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CONFERENCE REPORT

The EFGCP Annual Conference 2009

Research Integrity: a European Perspective

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Research Integrity: a European Perspective

EFGCP Annual Conference puts misconduct and fraud under the microscope

It was the first EFGCP Annual Conference to take place outside Brussels – and it proved highly successful, with a string of proposals of action emerging after two days of lively debate and discussion. Newsletter editor Peter Wrobel reports from Prague. Delegates to the EFGCP Annual Conference in Prague on 27 and 28 January had to grapple with one of the most delicate and seemingly intractable questions in research: integrity, and how to maintain it.

As EFGCP Chairman Jean-Pierre Tassignon said opening the conference, this means looking into the “dark side” of research: “If you want to improve, you have to look at what doesn’t go right.”

By the end of the conference a number of avenues for action had been opened up, with a series of recommendations (see cover story). But along the way it was clear that there were large areas of uncertainty around European research integrity: in particular, many delegates commented on the lack of data on fraud and misconduct in Europe (and elsewhere).

In addition, there seems to be no shared and settled understanding in Europe – let alone between Europe and other continents – about how to define fraud and misconduct.

Worse, too many people do not accept that there is fraud in the scientific community, said Detlef Niese from Novartis.

One thing was clear, though: you don’t have to go to far-off places to find fraud and misconduct. “You can find it in the heart of Europe,” said Klaus Rose from F. Hoffman–La Roche. Equally, delegates were unanimous that a lack of research integrity damages patients, academia and industry.

Integrity, said Povl Riis, Emeritus Professor of Medicine, Copenhagen, and founder of the first Danish Committee on Scientific Dishonesty, is “a key term for reliability” in clinicians and other health professionals doing research involving man. It’s the basis for confidence on the part of patients and healthy volunteers who take part in clinical and epidemiological research. Scientific fraud, dishonesty and non-reliability are “cardinal sins” in biomedical research, he said.

Pierre Lafolie, from the Stockholm Regional Ethical Review Board, Sweden, affirmed the central role of Good Clinical Practice in ensuring research integrity. It is not enough simply to discuss legal and regulatory environments, he said. It also requires “moral reasoning”, intellects trained to have respect for the research subjects. “Good clinical practice,” said Lafolie, “provides us with an environment that is detailed regulation but also takes into account the moral issues.”

His recipe for research integrity was to respect the research subjects, be scientifically sound, to adhere to laws, guidelines and regulations – but also to follow common sense.

Independence essential

Research ethics committees (RECs) overseeing trials must be independent, said Marcel Kenter, from the Central Committee on Research Involving Human Subjects, the Netherlands, giving negative examples from famous institutions in the US and Europe.

Inadequate assessment by an REC may not give the research subjects the protection they should have, said Kenter. Nor, he said, will inadequate assessment help to maintain research integrity or “a

culture and awareness in the institute so that misconduct is difficult". At stake can be the reputation of the researchers, the institute and even the country.

Michael Bone from the UK's Association of Research Ethics Committees agreed. Ethics committees, he said, must be independent of the institution – otherwise the conflicts of interest are "embedded". But, he noted, "[The UK] ethics service is heavily criticised by researchers reluctant to undergo ethical scrutiny, mainly our social science researchers, who feel we are limiting their right to challenge and to do exciting research."

All of this prompted a question from Jozef Glasa from the Institute of Medical Ethics and Bioethics, Bratislava, Slovakia: "Is there not something rotten in the clinical research field that so many structures must be in place to prevent fraud and cheating?"

More of a problem for academia?

Lafolie was also the first speaker – but by no means the only delegate – to address the differences between industry and academia. Industry, he said, "very rarely gets paperwork wrong", helped by sufficient staff who know how to follow the regulations. "This is not always the case with academics," he said, while noting exceptions to this.

Colin Wilsher from Pfizer agreed. "The public thinks that industry is unethical, but how do we get across to the public that it is easier for academia to be fraudulent."

Nicholas Moore from the University of Bordeaux, France, concurred, while noting that "the paranoid will say that if they can't find fraud then the perpetrators must be very good at hiding it". Academic research – or any research not used for regulatory purposes – lacks the checks that industry has, he said.

For Povl Riis, there are bad cases on both sides. Industry is not worse than academia, he said, adding: "In the long run we need independent bodies [supervising research]. I don't believe in academia as a self-regulating system."

Structures and processes

Can regulation work? Perhaps history can help. That was the subject of a plenary session at the conference, introduced on a somewhat sombre note by Michael Farthing Vice-Chancellor of the University of Sussex, UK. "We have not learnt from history, so it is appropriate to remind ourselves where we have come from," he said.

In terms of formal structures and regulations aimed at combating misconduct, the US has the longest record. Self-confessed "boring historian" Nicholas Steneck from the University of Michigan and the US Office for Research Integrity, took delegates through more than 20 years of policy formation and implementation across the Atlantic.

The result is a complex web of responsibilities, united by a common set of definitions: misconduct is limited to falsification, fabrication and plagiarism; fraud must involve financial gain or deception.

Are the policies effective? "It depends on how you are measuring them," said Steneck, before coming up with his own appraisal: better on coming up with guidelines than on protecting research – and definitely failing when it comes to protecting the public. "My guess is that your reporting system isn't any more effective than our reporting system," he concluded.

Steneck singled out the role of independent research ethics committees: “Without any doubt, if you have a bureaucratic, unrespected research ethics committee, researchers will not do what you tell them to do.”

And Steneck said that institutional governance is also key: “In my experience [...] there has to be a good institutional climate. Where the climate at the top is not supportive of these efforts it is very hard then to build it into the system.”

Reviewing the French and European inspection experience, Pierre-Henri Bertoye from the France’s AFSSAPS agency concluded that what is needed is multi-level collaboration and data flows between investigators, sponsors, competent authorities – both inside and outside the European Union, and the European Commission. His three watchwords were prevention, detection and information.

For Fergus Sweeney of the European Medicines Agency, proper investigative processes are vital. “We need processes that will lead to decisions, conclusions and where necessary to consequences [...] We need to be careful all the time that when we escalate things we get to a consequence.”

That, also, was the conclusion of the conference workshop on how to conduct an inquiry into alleged misconduct. Among the ideas that Pierre Mallia, a GP and ethicist from Malta, reported from the workshop was that an external, independent inquiry is always more reliable. The workshop also concluded that fraud and misconduct investigators must be properly trained.

One problem was highlighted by Detlef Niese from Novartis. “The belief that science can regulate itself is one of the symptoms of the issue,” he said.

But perhaps it’s not just a matter of regulations, speculated Melvyn Rapprecht, Head of Auditing Affairs, Clinical Quality, at F. Hoffmann-La Roche. Look at what happened in the finance industry, he said, which is even more tightly regulated than research. “Maybe it’s the integrity of people that is at the heart of how we conduct our jobs,” he said.

Ethics and training

Pierre Mallia said the problem with science is that we have gone away from teaching proper ethical conduct. “We have set ourselves rules and regulations and become like a religion,” he said, “which is why science is becoming the enemy [in society’s eyes]. There is misconduct in science because scientists are not bred in ethical conduct.”

The importance of ethical training surfaced again in the report back from the workshop on the role of national competent authorities by University of Groningen’s Professor for Quality Management in Drug Research and Manufacturing, JanHasker Jonkmann. “Competent authorities should use their political influence to come to a system where students are taught in medical training about the ethical standards in medical research: a good culture is the best way to prevent fraud and misconduct,” he said.

That workshop’s main conclusion was that if there is well documented suspicion it should be reported as soon as possible to avoid further damage – including to the national competent authority. But the workshop acknowledged that the authorities lack the resources to investigate all cases of suspicion of misconduct or fraud – they can only deal with “fully documented” cases.

Jean-Pierre Boissel of the University Claude Bernard Lyon, France, also stressed the importance of educating the investigators in how to design, carry out and report unbiased trials. This education is already implied in many parts of the syllabus, he said, but he called for it to become explicit. And that means teaching the epistemology of science: what science is for.

Ingrid Klingmann, from Pharmaplex, Belgium, and the EFGCP's Co-Chair of the Ethics Working Party, agreed. "Ninety-five per cent of the time medical students are learning about how the body functions and how to treat it. There is very little training about how to do research," she said.

Whistleblowers

Steneck was also the first in the conference to raise what would be a persistent, if not always unifying, theme: the importance of the whistleblower. In principle, though not always in practice, whistleblowers are protected in the US, but regulations about this extend only to federally funded research.

For Drummond Rennie from the University of California, San Francisco, who was later to deliver the Joseph Hoet Memorial Lecture, "unless whistleblowers are encouraged, you will never, ever, ever get anyone stupid enough to report misconduct – unless they are prepared to commit suicide in public".

In fact, he said, the report of the Commission on Research Integrity (on which he sat) was widely attacked as an attack on science by the leaders of the major scientific societies in the United States, mainly for encouraging whistleblowers.

Help the whistleblower blow, and offer protection, said Nicholas Moore from the University of Bordeaux, France – after offering a wealth of evidence that these two things are just not happening at the moment. He also called for rewards for whistleblowers, perhaps through financial support, help in publishing their own papers, or simply by proper recognition of their role.

Fergus Sweeney agreed: "People must have the moral certainty to know that if they stand up and say 'That is wrong' that their superiors will support them," he said. In the end, he said, what is needed is not just personal but organisational moral courage.

Whistleblowing, said Ingrid Klingmann, is hard enough when the misconduct or fraud is based on data. It's even harder to prove something when the issue is unethical behaviour.

But handling whistleblowers is not simple, said Jane Barrett from the Barrett Consultancy, UK. And, she cautioned, the accused need protection and care as well until proven guilty. That, she said, needs detailed policies that protect all staff, provide a mechanism for confidentiality and protection against retaliation.

"The only way to stamp out misconduct is to make it too risky so that people don't dare do it. We are a million miles away from that at present," said Barrett.

Whistleblowers, said Barrett, have everything to lose. They normally blow the whistle only as a desperate last-ditch action. Their handling cannot be ad hoc, she said, or be done by the inexperienced. "In a lot of cases it [legislation protecting whistleblowers] works, but until we can say it works in all cases, whistleblowers have no guarantee," she said.

However, the very term "whistleblower" sparked concern among some delegates. Jiri Simek from the Forum of Ethics Committees, Charles University of Prague explained that whistleblowing is both good and necessary, but it reminds people in post-communist countries of the system of whisperers built up by the secret police. If whistleblowing is to be perceived as positive, he suggested, we need first to establish "a positive image of honesty and science with integrity".

We face the same issue in Germany, said Detlef Niese, where anonymous whistleblowing is not accepted. It is the same in Belgium, said Robert Rubens from the Universitair Ziekenhuis Gent Ethics Committee: "As long as people talk about whistleblowing, we run," he said, saying the word is reminiscent of communist and fascist countries.

What's in a word?

But what is fraud? What is misconduct? Satisfactory or not, the definitions of fraud and misconduct in the US are at least clear. Not so in Europe. Frank Wells, co-chairman of the EFGCP Ethics Working Party, called for a clear statement of what is misconduct and what is expected. Once a statement is made, he said, we must make sure that publicly funded researchers sign up to it.

And it should be combined with complaints procedures and protection for whistleblowers – something “hugely important and inadequately addressed”, he said. What is clear, said Wells, is that internal institutional discipline is not working.

It would be good to reach agreement across the Atlantic about what constitutes misconduct and what might fall into the category of questionable research practices – such as methodology, or analysis – said Jacques Demotes-Mainard from INSERM, France.

Demotes did not provide his own definition, but set out the basis on which definitions might be made, primarily the risk to patients and whether the bias is intentional or not.

He drew attention to what he called the “underpinning mechanisms”: bias, insufficient training, conflicts of interest and pressure to perform.

Definitions, said Demotes, may also be based on the extent to which misconduct can be detected, or prevented. Some detection tools might suit some bodies but not others: for example, ethics committees, monitors, auditors, institutions and companies.

Yannick Plétan, from Pfizer, France, wondered whether there is a need for a clear demarcation between misconduct and fraud. “It may not be possible,” he added.

For many people, said Plétan, fraud and misconduct have the same meaning. And, he said, scientists themselves do not agree on the definitions. “There is very little evidence that there has been work to examine the perception of scientists of what constitutes fraud or misconduct,” he said.

Josef Kurě, from the Bioethics Committee of the Czech Governmental Research and Development Council offered some semantic clarity. Misconduct is misconduct he said – there is no such thing as scientific misconduct, only misconduct in science.

He defined misconduct as “any departure from the responsible conduct of science”, with fraud being a “serious form of misconduct in scientific performance/conduct” with the criteria of seriousness and intentionality.

But Povl Riis was wary of definitions. “I would warn as you have done against trying to find a few words that we agree upon. Nothing will be decided on,” he said. Instead, he suggested choosing “a couple of overall terms” and then forcing editors to accept that researchers will describe what they mean by them in each article. “Tell people what you mean in your papers,” he urged.

Detection – and prevention

The earlier misconduct can be spotted, the better, and the conference devoted some time in plenary sessions and workshops to a variety of topics linked around detection and prevention.

Yannick Plétan from Pfizer introduced feedback from the workshop on the role of monitoring: a good monitor, he said, will be able to recognise if misconduct is taking place – though he stressed that this is not a monitor's main role.

His recommendations centred on the role of the individual monitors, who wherever possible should be independent of the investigator. It's important for monitors to make good use of the initiation visit, he said, and to discuss misconduct and their role as part of that visit, so that the investigator is aware of their role.

That plea for transparency was reflected in the recommendation that publications should make clear whether the research had been monitored.

Plétan also suggested changing monitors, or having co-monitors. "You might have a regular monitor for a site, but it does no harm to have a second one appearing occasionally, particularly in long-term trials." But with the availability of monitors decreasing, we need to think about central monitoring, he said.

The workshop singled out the consent process for particular attention, since misconduct often centres on consent. It suggested the consent process be recorded, as happens with many oncology trials in the UK.

Can audit help? The workshop dedicated to this thought not, or at least, not much. As Kristel Van de Voorde Director, Worldwide Regulatory Compliance-Europe, BMS, reported back, if fraud or misconduct is detected at audit, it points to the failure of oversight and monitoring during the study. That view was echoed in a later presentation on the role of audit, Nicky Dodsworth of Premier Research Group, UK. "However good audit is, it will not eradicate fraud and misconduct," she said, adding, "but hopefully it will act as a deterrent."

But the workshop did come up with a number of warning signs: non-random recordings, recording all in the same handwriting, measurements that are too similar, events that cannot possibly have happened within the stated time frame, and so on.

The workshop did feel that internal auditors could play a role in preventing the creation of a climate where misconduct is possible, by determining whether the processes were robust – especially in statistical analysis and blinding.

Another workshop was charged with examining the role of research ethics committees in preventing misconduct. They could do so, reported Michael Bone, in several ways, both proactively and reactively. In terms of active prevention, they can help by looking at protocols and risk factors (such as whether the investigator has GCP training), at conflicts of interest, and at the site itself.

Over and above this, said Bone, the committees need to react when evidence or serious concern about misconduct is presented to them. That, the workshop had heard, doesn't always happen. An area where ethics committees can have a general effect, he said, is by being involved in training and education.

Tools to help

Melvyn Rapprecht started the discussion about the use of quality tools to detect fraud and misconduct. Routine audits, he said, conservative and infrequent, were insufficient.

He described tools that Roche had come up with, encompassed within the term QRM, or quality research management. This entails, among other things, amalgamating information electronically in order "to understand what is going on and identify any issues immediately, or at least very early on". Rapprecht warned, though, that it is "not helpful" to look solely for misconduct or fraud.

What he described was hailed by Michael Bone as “a tremendous stage forward”. Bone wanted to see findings from QRM fed back to research ethics committees.

In his talk, Pierre-Henri Bertoye of AFSSAPS had given examples where fraud or misconduct is discovered when the agency redoes the statistical analysis. So, can statisticians succeed where others are stalled?

Jean-Marc Husson from Eudipharma, France, and Co-Chair of EFGCP’s Geriatric Medicines Working Party, discussed the challenges inherent in systematic monitoring. There are clearly two thorny issues here: access to data, and standardisation of data (including of electronic health records). Sooner or later, he said, and preferably sooner, progress has to be made on both issues.

The subject was examined in depth by one of the workshops. Marc Buyse from the International Drug Development Institute, Belgium, reported on several case studies considered by the workshop. His conclusion: statistics can detect some fraud, but not all fraud.

There are in fact many ways statistics could help, said Buyse, but in practice lack of software, expertise or simply time can be limiting factors, as can lack of interest – “It’s quite boring to check data extensively!”

Automated systems could be useful, he said, but data are “generally noisy”, and automation may generate signals that are in fact explainable. “Signals that erroneously suggest fraud may have devastating consequences. So systems should be aimed primarily at checking and improving data, not primarily detecting fraud,” he said.

And finally...

What we see of fraud and misconduct is only the tip of an iceberg, said Jean-Pierre Tassignon in his closing remarks. We need some common terminology if we are to draw the line between misconduct and sloppiness, he said. Overall, he said, “clearly the message here is a multilevel fight against fraud and misconduct”.

The responsibility is a collective one, said Tassignon: “Fraud and misconduct are only symptoms of many weaknesses in the way we organise clinical research in our society.

For co-chair Josef Syka from the Czech Science Foundation, the answer lies in education. “I believe the best solution is to teach PhD students basic ethical rules [before they graduate]. Later is too late.”

The way forward

As the conference drew to a close, Frank Wells from the EFGCP consolidated suggestions and ideas from plenary sessions and workshops into a 12-point list for action, since taken further by the EFGCP.

1. Definitions of “fraud” and, particularly, “misconduct”, are needed with clear demarcation between them, across Europe and the rest of the World. This could begin to be progressed as a fact-finding task of what definitions already exist.
2. The case has been established in Denmark and the Nordic countries and in the USA (with the ORI) for a National Body on Research Integrity. The case must now be made for establishing such a body in every country conducting research.
3. The importance of training stakeholders in clinical research projects in the principles of research integrity and the prevention of fraud and misconduct cannot be over-emphasised. The Prague conference confirmed the support that would be given to the development of such generic training.
4. Allied to this, core training is necessary for research ethics committees on their role in the prevention of misconduct and in the management of misconduct if and when cases come their way. They have a duty of care which currently they are ill equipped to fulfil if research misconduct occurs. Additionally, information needs to be available for patients and patient groups, as they are the ones likely to be exploited when misconduct in biomedical research occurs.
5. Support is needed for research into research misconduct. We do not know the true prevalence of the various grades of research misconduct, nor do guidelines exist on what is acceptable and what is unacceptable. Structures must be in place to take action if this line is crossed. Processes are needed for prevention (of harm that could be done), for deterrents (that increase the likelihood that misconduct will be detected), for investigation if necessary and for decisions leading to conclusions and consequential actions. Transparency is needed so that every stakeholder is clear about what is happening, including publication policies and communication with others.
6. Guidelines are needed on encouragement for, and the protection of, the genuine whistleblower.
7. Monitoring is key to the detection of much misconduct and training in its detection is currently largely lacking. However, guidelines on the monitoring of clinical research already abound. They therefore need to be enhanced to include this particular topic.
8. Audit of clinical research projects is also invaluable in the management of research misconduct. The EFGCP Audit Working Party has recently produced excellent guidelines that might, however, need to be edited to include reference to this particular aspect of audit. In-house fraud must not be forgotten as it has been known to occur.
9. Statistical analysis of data can be invaluable in confirming or denying a suspicion that data have been fabricated or falsified. There is a need to remind sponsors and statisticians themselves that statistical methods can be of great value in this context.
10. The ways in which an enquiry into suspected research misconduct should or should not be conducted are interesting and are largely poorly understood. There is a strong case for independent forensic investigation, using recognised experts in their field.

11. National competent authorities should receive reports from sponsors, the public and whistleblowers of suspected research misconduct as soon as it is well documented. There should be clear processes and contact points for this to happen. Inspectors, sponsors and ethics committees should be trained in the management of research misconduct and there is a case for harmonisation between competent authorities, particularly in the context of misconduct within a multi-national trial.

12. It has been suggested to the EFGCP Ethics Working Party, and accepted, that a Research Integrity Sub-Group be created, under the chairmanship of Dr Frank Wells. Its members will include those members of EFGCP who have already demonstrated an interest in tackling the challenges that this subject presents. This Sub-Group will address virtually all of the above topics, or route them elsewhere if appropriate.

Frank Wells

How journals can help

When there is misconduct in scientific research, the spotlight often comes on the role of editors and journals. As Ana Marušić (above), Editor of the Croatian Medical Journal told the conference, fraud is often recognised only after publication.

So how can journals help? First, said Marušić, quoting Hugh Clegg, the eminent former editor of the British Medical Journal, by keeping the issue before the public until it is reformed.

Journals' strengths include their authority in the scientific community, particularly in smaller communities where editors are often working researchers. They are also independent, with the power to formulate editorial policies. Their place in the peer review process makes them well placed to detect misconduct in science. And, increasingly, they have tools at their disposal to help them detect data manipulation in figures, for example.

On the other hand, journals are exposed to the threat of legal action, and may be sued for trying to safeguard the integrity of what is published. Also, editors who are active researchers may be reluctant to get involved in what Marušić called "delicate issues" that might damage a journal's reputation.

One key advance has been the concept of retraction. PubMed started publishing retractions in 1977, and to date more than 1,000 articles have been retracted – although it is unclear how many of these are due to honest error or to misconduct of some kind.

Another has been the call from the International Council of Medical Journal Editors for the comprehensive registration of clinical trials – "the first step in alleviating selective data presentation on clinical trials in medical literature," said Marušić.

Marušić was candid about the problem journals face when seeking to safeguard research integrity: the lack of legal regulation, corruption in the scientific community and in governments – especially, she said, post-communist governments; the lack of training, the lack of support for journals from their publishers; and conflicts of interest.

She made a plea for quality assurance in editing, bolstered by a structure with guidelines, standards and editorial policies, and a process that requires authors to declare contributions and conflicts, that can verify the integrity of articles and handle allegations of misconduct and correct the literature if necessary. The outcome, she hoped, would be an improvement in the responsible conduct of research and editing.

How much fraud and misconduct is there

“Is fraud and misconduct behind us, or more prevalent,” asked the EFGCP’s Chairman, Jean-Pierre Tassignon. The question hung over the conference, but there was no clear answer.

Historian Nicholas Steneck from the University of Michigan thought that between 10 and 50 per cent of researchers indulge in what he called “questionable activity” that might not fall within the strict US definition of misconduct (falsification, fabrication or plagiarism). But most misconduct is not reported, he said.

Frank Wells, co-chairman of the EFGCP Ethics Working Party, and joint editor, with Michael Farthing, of the definitive textbook on Fraud and Misconduct in Biomedical Research, knows as much about this as anyone, having been involved in “fraud busting” for over 20 years. Reviewing practice and actual cases across Europe, he concluded that “the incidence of clinical misconduct is not known”.

Drummond Rennie from the University of California, San Francisco, told how he had tried in 1988 to get the US National Academy of Science to investigate the incidence and prevalence of fraud and misconduct by taking accepted papers and auditing, confidentially, to find out whether there were real data behind them. The results could then be published in aggregate, anonymised, he said. “Then you could discover whether the prevalence was 1 in 10 or 1 in 10,000.”

It never happened. “The moment I stopped [speaking] people started yelling I was destroying the fabric of science [...] So there went an experiment. We will never know the prevalence of this problem,” he concluded somewhat glumly.

Steneck was less pessimistic. The reason we don’t know the prevalence and incidence, he said, is “only the result of will, not that we don’t know how to go about it”. “Researchers are not using their own methods to study a problem that is their own problem,” he said.

For further information

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