

Will 2012 be a turning point for clinical trials research?

Reports of the death of the clinical trial in Europe may be greatly exaggerated, but the region is losing out to competition from overseas, and intervention is urgently needed. Helen Saul looks at ideas for change discussed at a forum at the recent ECCO meeting in Stockholm.

The parlous state of clinical trials in Europe at the close of 2011 is well-known. The introduction of the Clinical Trials Directive in 2004 led to soaring costs and precipitated a crisis, which is now coupled with funding pressures in an economic downturn, along with the lack of an effective model for partnership with industry. That's according to speakers and panel members at an Oncpolicy Forum session at the recent European Multidisciplinary Cancer Congress (Stockholm, Sweden; 24-27 September, 2011).

But could 2012 be the turning point and see a revival in clinical research in cancer? The European Commission (EC)'s decision finally to revise the Directive has been widely welcomed and demonstrates its commitment to research, according to Martin Seychell, Deputy Director of the European Commission (EC)'s DG Sanco. "The choice before us is actually very simple. Either Europe remains a key player in the area of research or we are increasingly sidelined," he said.

A new and improved Directive would certainly be a boost to Europe as a setting for clinical trials. But it will not in itself solve all problems. Other speakers pointed to the need for non-industry sponsorship of trials, particularly in Eastern Europe, and there were calls for a new model of partnership with industry in large registration trials.

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The first priority in introducing change must be not to make the situation worse. In re-visiting the Directive, this time round, the Commission has gone to some lengths to identify all the issues, all the stakeholders and all of the potential areas for improvement. Its consultation generated valuable feedback, Seychell said, which formed the basis of the EC concept paper earlier in 2011: "The aim is not to have cosmetic tinkering around the edges; the aim is to have a fundamental re-think."

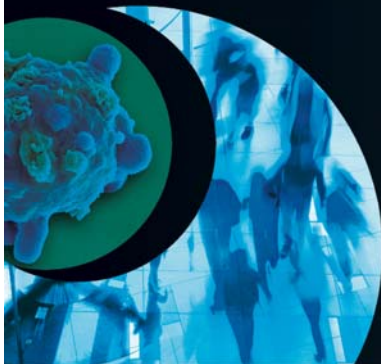
Proposals will be subjected to impact assessments, but these are not straightforward. "We have to look at possible negative side effects of anything we propose to do," said Seychell. "This is where it gets a bit tricky because very often you are trying to project what you know – existing data – on to a situation which may be different."

The laudable aims of the original Directive (essentially to increase the protection of trial volunteers and to harmonise the legislation and conduct of clinical trials) were derailed by

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unintended consequences. And many of them came about as a result of discrepancies in the way it was implemented by Member States. Jacek Jassem (Medical University of Gdańsk, Poland), representing the European Academy of Cancer Sciences, said that implementation in countries such as Poland has been more restrictive than the Directive itself. "In Poland, the ethics committee said that registration forms on medicines and medical devices must be completed in Polish. The same for correspondence with the ethics committee and legislation offices," he said. "There should be a balance between high quality and safety on one hand, and feasibility on the other. It is not the case in our area and independent academic studies in this part of Europe have almost disappeared."

Otmar Wiestler (University of Heidelberg, Germany) agreed vociferously: "If those member states which propose the most stringent regulations prevail in Brussels, then we have a

problem. There are only two ways round that: number one is leaving Europe and carrying out trials in some Asian countries. And the second is a fallback position to national solutions which we want to avoid because for many of the trials ahead of us in personalised medicine, we will need large numbers of patients. We will stratify our patients to ever-decreasing sizes of samples so we really must make a serious effort here for this is the last opportunity."

Seychell stressed that the Commission is well-aware of the problems intrinsic to implementation at national level: "The differences may be small, they may be great, but in practice they add layers of complexity," he said. "The end result is that Europe is far less competitive than other emerging and established regions."



Françoise Meunier

‘It is totally absurd that different patients in the same trial with the same disease, the same risk, following the same protocol can have a seven-fold difference in insurance premium’

The Commission has made moves to simplify implementation and these have been broadly welcomed. Françoise Meunier, Director-General of EORTC, said that her organisation supports the Commission’s proposed coordinating assessment procedure, which would entail a single electronic submission, in English, for each clinical trial. A further proposal, also backed by EORTC, is for there to be a single ethical committee for each country involved. "Not everything is sorted, there are still problems to discuss, but at least we have positive feelings about this proposal," she said.

The assessment of risk in clinical trials – and therefore the insurance premiums – has been a persistent thorn in the side of researchers. Again, national discrepancies have exacerbated the situation. Meunier: "It is totally absurd that a different patient in the same trial with the same disease, the same risk, following the same protocol can have a seven-fold difference in the premium required. This is totally unethical; the life of a patient is worth the same wherever they are."

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While insurance premiums can vary according to the country where volunteers are being treated, they do not take into account the inherent risk involved in a specific trial, meaning that patients taking aspirin need similar insurance to those involving first-in-man trials. Ingrid Klingmann, Chair of the European Forum for Good Clinical Practice (EFGCP), outlined a 3-category approach to assessing risk in clinical trials.

The first category would be for a test medication that does not have marketing authorisation; the second for medication with this authorisation being tested off-label; the third for drugs with marketing authorisation tested within the label.

Klingmann suggested further that new legislation could demand that liability insurance for patients in clinical trials be covered by national healthcare systems as part of the normal reimbursement strategies. "We know from insurance companies that the costs for reimbursement of patients are minimal amounts. The insurance fees are higher and higher but in fact the insurance companies think of this as 90% profit business. Costs are really minimal in comparison to national health budgets," she said.

Martine Piccart (Institut Jules Bordet, Brussels, Belgium), incoming President of ESMO, made a compelling argument for governments to take on the funding for the standard, control therapy arm of large registration trials. She was principle investigator of the groundbreaking Hera trial, which demonstrated that one year of treatment with trastuzumab reduced the risk of recurrence by approximately 40% in her2 positive breast cancer.

Other, shorter, durations of treatment were not assessed; they are riskier and therefore often not favoured by industry sponsors. Altogether, three large trials, plus Hera, including 14,000 women, demonstrated the very positive impact of trastuzumab. Those trials were largely sponsored by pharma. But the drug is expensive and 13,000 women are now currently participating in trials, sponsored by governments and foundations, looking at shorter durations of treatment. "This is ridiculous," said Piccart. "There must be a better way of doing these trials."

Worse, since Hera, several other interesting and potent anti her2 drugs have been developed. Some are now being tested in the adjuvant setting – and they are being given for a year. It has become an unofficial but accepted duration of treatment, when shorter durations have never been assessed.

Further, trastuzumab is only effective in around half of the women with her2 positive breast cancer. In other tumours with the target marker, different pathways compensate and the drug is ineffective. But because tumour blocks were only taken for 20% of the patients in Hera, it was not possible to identify biomarkers which would predict which patients would benefit and which would not.

These issues are unlikely to be addressed as long as the funding for trials comes only from pharma, Piccart said. "If you want to discuss some higher risk treatment arms looking at shorter

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Jacek Jassem,
European Academy of Cancer Sciences

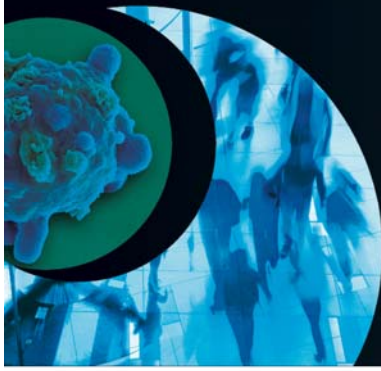
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duration of treatment with the new drug, usually pharma is not going to be in favour of that, so these treatment arms are simply not implemented. And you need to secure funding at the beginning of a trial to be able to collect tumour blocks from patients. If you don't do that, there will never be a possibility to go back and start studying why some patients benefited and some did not.

"Pharma sometimes tells you that they have other priorities. But at the end of the day, this is very detrimental to governments because this will lead to approval of a drug given for a certain time which may sometimes be far too long with no possibility of finding suitable biomarkers. We need much better design of these trials."

Piccart estimated that if all European countries approved trastuzumab for one year among eligible women, it would cost 2 billion Euro per year. Yet with a biomarker to identify the 50% of patients who would benefit from it, and shorter durations of treatment, the cost could realistically be 250 million Euros per year.

Her suggestion is that the standard treatment arm in large registration trials should be paid for by health insurers and national health systems. This money "would allow us to design trials in a much cleverer way. We could come up with treatment arms which are shorter, and do a really good job in translational research to try to understand who benefits and who doesn't."

"If we really want to move to personalised medicine but with affordable costs related to that, we will need a completely different model of partnership in large registration trials," she said.

Piccart acknowledged that this is a long term benefit "and right now it's very unlikely that governments will listen to this message, given the economic problems that we are going through."

The need for non-industry funding is particularly acute in central Europe, and Jassem warned of the critical state of clinical trials research there. "We are moving towards translational research rather than prospective clinical trials which are almost impossible because of financing problems. In central Europe, we have hardly any support from governments and the cancer leagues are weakened; they don't have enough resources to support this type of research. The interest of young investigators is vanishing in this situation. We try to participate in international studies with EORTC and other independent groups, but it's difficult."

Seychell agreed that the trastuzumab example demonstrates "the scope there is for potentially reducing costs by a very significant degree" with increased public funding. "On the other hand, raising the issue of greater member state expenditure in the short term also raises difficulties. We have to realise that in some member states, the short term outlook is very bleak. We all want long term sustainability, but to achieve that we have to survive in the short term. So where the balance is struck is a key political question," he said.

Issues of risk, of ethical reviews, of patient consent were discussed in detail at the Forum, but Seychell urged all those involved to see the bigger picture in the revision of the Directive.

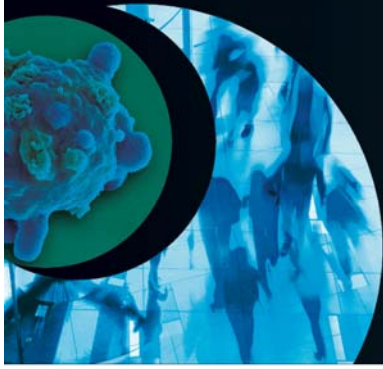
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"Sometimes we do not step back and realise the message we are sending out to the rest of the world. Sometimes we come across as a region that is very conservative and almost afraid of anything new; this is the impression that we are projecting in the wider world.

"Sometimes in Europe, issues such as protection of personal data, protection of intellectual property rights and so on, have turned into a political discussion and we fail to see them in a wider context. They are certainly important, I don't want to downplay them in any way, but sometimes at a political level – and this is the process we will be embarking upon in the coming months – let's not focus exclusively on these issues as if they were the beginning and end of everything. They are tools, they are important issues that we need to find a home for in a framework, but if the political discussion loses focus, and we lose sight of why we really want to have a review of the legislation, then I think we could end up in an even bigger mess.

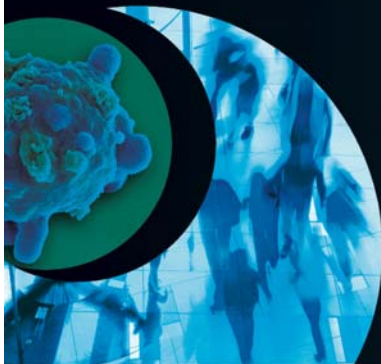
"The important thing is that at the Commission, we leave no stone unturned to make sure that we try to keep focus as much as possible. This will require a lot of dialogue with stakeholders, member states, legislators, and so on, and I am confident we can achieve that", Seychell said.

Helen Saul

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Reduced commitment to cancer in new IMI agenda?

A revised strategic research agenda has been released for the Innovative Medicines Initiative (IMI), the EU scheme to speed up the process of drug development in Europe. Cancer remains a priority, but there is no assurance of further dedicated calls for proposals in this area. It leaves cancer research to compete with other disease areas for funding.

Launched in 2008, the IMI is the world's largest public-private partnership in healthcare, with 1 billion Euro from the EU Framework 7 research programme to fund public sector participation until 2013. This is matched in kind by member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA) participating in research activities.

The revised IMI research agenda has been released in advance of discussions on future funding, due to begin in December 2011 as part of the budget negotiations on the next EU research programme, Horizon 2020. Drawn up in consultation with EFPIA companies and regulatory authorities, it contains an additional eight new research priorities which will form the basis for future calls for proposals:

- Stem cells for drug development and toxicity screening;
- The reclassification of diseases based on molecular, genetic, proteomic and other markers;
- Rare diseases and stratified therapies;
- Systems approaches in drug research;
- Beyond high throughput screening - pharmacological interactions at the molecular level; including the provision of tool compounds to academia for the evaluation of new targets and pathways;
- Drug compound development and active pharmaceutical ingredient technology;
- Advanced formulations;
- The integration of imaging techniques into drug research.

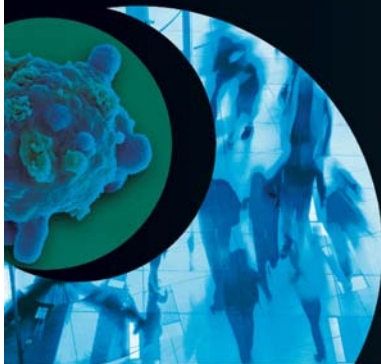
Cancer was an initial IMI research priority, and has benefited from dedicated calls for proposals since 2008. However, it is uncertain whether this will continue. According to Daan Crommelin, chair of the IMI scientific committee responsible for the revision of the research agenda, "The real drivers are the EFPIA companies. They are at liberty to define the specific topics of calls. It depends on what they want and if they put it on the agenda of a new call," he says.

Despite the prospect of having to compete with other disease areas, IMI executive director, Michel Goldman expects there to be opportunities for cancer research within the new areas. The building of a joint European compound library and screening centre for drug discovery is under discussion as a call topic in the first half of 2012. "Among the number of compounds that

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will be screened there, there will be anti-cancer drugs for sure," says Goldman. "Researchers should look carefully at future calls. There will be opportunities – the stratification of patients with cancer, combination therapies, and high throughput screening for anti-cancer compounds. It might also be that we have specific calls on pharmaceuticals for paediatric use. Nothing is fixed yet, but these are the things I anticipate."

Researchers across the board feel the new IMI priorities are a step in the right direction. "I think drugs and targets is the way to go and the IMI themes are interesting areas for the development of new cancer drugs," says Eduardo Moreno, who was awarded an ERC grant to investigate the way cancer cells can out-compete surrounding normal cells, and also jointly won the 2011 Josef Steiner Prize for cancer research.

"The use of stem cells for drug development and toxicity screening sounds reasonable as some cancers are based on mutated stem cells. If you have drug toxicity it will probably affect adult stem cells the most," he says.

'Among the compounds that will be screened, there will be anti-cancer drugs for sure'

Michel Goldman,
IMI Executive Director

"Combination therapies is also a good priority," he adds. "Several European research groups in Europe are excited about synthetic lethality – where the combination of two drugs activates the process of killing cancer cells, when independently, neither causes cell death."

Although in agreement with the priorities, Ulrik Ringborg, director of the Karolinska Institute and co-ordinator of the European Platform for Translational Cancer Research feels they don't go far enough. "These priority areas are relevant and important for cancer. However strategic discussions today strongly focus on personalised medicine, so they could have been a little more innovative in the selection of areas – such as the validation of biomarkers for the early detection of metastatic disease. Deeper biomarker research and the validation of biomarker response is the next step to individualise treatments and develop personalised cancer drugs. I hope that will be the next generation of IMI-EFPIA discussions," he says.

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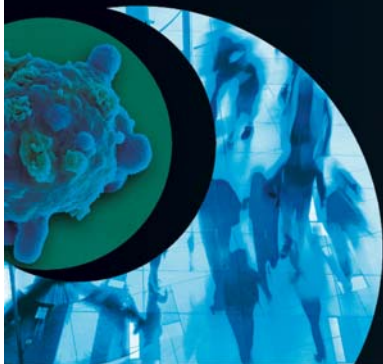
Pharmaceuticals companies have been conducting the mainstay of work in these priority areas in-house, out of sight of competitors. But growing external pressures are leading companies to revise their business models, according to Crommelin, who is also the scientific director of Top Institute Pharma in The Netherlands and a professor of pharmaceuticals at Utrecht University.

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"When the research is product orientated, companies do it themselves. When it is more concept orientated, they are moving to open-innovation models, doing it in a more pre-competitive setting because of sky-rocketing research costs, a rightly stringent regulatory system and an increasingly risk averse society. The financial crisis hasn't helped either. It makes sense to concentrate the activities in a public-private structure where everyone is interested," he says.

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Goldman feels the IMI will see an increased investment from the industry in the next round of funding. "It is becoming more and more a key part of the industry strategy, which it wasn't at the beginning. If the IMI process can be streamlined, the companies will increase their own investment. The projects also need to demonstrate real added value for this to happen and we now have good indicators," he says.

Looking back at the scheme so far, Ringborg believes it is too early to say if IMI has been successful for cancer. "We haven't seen many interesting calls in the cancer area despite cancer being a priority area. With the IMI partnership, industry matches the EU budget, and only in kind. In the US, the national institutes of cancer spend 5 billion dollars and pharmaceuticals companies spend 20 billion dollars. What we need is European industry to increase its spend in a similar manner."

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Brussels

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