the patient needs to know”, he said. Most sponsors are happy to do this, but ultimately it is up to them. However, some ethics committees tell it not to mention any payments.

To ethics committees that ask about patients without Internet access, Graiver said they respond that some “won’t be able to read or buy a newspaper”. Overregulation can be as harmful as underregulation, he said. Patient rights must be safeguarded, but patients suffer from this “lengthy and sometimes not very rational process”.

Then it was the turn of Deborah Mascalzoni from the Institute of Genetic Medicine, Italy, to examine how new technologies might improve the consent process.

The problems with the traditional informed consent process are well known, and have been aired at previous EFGCP and other conferences. For Mascalzoni, the idea of “dynamic consent” has a lot to offer. She described it as a range of approaches and IT tools put together in one conceptual framework to enhance consent and put the patient at the centre of decision making.

With dynamic consent, patients can determine their degree of control over personal information and the use of samples over time. They can, for example, choose how much information they need. Mascalzoni talked about the model of consent information “on demand”, with short, medium and full versions, depending on the level of trust and the individual’s requirement for information. “Different people want to know different things,” she said. “That’s a reality.”

Dynamic consent also allows patients to set their own level of participation and communication preferences (such as frequency). A variety of aids can help to overcome language barriers or problems with people’s capacity to absorb information. “The point is, really, we can do things the old way, but also use the new channels to enhance participation and engagement.” It’s about helping to build a consent culture “supported by all the means we can use”.

Describing in detail a project involving dynamic consent in South Tirol, Mascalzoni stressed that IT “won’t and shouldn’t” completely replace human contact. But the new model takes things further, allowing patients to change their ideas over time, and re-consent if a study changes significantly.

Importantly, the model seems to be good for research, even though at the outset scientists had been concerned that allowing clickable options not to share data, for example, would lead to problems. The results from the South Tirol showed, for example, that 99 per cent of patients were happy to share their data.

In fact, the benefits for research seem to be impressive. Online tools can be designed to ensure conformity with legal and ethical requirements both globally and nationally. Recruitment is easier and cheaper. And greater accountability leads to better science, Mascalzoni said.
How do ethics committees respond to dynamic consent? Favourably, she said, at least as far as the ethical board in her own region is concerned. She also cited the UK EnCoRe (Ensuring Consent and Revocation) toolset, saying that EnCoRe accreditation leads to greater confidence on the part of ethics committees.

The session was wrapped up by Pascal Ruyskart, head of IT at the European Organisation for Research and Treatment of Cancer (EORTC), Belgium, who gave an overview of the enabling technologies required for all these new clinical trial models, and an indication of some of the problems involved.

The EORTC knows more than most about the new world of the Web, covering as it does 180,000 databases, 650 studies and 370 institutions using the same data-capture technologies – and all using one single system. Out of this experience, Ruyskart drew a number of conclusions, both technical and policy-related.

For Ruyskart, it all revolves around Web 3.0. If Web 1.0 was basically pages and links and Web 2.0 added forums and social networking, Web 3.0 is another leap forward. While it is not clear exactly what shape Web 3.0 will take, it will revolve around a number of key concepts. These include: universality, the need to be able to run on any platform; accessibility (of data); semantics – data with meaning; integration with Web apps; BYOD – bring your own device – people want to use their own devices to connect to big systems; big data – “data warehouses”, potential goldmines for researchers; mobility – access on the move; and cloud computing.

One key lesson is the need for new standards so that new systems can run on multiple platforms. The EORTC faced that challenge for images, for example by building a new imaging platform.

Opening up new data sources brings its own issues. These include not just the technical ability to handle a variety of file formats and to guarantee confidentiality, but also ways of accessing anonymised (“de-identified”) patients if necessary.

**Intelligent data collection**

It is hard to predict where we will be in 2020, said Ruyskart, but when you look at what can be done, he suggested targeting new data sources, building big data warehouses and adopting open standards. Combine these with Web 2.0 and 3.0 apps and cloud computing, and it should allow the transition from merely turning paper records into electronic records, to intelligent electronic data collection.

When delegates reassembled on Day Two, the focus switched to ensuring quality in the new world. The morning began with auditing and monitoring, introduced by Paul Strickland of Strickland QA, United Kingdom.

While stressing that electronic, remote, auditing will not necessarily replace face-to-face contact, Strickland saw “ground-breaking” opportunities. He envisaged auditors and monitors sitting in their offices, accessing electronic medical records remotely and determining whether there is a problem. “There are some downsides, and it needs cautions, but the benefits could be absolutely huge,” he said – including running statistical analysis on incoming data to spot trends that might not yet be a problem but which might indicate issues in sites such as delays in entering data.

Among his concerns, Strickland mentioned the “sixth sense” that auditors often feel they have that enables them to pick up anomalies, though there is no science about it. Remote working might impede that sixth sense. It also tells you nothing about the crucial interactions between investigators, study nurses and so on – “all the people at the sharp end of clinical trials making the whole thing come together”.

On a more technical level, Strickland foresaw the need to ensure that access to an electronic medical record is only to the

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**From conference to…Vaudeville!**

On the evening of 29 January, delegates were invited to take part in the Annual Conference social event – a very special opportunity to network while finding out more about typical and cultural landmarks of the hosting city.

To celebrate its 20th anniversary, the EFGCP was delighted to invite conference participants to a cocktail reception hosted by the City of Brussels at the beautiful Town Hall on the famous Grand Place. The cocktails were preceded by a privileged guided visit of the building’s historic rooms, which are usually not open to public.

Participants then walked to dinner at the Vaudeville Theatre, located in the sumptuous Queen’s Gallery. The elegant Vaudeville Theatre has a legendary place in Brussels life and its collective memory. It was inaugurated in 1884 and is now listed as a historic monument.

In this artistic environment, dinner could only end on stage, with the apparition of a great birthday cake applauded by all. The show will now go on in 2014…

Fanny Senez
E-care and research in war-torn Somalia

Latifa Ayada from Médecins Sans Frontières (MSF), Luxembourg, enthralled the conference with a gripping account from one of the front lines of paediatric care – war-torn Somalia. Ayada reported on an observational study looking into the impact of telemedicine on the quality of care.

The study took place in a 100-bed hospital in the Galdugud region of the country whose clinical staff generally had poor background education, coupled with a lack of continuing training and on-site supervision. Faced with this, MSF brought in telemedicine to support clinical care.

MSF started with paediatric care, as this was the area with the highest mortality in the hospital. In practice, that meant a mobile camera device and a microphone in the hospital, connected to a computer in Nairobi, in neighbouring Kenya, staffed by a senior paediatrician. The idea, said Ayada, was to “export expertise, not experts”.

The results from the trial cover around 4,000 admissions, of which 9 per cent were referred to telemedicine. In 64 per cent of cases this resulted in significant changes to case management – and the children in 25 per cent of the referred cases had life-threatening conditions missed by the Somali doctors. Overall there was a 30 per cent reduction in adverse outcomes.

A striking observation was that by the end of a year of telemedicine, only 20 per cent of convulsions cases, for example, needed changes in management. Clearly, an entirely “virtual” study – such as that described by Miguel Orri from Pfizer earlier in the conference – can work. Strickland noted that most of the concern seemed to be coming from the quality assurance community, rather than from the regulators. What is important is not so much the technology, but how the technology is used.

One area with considerable potential is the enhanced use of metrics. Metrics, of course, are not new, but Strickland thought that we could learn more about what’s actually happening. Electronic records will tell you, for example, not just blood pressure readings but the date and time when taken and recorded. For an auditor, information indicating a delay between making readings and entering them might raise a number of questions.

Metrics don’t tell you everything, and Strickland emphasised that you still have to find out what’s going on. At their best, metrics can suggest to auditors where they should be looking. But when safety is one of the main criteria of a study it is not good enough to look at individual readings: “In most cases there is no alternative to reading the whole record,” said Strickland, warning against a “check-list” mentality.
Like other speakers, Strickland stressed that new technologies don’t alter the basic principles of good practice. Above all, “Consider what you are doing before you do it…time to think saves time later on.”

**Risks of misconduct?**

Are fraud and misconduct more likely to emerge in the virtual world – or will the new technologies make it easier to detect them? That was the question addressed by Beat Widler, a clinical QA and risk management expert from Switzerland.

Widler identified as a key problem the absence of face-to-face communication. There is plenty of research, he said, to show that people are quite prepared to cheat a machine or even a person with whom they communicate remotely, but not a person sitting in front of them.

Who would start cheating in a trial? To the old list of usual suspects – investigators, CROs, sponsors – Widler added the new possibility of the cheating patient. Patients, he said, might have more incentive to misbehave, especially in countries where access to clinical treatment is not taken for granted. “As a patient I might have a vested interest to stay in the trial, so I won’t, for example, say I have chest pain, because I know I will be dropped out of the trial.”

With controls so that if something goes wrong we learn about it in real time, and not at the end of the trial.”

The ability to monitor large amounts of data electronically will have spin-off advantages for ethical behaviour. Most true misconduct is about bad decisions, not bad people. People make a mistake, then cover it up. “If we tell people we are monitoring patterns, that in itself is protective,” said Widler. “Knowledge about oversight drives behaviour.”

In the end, we will have to re-invent the way we monitor and audit, digging at data that otherwise we cannot obtain. And critical to the successful deployment of the new technologies will be the sharing of QRM data from different trials. Virtual is not necessarily riskier, said Widler, but with a caveat: as long as we do not forget the human factor. We will still need investigators, auditors and monitors…people on the ground. But we will also have real opportunities provided that we start sharing our tools and our best practices.

**Talking, together**

For Klaus Rose of Klausrose Consulting, Switzerland, a major advantage of the new technologies is that they help parents of children with rare diseases to get together. Rose has not only had a long career in the pharmaceutical industry, he is also the parent of a child with Sturge Weber syndrome, a very rare condition involving capillary malformations of skin and the coatings of the brain and eyes.

The only treatment on offer is for the symptoms, which vary greatly from child to child. But at least now, with email and global communication, parents can find each other and get together to talk. More than this, they can take part in the scientific discussion.

But Rose also had a note of caution for optimists who might run away with the idea that the Internet will solve everything. Yes, parents can find their way onto the Internet and lay their hands on the latest academic papers, but these are likely to be in English. And despite what they say, most GPs in Germany, for example, do not read English (even though they say they do). So today’s patients may indeed be better informed than their doctor – but still fall down at the communications barrier.

**Digital natives**

The final presentation at the conference looked to the next generation. Are young people “digital natives” born into the Internet, such that they will take easily to health interventions online? Or to put it another way, can we confidently expect that the figure of 80 per cent of people using the Internet will inevitably increase as the new generations replace the old?

In the event, the talk by Ellen J. Helsper, from the London School of Economics and Political Science, United Kingdom, will not have encouraged anyone with the fond hope that things are bound to get better. Basing herself on a raft of research, Helsper called the idea of the digital native “a myth”. Yes, if you want to reach children you can probably reach them online. But that is not true for all children everywhere, and national differences are important.

We think children are confident online, said Helsper, but where the Internet becomes complicated for adults, it tends to get complicated for children as well. Only half of young people know how to change their privacy settings, for example. And Helsper said it was clear from the research that those children who are most vulnerable offline are the most likely to have low levels of skill online. Even among young people, those who are disadvantaged are less likely
to be Internet users.

This brought Helsper to the concept of duty of care in public health. For a large section of the population there is seamless integration between life offline and online: for them the Internet is the first port of call when they want health information. But this is not true for everyone, especially people with low incomes and the unemployed.

In designing services predominantly for online delivery we might be missing out on those most vulnerable, she warned. Forcing services online does not mean that those who need them most will find them – and when they do access the platform the vulnerable get a lot less from it.

More broadly, Hugh Davies noted in his summing up that there were many issues on which there was no consensus. That keeps ethicists in business, he said, and he is one himself. But more seriously he called for continuing open discussion, rather than argument and disagreement.

We need to consider the views of those who actually participate in research, and collect, learn from and disseminate good practice. Read and learn, he said; use guidance and codes of practice; seek evidence; and marshal the moral arguments with care. Start with “I”, but finish with “We”.

For Davies, the message from all the workshops was the centrality of trust, though it is very difficult to measure. "Given the power of modern computing to collect and link data, the inevitable distance in e-research between researcher and participant and evident differing views, the trust of public, patients and patient groups is going to be vital," he said.

Trust is easily lost and hard won, warned Davies. And if they lose it, e-researchers will find their work, and any possible advances from it, seriously jeopardised.

EFGCP Annual Conference 2013
In depth: workshop reports

The heart of any EFGCP Annual Conference is to be found in its workshops, where delegates can get to grips with issues in depth. This year eight workshops dealt with issues as varied as the difference between traditional and Internet-based research, and how to really involve the public in e-research.

Workshop 1: Traditional and Internet research: are the ethical issues different? Chair: Heather Sampson,
Toronto East General Hospital, Canada

With the Internet affecting almost all kinds of research, what happens to the ethical obligations of researchers? Rapporteur Effy Vayena, Institute of Biomedical Ethics, University of Zurich, Switzerland, said that while there was no absolute consensus, the workshop tended to think that the ethical principles remain the same. But there are some new ethical considerations, and we need to find new ways of dealing with them – supported by a healthy scepticism about how to deal with the novel.

Discussion ranged far and wide, taking in the issue of trust –what it is, how to maintain it, what it means in the world of big data – and the (to many unfamiliar) concept of the “e-me”, the way we are when we go online. ("Most of us now like the term,” noted Vayena.) People have to adapt to novel transactions, including how we identify, control and store data, and better understanding of risks and benefits.

Are the risks the same, or is it just perception of the risk? We need to understand what those new risks are and catalogue them. The overall feeling of the workshop was that we need practical applications and best practice guidelines to address the new risks and new issues, utilising the new technologies.

Workshop 2: Recruitment and new technologies. Chair: Bobby James, Quintiles, UK

Patients increasingly expect to be able to find information about trials online, outside of the traditional dialogue they would have with their doctor, said rapporteur Denis Costello from EURORDIS, Spain. So the workshop started from the paradigm that engagement is key, and that unless technology solves a real problem it’s “nothing but a gadget”.

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“We dwelt a lot on the future,” said Costello. Workshop delegates felt that in this future GPs would be more involved in referring patients. That in turn needs trust between GPs and primary investigators, also raising questions about how the regulatory framework might look when we are asking GPs to play such a role.

There was much discussion about the websites and platforms that exist to facilitate recruitment, and whether they are patient-friendly. The Internet website clinicaltrials.gov, said Costello, is clearly not, prompting an interchange about the relative benefits of public solutions (slow) and private ones (quick, but with concerns about commercial branding). One comment from the floor: every study should have a website that explains the trial to patients.

**Workshop 3: Consent and new technologies. Chair: Heather Draper, University of Birmingham, United Kingdom**

The workshop started with a case study on a patient information sheet e-form from Birmingham that used a three-level approach, from simple to detailed, leaving it to patients to decide which level to use.

In the event, said rapporteur Gerhard Fortwengel, of the University for Applied Sciences and Arts, Hanover, Germany, very few went to the detailed level, and users spent an average of 57 seconds accessing information. Almost 60 per cent accessed no information but still expressed an interest in taking part. Oddly, questionnaires indicated the same understanding from those who didn’t read the patient information as from those who did.

So should participants be allowed to choose not to get information before consenting? Most at the workshop felt it is up to the patient, and a matter of trust between patient and doctor. Others said researchers are entitled to have informed consent interview than to the written information aggregated from multiple sources, and have a negative impact on privacy. Subjects rarely know what company has their information or how it will be used. Yet it seems that patients are often less concerned on privacy than are the ethics committees, and that the least concerned are academic researchers.

Is it a moral imperative to share your data? The workshop preferred individual rights above social need: patients have a right to privacy and not to share. But they have a right to have their data exploited.

One conclusion is that we must be transparent with patients and tell them it is very difficult to ensure 100 per cent security. But if we are too focused on privacy we will just block research.

**Workshop 4: Privacy, confidentiality and electronic media: Data storage/confidentiality. Chair: Michael Bone, Consultant Physician, United Kingdom**

Some workshop delegates were surprised that TrialReach had been invited to present in the morning (see page 15), given the ethos of the EFGCP, said rapporteur Petra Knupfer, Landesärztekammer Baden-Württemberg, Germany. It is not acceptable to encourage patients by promising them payments for participation, she said.

More widely, data security in most clinical research is “hackable”. What we need is anonymisation, which is not the same as coding. In this regard, the first line of defence is not coding but the firewall, which should only allow logging in from specified IP addresses, not from home or elsewhere. Physicians should only be able to access their own patients. And, thought the workshop, the Cloud is not data secure.

Data warehousing, mining, fusion and mashing technologies all exploit information aggregated from multiple sources, and have a negative impact on privacy. Subjects rarely know what company has their information or how it will be used. Yet it seems that patients are often less concerned on privacy than are the ethics committees, and that the least concerned are academic researchers.

Is it a moral imperative to share your data? The workshop preferred individual rights above social need: patients have a right to privacy and not to share. But they have a right to have their data exploited.

One conclusion is that we must be transparent with patients and tell them it is very difficult to ensure 100 per cent security. But if we are too focused on privacy we will just block research.

**Workshop 5: Conducting clinical trials on the Internet. Chair: Ingrid Klingmann, Pharmaplex, Belgium**

Clinical trials with strong e-tools are already under way, but there are still no standards for electronic patient records in Europe, despite progress with interfaces and harmonisation. Healthcare providers are still reluctant, with only a few exceptions so far – the UK NHS has used one system, for example.

There was much discussion about patients directly providing the data, noted rapporteur Josef Glasa, Slovak Medical University, Slovakia. This development is seen as useful and promising, despite issues of reliability and privacy. But we need to preserve face-to-face interaction as well.

The EFGCP must be vigilant, and involve itself as much as possible in initiatives to harmonise, integrate and develop standards. There should be no compromises on quality.

Some criticised ethics committees for being too rigid, demanding and variable – they should “adapt to the e-trend”, be on the Internet, accept e-submissions and so on. Glasa noted “not many voices” from ethics committees to counterbalance the criticism.

One clear opportunity is in rare diseases. Where trials need many centres worldwide, the Internet might enable things that were impossible before. Other opportunities include improving the process of informed consent by e-tools that check comprehension.

**Workshop 6: Preparing for the future: training needs analysis: researchers and research ethics committees and reviewers. Chair: Anna Chiotti, Clinical and Epidemiological Investigation Center – CRP Santé, Luxembourg**

The workshop started with three questions: What training needs can we identify for the future environment? What are the priorities for training in emerging e-clinical technologies? And how should it be organised?

Rapporteur Gerald van Roey from the European Centre for Clinical Research Training, Belgium, said the group quickly came back to the results of the EFGCP’s 2011 conference on training: no one should have to do the same training twice – we should either accept each other’s training, or train at a pan-European level (though adapted to uneven national levels of IT use).

Investigators, study nurses, pharmacists and monitors should be fully trained in what new systems might mean for a study.

Patients, too: we cannot rule technophobic patients out of future trials. All training should recognise that some people are resistant to new IT.
Training should be organised nationally or internationally, with a basic set and add-ons, enhanced by continuous training, and requirements for periodic courses. It should start face-to-face, using e-learning modules as refreshers or add-ons. Records should show on a specific level the training someone has taken, especially on e-tools.

Who will pay for training? Hospitals and ethics committees often lack the budget. Industry would like to pay for good trainers, but as yet there is nowhere for industry to fund this kind of training.

A final recommendation was that ethics committees might soon need an IT expert just to advise on how these tools affect clinical studies.

**Workshop 7: How should ethics committees review e-research? A discussion using an example of e-research, Sharptalk. Chair: Tobit Emmens, Exeter Medical School, United Kingdom**

The workshop examined experience from a UK project called Sharptalk looking at discussion groups for young people who self-harm, which received ethics approval the second time round, after changes in presentation.

An important message was do not assume that the ethics committee will know everything. Healthcare for young people can be very different from adult healthcare and may require different research. So, make sure you represent the voice of those involved – “lived experience” as rapporteur Hugh Davies from the UK Health Research Authority relayed it. It helps to give log-ons to ethics committee members so they can see for themselves what the e-research involves.

Among the issues considered was remote consent. Not only are there different national laws relating to consenting children, but also possible differences between what is legal and what is ethical.

A key issue was deception online: Internet research and deception don’t mix. Deception is hard to guard against because debriefing is not easy online, so if the scientific validity or safety could be jeopardised by subjects who mislead, then Internet research is probably not appropriate. Ethical considerations in trials such as Sharptalk might suggest the need to provide care for the researchers themselves, who were hearing, remotely, distressing stories.

Whether researchers and research subjects participating in Internet discussions need added protection will depend on the end-of-study arrangements and on the study risk. But in the end it comes down to what is practical: if someone posts on the Internet that they will self-harm, what can you do?

**Workshop 8: REALLY involving the public in research using new technologies: Citizen Science. Chair: Amy Carton, Cancer Research UK**

Discussion began with a report on a project called Citizen Science. Still in its research phase, the project aims to engage the public in academic research – in this case, the analysis of tissue slides.

Cancer research generates immense numbers of slides to be analysed. Current algorithms are not good enough for computers to do this, so we need human intuition and the human eye. But with pathologists overwhelmed by the amount of data it can take months for these slides to be evaluated.

In the project, a cooperation between the Citizen Science Alliance and Cancer Research UK, a team of scientists and developers created a Web interface for the public to analyse real-life cancer data, scoring slides for the intensity and amount of staining. The hypothesis being tested is that citizen scientists pathology scoring is as accurate as scoring by pathologists.

So far more than 60,000 people have visited the site, and half million images have been classified, and the community has been positive. Amy Carton stressed that this was not an NHS cost-cutting exercise. “We’re just looking to accelerate cancer research,” she said.

Carton’s presentation of the project generated many questions from the workshop, said rapporteur Maja Conkic from the Klinis Association for Advancement of Clinical Research of Serbia. These covered: the idea of the public as co-producers of science; opportunities to extend citizen science to other countries; validating and publishing the associated evidence; and incorporation into current ethical processes.

“Who should have access to the data outputs?” asked Conkic. “Should it be published?” There were also concerns about commercialisation and privacy. And informed consent procedures might need amending.

The workshop reacted positively, concluding that citizen scientists could run and control both data analysis and data collection. There was talk of broadening out from cancer to cardiovascular disease and endocrinology.

“This is a world first,” said Carton, “and we didn’t start with an evidence base.” That prompted Jeremy Wyatt, from the University of Leeds, UK, to observe the need to understand what brings participants in and what helps them to make informed judgements or provide data.

He identified a “real opportunity” for research, including randomised trials, on the methods of citizen science.
The EFGCP News

The EFGCP News is an open forum for discussion and information on practices and developments relating to Good Clinical Practice. Comments, letters, contributions and general input are welcome.

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