



WORKSHOP REPORT

Multi-Stakeholder Workshop of the Joint EFGCP-MedTech Europe
Medical Technologies Working Party on

Mitigating Risks in the Lifecycle of Medical Technology Products: Options and Challenges in the Upcoming Regulations

4 December 2014 – The Hotel, Brussels, Belgium

Organised by the newly formed
Joint Medical Technology Working Party of



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Multi-Stakeholder Workshop of the Joint EFGCP-MedTech Europe
Medical Technology Working Party on

Mitigating Risks in the Lifecycle of Medical Devices: Options and Challenges in Building Clinical Evidence

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This report has been written by the workshop rapporteur, Peter Wrobel, who takes responsibility for its content.

1. Executive Summary

When it comes to the attention and interest of regulatory bodies, it's fair to say that the development of medical devices has for a long time been in the shadow of medicines development. So when delegates came together for a multi-stakeholder workshop in Brussels on 4 December organised jointly by the European Forum for Good Clinical Practice (EFGCP) and MedTech Europe, they were breaking new ground: it was the first stakeholder meeting on medical devices organised by the EFGCP in its 21-year history.

The regulatory landscape is shifting (and needs to shift): in the wake of the PIP breast implant scandal, the regulators are interpreting current legislation more stringently, and a new Regulation covering medical devices is on the horizon.

A revamped regulatory environment is in the making, with a new draft European Regulation, replacing the now 20-year-old Directives, currently under review by the European Parliament. But – and this was the central question behind all the discussion of the workshop – how should a new framework look? Is it a simple matter of taking the principles and practice of the regulation of medicines development and transposing them to medical devices?

These are important questions, affecting as they do the wellbeing of millions of people and the viability of tens of thousands of companies in Europe alone. In that context, the workshop was intended as a first step.

The key messages to emerge from the workshop are as follows.

1. **We need to talk – all of us.** There is pressing need for the kind of discussion that took place at the workshop. In this regard, the EFGCP multi-stakeholder approach is ideal for elaborating the best methodology for studying the clinical impact of devices.
2. **We have to get it right.** With the hopes of patients and the health of an entire industry resting on the right regulatory outcomes, all stakeholders must join to seek to shape the outcomes – and avoid the kind of problems that arose with the initial implementation of the Clinical Trials Directive.
3. **Devices are not pharmaceuticals.** Medical devices and medicines are not the same, neither in nature nor in their mode of action, which for medical devices is physical and for medicines is pharmacological, and their development paths are very different. Devices are also subject to constant stepwise and iterative development, with typical life cycles for a product of 18 to 24 months before a new improved version is produced.
4. **SMEs are the innovative engine.** The world of medical devices has its large companies, but overall is dominated by small and medium-sized enterprises, which make up over 80 per cent of the industry. So legislation needs to take account of the reality of smaller companies.
5. **GCP must take account of differences.** The fundamentals of Good Clinical Practice apply just as much with devices as with medicines, but the way they are implemented is not identical, and needs to take account of differences. One example is the frequent inappropriateness of the clinical trial “gold standard”, the randomised double-blind placebo-controlled trial – no one would consider carrying out a surgical intervention without an intended treatment.
6. **One size will not fit all.** Significant differences between devices and medicines call for different scientific, ethical and policy approaches for pre-market evidence. Some cross-

fertilisation between the two fields is appropriate, but devices and medicines require different regulatory schemes

7. **Respect variability.** Any legislation enacted should respect variability at all levels: companies, products, patient populations, surgical expertise. There are also areas where the devices industry can learn from the medicines side, not least in terms of involvement with patients and the maintenance of patient registries, and in the improvement of vigilance systems.
8. **Much to discuss.** Finally, the workshop can be said to have over-delivered. Called on to find topics for more detailed workshop discussion, delegates had such a rich discussion that they came up with a list (see Conclusions, section 7) that will need some kind of trimming if a practical programme of future workshops is to be agreed. The EFGCP and MedTech Europe now have the task of drawing up that programme.

2. Introductions

Welcoming the 90 delegates from academia, clinical research, regulatory, industry, patient organisations, EFGCP Chairman Ingrid Klingmann explained that this workshop was designed to be the first of several events. The idea was to define the basics, the differences between the development of new medicines on the one hand and medical devices on the other. "What should be changed," she asked. "What should be different?"

Eric Klasen of MedTech Europe and Medtronic, opening on behalf of the devices industry, looked forward to transparent and open debate. "The best approach is to listen first to the other party and understand where they are coming from," he said. Noting the need for better control of the regulatory system, especially the designation and oversight over Notified Bodies to ensure that outcomes for patients are safe and effective, Klasen said, "Those who do not behave ethically shouldn't have a place in the system."

That, then, was the challenge. In practical terms, the task of the workshop was to identify topics where there is disagreement, and perhaps lack of clarity, and seek out ways of coming to what Ingrid Klingmann called "a more harmonised viewpoint". These topics would then form the basis of further workshops, leading to concrete recommendations on the way forward.

3. Keynote presentation

Why is there a need to define ethical and quality conditions for clinical development of medical devices – does one size fit all?

Ingrid Klingmann, EFGCP and Pharmaplex, Belgium

When it comes to ethics and clinical trials, Ingrid Klingmann has what she calls her "bible" – the World Medical Association's five-page Declaration of Helsinki, written in 1964 and last revised in 2013. She examined some of its principles to see how it might apply to the development of medical devices.

The Declaration acknowledges that research-based medical progress must include studies involving living people, and lays down principles for protecting research subjects. But experiences with medicine regulations have shown that overprotection can lead to excessive

testing, with duplication of effort. The Clinical Trials Regulation is trying to structure processes to avoid the problems created in, for example, the earlier Clinical Trials Directive, and the lessons should be learned for medical devices.

On the other hand, the ethical standards in the Declaration are crucial. They seek to ensure the protection of research subjects' life, health, dignity, integrity, right to self-determination, privacy and the confidentiality of personal information. "These are absolutes," said Klingmann.

But the principles are not without their problems. The Declaration specifies the need for freely given informed consent, but is that what happens? "Ultimately we don't know what happens in the moment when the physician is explaining the process to the patient," she said. "We don't know whether the patient really does understand... and we are taking this burden into medical device trials."

Throughout her talk, Klingmann stressed the need for quality. That starts with ensuring the competence of the whole investigation team, and extends to the ability to recognise fraud and misconduct.

Last but by no means least, ethics require fair access to treatment, including equal access to clinical trials across different countries, different social classes and different insurance systems.

In medical practice and medical research most interventions involve risks and burdens to those taking part. One lesson from medicines development is that the risks must be continuously assessed and documented throughout a trial. Indeed, the risks may arise not so much from the treatment but through the way a trial is organised.

So we need a quality environment to minimise risks to study participants, said Klingmann, as well as to ensure the generation of reliable data that can be interpreted and lead to concrete clinical recommendations. That said, a quality environment must be implemented "in a smart way, not holding things up".

These considerations led Klingmann to a checklist of pre-requisites for the ethical development of new treatments:

- Integrity and competence of all parties involved
- Quality mind-set and infrastructure
- A regulatory framework that ensures patient protection and research quality but gives flexibility for treatment-adapted research approaches
- Ethical and regulatory oversight
- Adequate human, financial and infrastructure resources
- Transparency
- Active involvement by patients in the research for their treatments.

The principles, she stressed, must apply to all types of research involving human subjects – regardless of who the sponsor is, or whether a trial is about devices or medicines. "No compromises."

In implementing the principles, said Klingmann, the ethical environment might need to be adapted to the type of treatment, the treatment-related needs of the patients, its risk level,

specific technical requirements of the treatment, and the sponsor's organisational and financial resources.

How might that adaptation work? Will one size fit all? What are the lessons from the framework developed for new medicines? Those were the questions for the workshop as it moved towards its discussion of the ethical development of medical devices.

4. Session 1 – Clinical Development in Medical Devices and Medicines: Similarities and Differences

Chairs: Eric Klasen and Ingrid Klingmann.

As Eric Klasen explained, the world of medical devices differs in many respects from that of medicines. First, the facts: there are more than 20,000 medical technology companies in Europe, 80 per cent of them SMEs. "That doesn't mean ethical leeway," he said, "but we have to consider that their resources are more limited than for the major companies." The industry employs some 500,000 people, spends about 8 per cent of its turnover on R&D – about half the rate in medicines – and produces one patent every 30 minutes. Devices are categorised into four classes on the basis of risk; the highest risk class includes implantable devices such as pacemakers.

The lifecycle of devices is very different from that of new medicines. A new, breakthrough medicine will often develop into a new class of medicines. In devices, a breakthrough medical technology will develop through a long period of continuous, stepwise, development. For example, pacemakers started in 1958 as external devices, then became implantable, smaller, with improved battery life, and so on. Medicines once developed tend to stay the same, but ("we hope") medical devices become more useful over time.

This stepwise development is an iterative process, with customer feedback being incorporated into design, manufacturing and distribution. "Complaints are very important information for a manufacturer," said Klasen. On average a medical device will be superseded by a new version within 18 to 24 months.

Access to the market is regulated differently in Europe, the US and Japan. In Europe the CE mark allows market access. This system, which has been in place for nearly 20 years, has served patients and European medical innovation well, but the system needs improvement, said Klasen, and is not always applied as thoroughly across Europe as it is meant to be. As with medicines, Competent Authorities are responsible for overseeing and implementing the legislation, including market surveillance. However, while for medicines Competent Authorities are responsible for granting marketing authorisation, for devices, Competent Authorities designate this task to Notified Bodies who are responsible for granting the CE mark for medical devices. Competent Authorities then monitor the work of their Notified Bodies.

Having a single regulatory agency responsible both for granting marketing authorisations and conducting market surveillance has been debated by some stakeholders in medicines at the time of the recall of Vioxx. The argument has been that combining these two critical responsibilities within one single agency could constitute a conflict of interest. We have that separation of responsibilities for devices in Europe, said Klasen – but does it work well? "Conceptually, it would be ideal to maintain this but have a system that is rock solid and ensures that Notified Bodies can only behave ethically and that Notified Bodies are all doing the job to the same high level," he said.

There are other differences. Devices are often complex engineering systems with relatively weak patent protection – you can't patent the concept of a pacemaker, for example, unlike new chemical entities, which can be patented. What's more, patents provide medicine manufacturers with ten years of market exclusivity, giving them time to reap a return on investment. Not so with devices.

A device can have defects that can only show up through real-life medical practice, said Klasen, in contrast to a medicine, where premarket clinical trials can tell you if it's "either going to work or not". Human factors are important, too. A physician prescribing a medicine needs to decide on dosing and length of exposure, but with devices they need to be trained in how to use a device– and, of course, the technology behind the device keeps evolving and improving.

There are areas where the devices industry can learn from pharma, such as the vigilance system and periodic safety updates, as well as patient registries and different kinds of trial. "But don't forget the differences," he said. "Maybe clinical trials need to have a specific approach depending on the device," he added, noting that postmarket feedback can enable a device to be improved. We should learn from the medicines side, he said, but apply it with "smart thinking".

Equally, the European Medicines Agency has learned a few things from the medtech industry. Risk management, for example, which companies in the devices industry apply routinely, is something the EMA would like to see applied to all medical products. "Learning from each other's regulatory approach – is that not the best way forward for both medicinal products and devices?" wondered Klasen.

Discussion: Similarities and differences in the clinical development of medicines and medical devices.

Industry position: Philippe Auclair, Senior Director, Abbott, Belgium

The standard development path for a new medicine is well known and well established, proceeding through the various clinical trial phases to the double-blind placebo-controlled clinical trial, followed by postmarketing surveillance – said Philippe Auclair, and the pharma industry has been working on it for over a century.

Devices are different. "We in the devices' arena are at the opening stage of setting our clinical study methodology," Auclair said. First, devices are used primarily by healthcare professionals or patients, and their effectiveness relies heavily on the skills of the user. This brings variability, which needs to be taken fully into account in the trial design. Secondly, with most devices it is impossible to "blind" the patient. And a third limitation is that the control group may be limited by ethical considerations – you wouldn't put a hip implant in a healthy volunteer, for example.

This does not mean that trials are not run for devices. Some 250 cardiovascular device trials, for example, are currently running in the EU. In the past five years, about 100,000 patients have been enrolled in pre-market clinical trials on these devices. This represents a €250 million investment in EU clinical research in cardiovascular devices.

Essentially, the device industry uses international standards to assess whether a device is fit to be used.. But there are limitations with this approach: standards are slow to evolve, and may not apply to breakthrough technologies. "But we have to persist," said Auclair. And that, he said, requires more involvement from the entire stakeholder community, including scientists and patients.

More work is needed to establish a methodology for devices, he said. “We can make use of historical controls, cohort studies, specific statistical testing such as propensity analysis or develop methodology where the patient is his own control.” He said he was interested in the methodologies that take into account patients’ views or those that are being developed in academia and elsewhere on assessing the effectiveness of surgical interventions.

For devices, a clinical trial is part of the clinical evidence – “but it is not the only one,” said Auclair. The continual development that devices undergo makes feedback on clinical effectiveness increasingly important. You cannot wait until the end of a clinical trial – maybe 20 years for a hip replacement. That is why the draft Regulation before the European Parliament refers to permanent post-market clinical follow-up to allow early detection of warning signals, so that a device can be adapted to make it more suitable, safer or more affordable, for example.

Another reason for the importance of post-market surveillance lies in the difference between the skills of an implanter in a clinical trial and those found in real-life practice. “When moving from controlled testing to the larger real-life use, you move from one highly trained and highly supervised physician, implanter or surgeon to multiple users, people from different background training, education and varying countries’ codes of clinical practice,” said Auclair. These may use different surgical techniques, which may differ depending on the country or even the hospital. “Some of the body of evidence [relating to a] medical device must therefore be transferred from premarket to postmarket phase, so we can keep on improving the device and make sure patient gets the most appropriate treatment for his care.” Medical device development is an iterative process – from testing a proof of concept and testing a prototype through to continuous refinement and improvement based on real-life use.

So one size may not fit all. Significant differences between devices and medicines call for different scientific, ethical and policy approaches for pre-market evidence, said Auclair. Some cross-fertilisation between the two fields is appropriate, but devices and medicines require different regulatory schemes. And the EFGCP multi-stakeholder approach, he concluded, is ideal for elaborating the best methodology for studying the clinical impact of devices.

Patient Position: Nicola Bedlington, European Patients’ Forum, Belgium

From the patient point of view, the fundamental underpinnings of any regulation on devices are the same as in medicines. They start from the recognition that medicines and medical devices are not goods like any other: they impact hugely on the patient in terms of life expectancy and quality of life, said Nicola Bedlington. “Safety and quality must come first,” she said, with similar principles applying in terms of reliable data, patient involvement and transparency.

Data need to be strong to ensure patient safety and quality of care, and provide a basis for pricing and reimbursement – all ultimately affecting the ability to access innovative devices. Patients also have the right to be involved in the way research is developed, managed and evaluated. As with clinical trials on medicines, the development of devices needs to be transparent, with clear summaries that lay people can understand.

The idea of patients as partners in research, not subjects, means involvement at all levels, including in ethics committees. The European Patients’ Forum supported the European Parliament’s proposals (eventually dropped by the European Council) to require patient involvement in ethics committees overseeing clinical trials for medicines – and it will work hard to include the principle in any Regulation on devices. That, noted Bedlington, points to the need for something similar to EUPATI, the European Patients’ Academy on Therapeutic Innovation, but directed towards devices.

Although the fundamentals are the same, it does not follow that the systems for assessing quality and safety in devices need to be identical. “We don’t need the same [pre-market] system as with medicines,” said Bedlington, and the post-marketing system will probably be different too. “But we need to acknowledge and address the system of Notified Bodies,” she said, explaining why the European Patients’ Forum wants the European Medicines Agency to designate special Notified Bodies for high-risk devices, and is calling for a requirement for Notified Bodies to include clinical expertise.

Academia Position: Christoph Schuhmacher, European Clinical Research Infrastructure Network (ECRIN) France

There is the best world, and then there is the real world, began Christoph Schuhmacher. In devices, the real world is that from an industry point of view the devices have a life cycle of 18 to 24 months, yet the planning phase can take two to three years.

One solution is to go the ECRIN way, he said. With a huge cohort of patients and access to them, a network like ECRIN might facilitate quick trials set up in a short time with good surrogate parameters.

Methodology is crucial. If device makers have to go through all the requirements as set out for pharma, collecting ethics opinions from 27 committees and so on, they will fall behind the 18- to 24-month life cycle. “So we need templates ready for device categories so we can have a trial ready within weeks,” he said. That includes timely ideas and pragmatic ways to be able, for example, to stop a trial when one treatment arm quickly emerges as being clearly better.

Should we be starting trials in expert centres, he asked? Or should we be more pragmatic, as in the UK? There the approach is to take all the patients into the trial, and then find out who did well. It’s an approach that changed therapy when it was applied to gastric cancer in a 75-centre trial over eight years.

We all want the best treatment. But what if your doctor tells you there are one or two treatments and you could be randomly assigned to one of them? “You would probably leave the doctor’s surgery...That might work in northern countries but not in other parts of Europe,” said Schuhmacher.

He warned, too, that being an academic doesn’t mean you are always “very clear and clean”: you might have interests. And then there is the question of outright fraud.

The way forward, he said, is to forge an ethical network with “the best kind of academic thinking”, working with industry: “A good collaboration is the best soil for an innovative environment.”

But Schuhmacher ended with a stark plea: don’t just take over the same system as in pharma. The Clinical Trials Regulation is “not ethical”, he said, because “it delays”. While pharma can probably live with the delay, it would bring devices development to a stop. “So we need to find another way,” he said.

In the discussion that followed, Joachim Wilke from Medtronic, Germany, wanted to know which came first: procedure or innovation? Should the time required to develop a new device stay the same or be adapted to new clinical investigation requirements? For Schuhmacher the answer was clear: “Innovation should come first and procedures should follow.” For the sake of the patient we need to adapt procedures to allow faster development, he said.

Likewise, asked Wilke, if SMEs cannot adapt to new clinical investigation needs, should the structure of the industry be changed? Eric Klasen – himself part of a large company – stood up

for SMEs. "If you go into a system where SMEs cannot survive any more, you have the risk of choking ideas," he said. "We have big pharma, but big medtech is not the way forward." He warned against a simplistic solution that says SMEs that cannot afford to survive will disappear: "If they cannot afford it, we have to find a way they can, giving patients access to new devices within reasonable timescales and at affordable cost."

Tomasz Szelagowski from the Polish Federation of Patients highlighted the need to go beyond training physicians. Patients, too, need to be trained, and devices should be designed with them. He also pointed to national differences. Industry in Poland is not collaborating with patients, he said, whatever might be happening at the European level.

Earlier, Christoph Schuhmacher had queried how far patients would want to be part of a "learning curve". Robert Johnstone, from the European Patients' Forum, UK, suggested a pragmatic approach. "Patients are not all the same, strangely enough. Some would want to be part of a learning curve, some not." So involve patients, but treat each patient as an individual, he said.

For Ivo Schauwecker from the surgery network AO Documentation and Publishing Foundation, Switzerland, "iterative development" could also be described more negatively as "trial and error". We need to regulate the learning curve more, he said: "I would propose industry takes action here and does not sit back and let the regulators do it." Why not, for example, define and regulate the training required for a specific device, and link a requirement for training to the CE mark?

The attitude of ethics committees concerned Sarah Sorrel from MedPass International, France, a contract research organisation which has trialled many products developed by SMEs and subsequently bought by large companies. A major difference between pharma and medical devices found by MedPass in developing breakthrough technologies is "first in man". For devices, the phase 1 state in healthy volunteers does not exist. "So when we trial a high-risk device we have difficulty getting ethics committee approval."

We are learning how to get this done, said Greet Musch from Belgium's Federal Agency for Medicines and Health Products. The difficulty is in proving safety and efficacy quickly. But we are trying to work together with the industry to share assessment work on critical and first-in-man trials, she said.

5. Session 2 – Ethical Considerations: When Are Clinical Trials Necessary?

Chairs: Yves Geysels, Quintiles, EFGCP, Belgium, and Aran Maree, Johnson & Johnson, USA

What are ethical constraints for randomised clinical trials in medical device development?

Hugh Davies, Health Research Authority and EFGCP, UK

Ethics is basically about being good to people, said Hugh Davies. So by extension, he argued, every aspect of research is an ethical process. The utilitarian approach offers one guideline: "If the net benefit outweighs the net harm, then *ipso facto* it's ethical."

But there's more to ethics than that. You have to consider the benefits and harms to all populations – patients, research participants, and the general public. That includes the risks of

unresearched healthcare, for example Benjamin Spock's advice about laying your baby on its front. "Make sure you think of the benefits and harms to everyone involved," said Davies. "If you want to benefit research participants [alone], then don't do research."

So do good, try to avoid doing harm, and respect the patient.

Informed consent is not about protection, he insisted. Despite all the attention in European regulations paid to informed consent, consent is about permission to do something. "Yes, it may protect, but that's not its primary research role," said Davies. The responsibility for protection lies chiefly with the manufacturers. It's their job to ensure that they are safe, that their studies are well designed. "Look at where things go wrong, and the process that has gone wrong is independent scientific review."

Davies summed up his advice on ethical conduct in four words: Think, Reason, Consult, Conclude.

THINK. Under thinking, he talked about defining your problem and thinking about whether it is a fair question. "My experience on ethics committees is that in the vast majority of studies the question has not been thought through."

REASON. If you are to go further than simply a personal view, you need other reasons to underpin your arguments. Talk to other people involved, he said, and find out what they think. "Don't imagine you know – ask them." Seek out the evidence, the established guidance and expertise. "The best protection may lie with independent scientific review."

CONSULT. Talk to your patients and your patient groups. "It will be time well spent – if you are going to an ethics committee there's no better argument than saying you have consulted with your patient community." By talking to patients you can make sure that the endpoints you choose "actually matter", he said.

CONCLUDE. "If you have thought, reasoned and consulted, your conclusions will hold water," said Davies. And make sure you report your results: "If you hide them, someone will find them."

Beyond that, Davies had some specific advice on some of the issues raised earlier in the workshop. We need to "seek analogies", he said, people who have done the job before or have similar experience. The issue of phase 1 studies for first-in-man devices is not unique, he said: you don't give a cancer medicine to a healthy volunteer either, so what can we learn from that?

Yes, he said, randomised controlled trials are the best level of evidence – but not the only level of evidence. "If you can't do randomised controlled clinical trials, then argue the point – talk about different levels of evidence."

What Is a Fair Clinical Pathway from Innovation and Research to Practice?

Quentin Pankhurst, University College London, UK

Quentin Pankhurst is both an academic and an entrepreneur in the field of medical devices, which gives him a particular perspective on how to move from research to practice.

He began his presentation with an account of the development of a device, the Sentimag, which uses magnetic resonance imaging to locate lymph nodes in breast cancer. He took the workshop through the process from its first clinical trial to CE marking and beyond.

What had he learned from the experience? First, that innovation can take time, something that an academic setting can allow you to do. Second, he learned a lot about...money. There is "masses" of Horizon 2020 money and other cash around innovation. It has to go somewhere.

On top of this, there is a great deal of esteem (at least, in the modern British university) to be gained simply by obtaining money. And academics, he said, are particularly good at pitching for it. If that means they are less than rigorous when making their bids, well, “you can’t complain if you make them bid for support”.

Importantly, the research environment means that there are “huge freedoms” for academics to pursue technology transfer, along with “a lot of money [from government and charities] that can be used for risk mitigation”. In the case of Sentimag, the early trials were critical in identifying what needed to be done, and the money was there to do those early trials.

Pankhurst’s implicit message was that academics should go out and grab the opportunities in front of them. But, he warned, chasing money can become addictive – you need to keep a close eye on what he called “the delivery side”. He also admitted that it might have gone more smoothly had he and his team known what they were doing at the start.

That formed an introduction to what Pankhurst is trying to do at University College London’s Institute of Biomedical Engineering: to set up a principled R&D process for medical devices.

The case for investing in innovation is straightforward, particularly in the UK. Globally, turnover in medtech is set to reach £300 billion by 2018, with a compound annual growth rate of 4.4 per cent – equalling and then overtaking pharma. The UK, though, is falling behind Germany and France, and according to the UK government the number of new device approvals has flatlined since 2010.

Against this background, the Institute of Biomedical Engineering is “effectively a 1,000-strong contract research organisation”, said Pankhurst. It works with a group of hospitals whose mantra is that every patient should be a trial patient.

Among the areas of research his institute is pursuing, Pankhurst stressed aspects such as health economics, socioeconomic impact, implementation science and adoption roadmaps. Such issues are often not considered when starting a study: “If you put those into a grant application you are more likely to get funded.”

The idea is to find out mistakes early. “If the results are not encouraging, it’s early enough to change,” he said, calling it “unethical” to go so far down the line that you are tempted to ignore feedback that undermines your assumptions. Fast and cost-effective research is the way to deliver medtech benefit to patients.

Pankhurst was adamant that clinical and academic invention can work well alongside “the commercial perspective” – which is another way of saying that a device either works and will be used, or it is a waste of money.

Like Christoph Schuhmacher before him, Pankhurst ended with a warning. Academic innovation is a “fragile ecosystem”, he said: “If we’re not careful, we could become a US-style system where everything takes five years longer than it should.”

When it came to general discussion, Pankhurst used a question from session co-chair Aran Maree to elaborate on his comments about the US system. Maree – who is also on a US Food and Drug Administration (FDA) board – had asked what involvement Pankhurst had had with the Competent Authority when the pivotal initial study started.

Pankhurst had indeed approached the UK Competent Authority, the Medicines and Healthcare products Regulatory Agency, but had been told to proceed through the Notified Body (for which there is no US equivalent – the FDA performs both functions in the US). That led to the first-in-

man study, and “significant” amounts of government funding to take the spin-out company forward.

But in the US things have been much slower. First, while the device is rated in Europe as Class II (the risk rating goes up from I to IV), the FDA sees it as a “combination product” because it involves using a patented tracer. Secondly, there are ethnographic issues: the FDA believes that a product sold in the US has to have US clinical data behind it.

The hurdles posed by the FDA are one reason why Europe is already de facto the world’s primary site for first-in-man studies – “but we hide our light under a bushel”. Pankhurst said the FDA was looking to bring that business to the US, “but they have to be a lot faster”.

Anna Sohlberg from CVRx, a Swiss SME, was also worried about the “fragile ecosystem” and the access of patients to innovation. For her, the question was what information a decision maker needs, and at what point in the development cycle. “We need to ask for the right information at the right time,” she said, and called for more involvement with health technology assessment agencies.

That led Ingrid Klingmann to note that with the medical device field being so broad, it is difficult to lay down what the right questions would be and when would be the right time to ask them. Her conclusion: systems need to be flexible enough to take into account the particular devices that are being developed.

From the patient side, Souzi Makri from the rheumatic patient organisation AGORA, Cyprus, wanted to know what happens in the case of adverse events during a clinical trial – how is the patient to know about the risk of the unexpected? The best way forward, said Hugh Davies, is for those running a trial to talk to patients in a collaborative partnership. Trials involve uncertainty, he said, warning against seeing access to innovation as a right: it can be dangerous. “In a lot of research there is not much evidence of benefit,” he said, so be careful about innovation.

6. Session 3 – Quality Requirements

Chairs: Ian Banks, European Men’s Health Forum, Ireland, and Nicky Dodsworth, Premier Research, EFGCP, UK

As Nicky Dodsworth said in her brief introduction to the session on quality, you need a good quality environment to minimise risk and produce good data. But compliance with the regulations doesn’t necessarily mean good quality.

Importance of Quality Outcomes: The Role of Training for Investigators and Patients.

Sarah Sorrel, MedPass International, France

Since it was founded in 1991, MedPass International has conducted more than 500 device trials, which gave Sarah Sorrel a good vantage point from which to talk about quality – an issue relevant to all stages, from design onwards – and training.

Study design

Unlike with medicines, the training of those investigating devices is not regulated. That could be seen as a weak link, but Sorrel was quick to reassure the workshop that two key issues are

“very much controlling the quality of the clinical investigation of medical devices today”: study design and good clinical practice.

Device trials are different from medicine trials. Many of them are classified as high risk, involving surgery and other interventions. “These doctors are not used to performing clinical research,” she said. “They don’t think like researchers. They think like surgeons.” In particular, how well a device performs depends on the skill of the user: devices are applied, not administered, and that makes them technique-sensitive.

Sorrel illustrated this with a story about a trial for replacing the anterior cruciate ligament. The four surgeons taking part in the trial each had different operating techniques, so an important part of the protocol involved getting the surgeons to agree on a single technique.

And with devices, *ex vivo* and *in vivo* development is often needed to refine a technique. For example, devices are often implanted in animals and cadavers before going to live humans.

Since the Directive was introduced more than 20 years ago, the regulatory landscape has shifted greatly. At first there were issues over interpretation, which led to an amendment in 2007 and the implementation of guidance. But the biggest shift has come from the reaction to the PIP breast implant fraud: the Notified Bodies and Competent Authorities are becoming strict. “What is supposed to be happening in Brussels is happening.” So labelling is becoming very specific, Notified Bodies are requiring post-marketing follow-up and sample sizes need to be justified on a statistical basis, for example. And controls are being designed.

The latest revision of the Directive spells out to device companies the kind of trial they need to get CE marking. If a device is really equivalent to an existing one, the company can go straight to a clinical evaluation report and on to iterations and improvements. Otherwise you move to a gap analysis: what is new about the device, what are the new risks, and which of them can be mitigated by design. That will be followed by clinical testing in people to see that the benefits outweigh the risks.

There are still some issues, said Sorrel – but relatively few. Study designs need to ensure that their endpoints and timescales are right, for example, and local clinical circumstances need to be considered. But most of them can be overcome with good training and a thorough understanding of the literature. One less easy problem is the difference between EU and US regulators – though overall research suggests that the quality of EU study sites is “actually quite good”.

Good clinical practice

Essentially, said Sorrel, ISO 14155 (“very close to ICH GCP”) provides all the tools needed to ensure good clinical practice. But what is not covered is the issue of training – of investigators, and of patients.

Investigator training may not be regulated, but companies understand its importance: if the training is insufficient, serious adverse effects will follow. That has consequences, partly because all serious adverse effects have to be sent to the European Databank on Medical Devices (EUDAMED) and reported to all countries involved in the trial. “In theory your trial can be suspended, and investigators know this,” said Sorrel. Serious adverse effects can also lead to a product being recalled.

This puts particular focus on the “initiation visit” to a trial site, which is when both investigators and patients are trained. True, admitted Sorrel, many devices involve a learning curve in their application, but with high-risk devices that can be mitigated by the use of specialist physicians.

The importance of training patients is a key difference between devices and medicines, and it is becoming even more essential. With an ageing population and more and more people to be treated, patients will have to be involved in their treatment and the monitoring of their situation at home. If their training is inadequate it can result in a lack of understanding – and hence a lack of compliance.

These issues can be avoided by training investigators and patients, and sharing training with study coordinators and study nurses. Patients may not be familiar with iPads or new tech etc. Training also needs to be adapted to the patient population where it's intended – do they know how to use any new technology involved? – and may have to be extended to family and carers.

Co-chair Ian Banks noted here that patients – particularly low-income men – are generally not good at reporting adverse events for medical devices. That points to the need to educate them about how the reporting of adverse outcomes can help improve products.

So clinical investigations play a vital role in market entry and post-market surveillance, concluded Sorrel, and careful attention is needed to ensure quality outcomes. Europe lacks the US system of “blacklisting” incompetent investigators, she said. “But we do have investigators who realise that not being good will impact on your site’s academic reputation, the usefulness of data, and patients’ willingness to engage in research.”

Clinical Data and the Enhanced Role of Notified Bodies and Competent Authorities

Niall MacAleenan, Health Products Regulatory Authority (HPRA), Ireland

Niall MacAleenan began with the role of Notified Bodies and Competent Authorities, but his talk ranged far wider, including comments about how he would like to see the new regulation evolve. It was a reminder – should any be needed – of how much can be gained by dialogue with the regulators.

Ireland’s Health Products Regulatory Authority is primarily a regulator, there to protect public health and patients. “But we are also there to enhance public health,” he said. So it sees its role as more than just ensuring that products are of benefit to patients: it wants to be part of “an environment that helps bring products to patients in a safe and timely manner”.

As a Competent Authority, it is involved in all stages throughout the life cycle of a medical device, and tries to input as much as possible in the preliminary stages. It also reviews applications for clinical investigations, ensuring they are robust, safe and of value to patients. But it does not authorise the devices or issue the CE mark – that role belongs to Ireland’s (sole) Notified Body, which it oversees.

Like others before him, MacAleenan noted the differences between the regulation of medical devices and other health products, the differing roles of users and the different training requirements. The system of Notified Bodies is decentralised – “and in any decentralised system the chain is only as strong as its weakest link”. So one task of the Competent Authority is to ensure consistency. That’s not easy, with about 31,000 product technologies, 500,000 devices and just one piece of legislation to cover them all.

But don’t overlook the similarities, he stressed: “It’s still about health products that need to be safe and effective.”

Clinical data

A great deal hangs on the quality of the clinical data – the requirements for which are described “in very general terms” in the Directive. As a consequence, the system as originally

implemented relied on data from equivalent devices. Recently that has changed, with Notified Bodies now assessing data themselves. But fundamentally – “across the system”, said MacAleenan – there has been a lack of transparency and a lack of emphasis on clinical data.

Different Competent Authorities review clinical investigations in different ways, and the landscape is shifting, but MacAleenan could only describe how things work in Ireland. It helps to be open and transparent, he said, describing a system that encourages anyone considering a device to come and talk to the authority first. It also recognises and accommodates the difficulty that some organisations – “especially SMEs” – may have in answering questions within rigid timescales. And it operates in tandem with ethics committees.

What would MacAleenan like to see in the forthcoming legislation? “Hopefully, a more scientifically driven, systematic approach.” The original legislation was written “by engineers, for engineers”. The aim must be to continue to meet different needs, regaining flexibility and adaptability, along with providing clearer requirements for clinical investigations specific to patient needs.

MacAleenan would like to see clinical evaluation – the overall data set and its collection and analysis – as a life cycle, where all data are assessed continually, including post-marketing surveillance and follow-up. “No matter how many wonderful hip implant tests or computer modelling we have, we have to be able to look at clinical data over the lifetime of a device.”

That way, clinical investigation will be something that evolves, continually updated with all relevant data, and with periodic assessments of benefit and risk to ensure that the device, standards, requirements and specifications remain state of the art.

Many devices are developed by modification of existing ones, so equivalent data are “very relevant”, said MacAleenan. But they should only be used as a single source when they are scientifically valid in the specific technical, biological and clinical circumstances – and where there is “clear access to the relevant data”.

The role of the regulators

Turning to the role of the Notified Bodies, MacAleenan said they should be paying “a lot more attention” to certification decisions. For example, they might wish to consider changing the period of CE mark for high-risk devices.

Prompted partly by the PIP breast implant fraud, there has been much discussion about the regulatory system, and much work done. MacAleenan noted here a joint plan for immediate actions, with coordination both of the decentralised system and among the Competent Authorities.

Like industry and academia, MacAleenan was keen to keep the innovation environment healthy. The regulatory framework that should be secure and protect patients, but should also enable innovation to continue. An evolutionary approach, he said, is the way to meet the specific needs of the devices world and its stakeholders: build on the existing system. Robust surveillance mechanisms are needed at each point in a device’s life cycle to enhance pre- and post-market oversight, with a key focus on clinical data.

There is a lot of discussion about ethical considerations, informed consent and vulnerable populations. Against this background, MacAleenan wanted to see the clinical investigation process become more transparent, with ample opportunity for dialogue with innovators, healthcare professionals and patients. Ethics committees are vital in this process, he said– “the only way to obtain objective assessment”.

MacAleenan foresaw many more European level requirements – including for inspections – and some form of cooperation among Competent Authorities. Hopefully, he said, multinational trials would require just one submission and one approval, with the best available expertise in the network assessing proposals – including non-commercial studies.

7: Open Forum Discussions and Conclusions

Chair, Frank Wells, Lead Advisor on Integrity, Fraud and Misconduct, UK Health Research Authority

Panellists: Christoph Schuhmacher, ECRIN, France; Greet Musch, Federal Agency for Medicines and Health Products, Belgium; Niall MacAleenan, Health Products Regulatory Agency, Ireland; Ernst Singer, Medical University of Vienna, Austria; Serge Bernasconi, MedTech Europe, Belgium; Lynne Van Poelgeest, World Federation of Incontinent Patients, The Netherlands.

Aided by an impressively broad panel, Frank Wells set about the task of reaching conclusions. First, he asked each of the panellists for a short statement setting out their views on future workshops.

For Christoph Schuhmacher from ECRIN, one of the workshops should be about trial design, with design adapted for different devices. The next would be on the problem of the person implanting the device: “We have very nice devices and post-market people say this and that, and then you look at the data – 80 per cent of the problems are user-related rather than device-related.” A third workshop would be on the kind of data registries needed for long-term follow-up.

Experience with the Clinical Trials Regulation on medicines gives us a head start, said Greet Musch from Belgium’s Federal Agency for Medicines and Health Products. One workshop could reflect on how we can enhance Member State cooperation through the voluntary model; it could also look at whether a new system should reflect at national level the division with medicines between ethics committees and Competent Authorities. She called for a workshop on combination devices, with a third on how to align the system with *in vitro* diagnostics.

Niall MacAleenan from Ireland’s Health Products Regulatory Agency concentrated first on clinical evidence – how to gather it, with clear and specific criteria. So he suggested a workshop looking a clinical evaluation as a process in itself, on a multistakeholder basis, to help regulators understand the interactions between innovators, manufacturers and academics.

Secondly, MacAleenan thought it would be useful to discuss how to dialogue and communicate: with whom, how and about what, and in particular to understand the mind of the clinical community. Finally, in order to develop a life-cycle approach to market surveillance, he proposed a workshop on the criteria and specifications, the endpoints and metrics, required at each stage of the life cycle.

At the Medical University of Vienna, Ernst Singer’s ethics committee handles about six to ten studies with medical devices a month. He sees no difference between examining a study with a device or one with a medicinal product. That said, he would like a workshop looking at CE certification – less than a year ago, he said, device got a CE certificate without even meeting a human, which is “a problem for an ethics committee”.

Another practical issue is the combination of device and medical product. There should be some discussion here, he said: too much diversity we will require new workflows, and things are complicated enough as it is. Singer's third topic related to the increasing number of apps, with software as a medical device (an issue raised earlier in the workshop by Polish patient representative Tomasz Szlagowski). Apps that tell you when to go to the psychiatrist or send personal information to your doctor need some kind of regulation, he said.

From the industry side Serge Bernasconi of MedTech Europe noted the discussion on the role of Notified Bodies and their capacity to perform clinical reviews. "I would love to see Notified Bodies doing what you are saying, but we are very, very far away from this," he said. In terms of clinical evidence – "a subject of great interest to industry" – whatever system is in place in future must respect the diversity and complexity of the industry. One size does not fit all.

He warned that preclinical evaluation "can only tell you so much" about a device. The environment is so controlled that an evaluation cannot predict how the device will work out in the market, which puts a lot of stress on post-marketing follow-up. He noted, too, the need to find the right balance between transparency on the one hand, and IP and data protection on the other.

With those comments as a background, Bernasconi recommended two workshops: one on linking to experts ("there aren't that many, and all of them or most of them work with industry"); and a second on *in vitro* diagnostics, which he said needed the same process as medical devices in general.

Finally it was the turn of the patients. Patient participation sounds a cliché term, said Lynne Van Poelgeest from the World Federation for Incontinent Patients, but patients must be involved. "There are an awful lot of patients out there, but again there are a lot of patient populations." Once again, one size doesn't fit all. So she called for one workshop looking at the needs of different types of populations. Another should focus on reimbursement, "something extremely close to home to me at the moment".

Van Poelgeest's third point related to data and ethics. "Patients couldn't care a damn about data in the long run," she said. "You need to think about how this data is used. And how not only data but other considerations can be brought into the picture, especially in rare disease populations." What is ethical use of data, and what is not?

In discussion, several people brought up the role of ethics committees, and in particular of patient representatives on those committees. Joachim Wilke from Medtronic asked whether patient representatives are really able to bring the patient viewpoint into ethics committee decisions. And do they have conflicts of interests, for example through links to trade associations? Ernst Singer's experience in Vienna is that though patient representation is obligatory for ethics committees, he generally has to prompt them for an opinion. "Sometimes we do get a contribution, and it's very appreciated and respected – but not frequent."

One patient representative cannot speak for all patients with all conditions, said Singer, prompting Frank Wells to interject that in his committee in Cambridge – with four lay members out of 12 – they ask a patient support group for comments if need be. Meanwhile, said Lynne Van Poelgeest, the Competent Authority in the Netherlands has no patient representation at all. All of which led Robert Johnstone from the European Patients' Forum to suggest a joint seminar between the EPF and the EFGCP on working with regulators to maximise the role of patients.

Goran Ribaric from Johnson & Johnson, Germany, suggested a workshop on working with the media. He received support from Niall MacAleenan, who said all the senior staff in his authority

had been interviewed by the media in the wake of the PIP implantation scandal. "It is difficult to explain a system when there is already a crisis," he said – there must be a much more proactive dialogue.

Still on communication, Matthijs Killian from hearing implant company Cochlear, Belgium, suggested a workshop on how patients could use apps and the Cloud to communicate directly with companies. That would give industry a larger repository of data, and greater insight into the whole patient population, he said.

Conclusions

It was not an easy workshop to sum up. As the first multi-stakeholder meeting on this topic, much had been said that was new to many of those present. But between them Frank Wells and Ingrid Klingmann came up with a number of suggested workshops:

- How to do effective research in an ethical way, including issues such as patient involvement, transparency and compliance;
- Clinical trial methodology, including the relevance of GCP to devices, and in particular to the "thorny question" of first-in-man trials;
- The potential to better optimise clinical evaluation, minimising the need for unnecessary or redundant clinical trials;
- Linked to that, the quality framework for clinical trials in devices, and its variability;
- Regulation and oversight – "it's a bit haphazard" – in the context of the coming Regulation, and how it can work in practice in different countries;
- Health technology assessment, the value of treatment and the principles of reimbursement (possibly linked with life-cycle surveillance);
- Post-marketing surveillance;
- Risk assessment over the life cycle of development – what questions need to be asked, and at what stages?
- The proper handling of apps as medical devices;
- Working with the media.

How many of those topics might be combined, and which will be chosen for workshops, are tasks that now fall to the organiser, the EFGCP and MedTech Europe. Their proposals for the way forward are expected early in 2015.