EFGCP Workshop on
Indemnity Schemes for Clinical Trials: A Societal Obligation?

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EORTC Headquarters, Brussels, Belgium

Organised by

European Forum for Good Clinical Practice

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1. The workshop and its aims

The workshop was organised at short notice by the European Forum for Good Clinical Practice (EFGCP), with support from the European Cancer Patient Coalition (ECPC), the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Organisation for Research and Treatment of Cancer (EORTC). Some 40+ multi-stakeholder delegates from 16 countries convened on 5 December at the headquarters of the EORTC in Brussels, Belgium, to debate the preferred options for a future European patient indemnity system in clinical trials.

In its draft Regulation on clinical trials the European Commission has proposed that each country implement a national indemnification mechanism at a not-for-profit level and coverage of indemnity in “low-intervention” studies by the national healthcare system. The European Parliament agreed to this approach and specified further details relevant for such a system. The Council of Europe, however, has suggested the complete deletion of this paragraph, which in practice means that the current system is to be maintained.

This workshop aimed to learn about the national differences in indemnity coverage, about how academic and industry sponsors handle indemnity coverage in their trials, and about the problems, challenges and advantages of their approaches. Ultimately it sought to provide recommendations on important aspects for the “Triage” of Commission, Parliament and Council to consider in their current negotiations on a future system for protecting patients from damage in clinical trials.

2. Key recommendations

- Put patients first!
- There should be equality of indemnity coverage for all European study participants
- “No-fault” schemes are preferable
• Indemnity coverage fees must be reduced
• Coverage conditions must be clearly defined and easy for patients to understand
• A guideline is required to provide better and harmonised definitions of "risk in clinical studies"
• Academia needs the implementation of national indemnification mechanisms on a non-profit basis as, for example, exist in Sweden or Denmark

3. Where we are now: a crisis in policy

Since the Clinical Trials Directive came into force in 2004 the number of clinical trials performed in Europe has fallen by 25 per cent, and while insurance is only part of the problem, it is clearly a major contributor to the current disarray faced by academic investigators. By itself the Clinical Trials Directive is not the cause of all the problems. Rather, as Françoise Meunier, Director General of the EORTC, put it, it is the way it was implemented by various Member States. The complexity and range of insurance options is not helping research, she said, reporting that the organisation currently has to cope with 67 individual insurance policies. And the way insurance is required in various countries has led to chaos, bureaucracy and different levels of risk coverage for study participants. Meanwhile, society’s obligations to the participants and potential beneficiaries of clinical trials are not being reliably met.

The European Commission tackled the concerns about indemnity insurance head-on with two proposed Articles in the draft Regulation. The first, Article 72, seeks to clarify that “low-intervention” trials should not require separate insurance: the risks should be covered by the appropriate national healthcare systems. The Commission’s Article 73 would require Member States to provide a national indemnification mechanism for compensatory damage payments to clinical trial participants. This mechanism would be free of charge for non-commercial trials (those not intended to be used for a marketing authorisation). For other trials a fee would apply, but it would be set on a non-profit basis taking into account the risk of the clinical trial and the likelihood of damage to trial participants.

The European Parliament is seeking to amend Article 72 to change “low-intervention” to “low risk”, a move with implications welcomed by many participants at the workshop. It would also require “adequate and comprehensive information” to be provided to trial participants on what would be indemnified, the limits of indemnification, and the way the indemnification system would work. And in Article 73 it seeks to allow a charge to be set retrospectively if a non-commercial trial was later used in an application for marketing authorisation.

The European Council, however, proposed on 29 October 2013 to delete Article 73 in its entirety – effectively leaving the indemnity system as it is now: broken.

4. Urgent messages from the workshop

The workshop was not a consensus conference. It included a variety of stakeholders: academic and commercial clinical trial sponsors, members of ethics committees, patients, a regulator, and people from the insurance industry. So not all the messages were endorsed by all stakeholders. Where there was disagreement, this is indicated below.

4.1. Put patients first

There was definite agreement among all that the guiding principle of any indemnity system must be to put patients first: whatever system is in place, the patient and the volunteer must be protected. The workshop was clear that this involves three vital principles: that patients are protected from any injury sustained through taking part in a trial; that it should be clear to them how such protection will operate and how redress may be claimed; and that patients desperately waiting for new treatments should not see clinical trials unnecessarily dropped due to unaffordable insurance fees or delayed by the complexity of different national indemnity schemes.
These principles are completely consistent with those agreed in 2010 at an EORTC workshop on the need for harmonisation of clinical trials in Europe\(^1\), and inform the points below.

### 4.2. Cost must come down, particularly for multinational clinical trials

The costs of trials, and of multinational clinical trials in particular, are frighteningly high. While in the UK liability in national multi-centre trials is covered by the NHS system, the experience is that premiums in multinational trials are usually charged according to the number of participating countries rather than the number of patients. In one international trial comparing treatments in acute lymphoblastic leukaemia, it cost academic sponsors €643,519 to insure 4,200 patients in four countries. In addition, it can take academic sponsors between one and two years to arrange the insurance for overseas participation in multinational trials – causing unacceptable delays in opening a trial.

And it seems that the cost of insurance is out of all proportion to the benefits. As things stand, said Ruth Ladenstein, from St. Anna Kinderkrebsforschung e.V., Austria, who had surveyed a number of clinical trial sponsors in Europe, the pay-outs from insurance policies amount to a tiny one per cent of the costs of those policies.

Claims are extremely rare, said Anastassia Negrouk from the EORTC, yet fees have rocketed since 2001, when the Clinical Trials Directive was passed, and can easily represent 10 per cent of the trial costs. “Some insurance costs are high enough by themselves to fund a clinical trial,” she said. The costs of insuring multinational trials are a big part of the increase, but other factors are in play as well. Ingrid Klingmann of the EFGCP, for example, pointed to the switch since the introduction of the Directive to risk-based per-trial policies rather than annual arrangements simply based on the number of patients involved.

### 4.3. National indemnity mechanisms work well – and cheaply

Beyond that, there was much discussion about the merits of national indemnity mechanisms such as exist in Denmark and Sweden. Strong arguments and evidence were advanced to suggest that such systems are not only vastly cheaper than ad hoc per-trial insurance policies, but that they present patients with the greatest clarity about their options in the event that they suffer harm through a trial. They also solve the problem that arose in the disastrous Te Genero trial at Northwick Park Hospital, UK, in 2006, where the damages to the volunteers exceeded the sums insured, and the sponsor became insolvent.

The Danish system is backed by the state, with no involvement by insurance companies. Clinical trial sponsors pay no fees. In the 16 years from 1996 to 2012, a total of 16 claims were accepted, involving payments to patients of €544,433 and associated administration costs of €60,000, according to figures gathered by Peter Jakobsen of Denmark’s Patient Insurance Association. With a total cost per year of less than €40,000 for a system that gives automatic cover to trial sponsors (both commercial and non-commercial) and consistency and transparency to patients, no wonder it looks attractive to many.

The Swedish scheme is owned and run by over 200 Swedish pharmaceutical companies, and covers their own costs. It also covers the costs of R&D companies without a current marketing authorisation, charging them €6,200 for the first five patients, and €24 per patient thereafter. By agreement with the Swedish state, academic trial sponsors not covered elsewhere are covered by a fee of €24 per patient. To be covered, the trial simply has to be approved by Sweden’s Medical Products Agency and by the relevant ethics committee. There is an individual cap of €1,081,000 per injury, said Philip Lange Møller of the Danish Health and Medicines Authority, presenting information from Anders Öhlén, from Sweden.

In the UK, the NHS covers insurance for negligence in hospitals, so insurance costs are not an issue for clinical staff. But universities and separate clinical trials units must provide their own insurance. Generally, UK academics experience problems only when they wish to sponsor multinational trials – though sponsors outside the UK have to take out separate insurance policies when they want to include the UK in a multinational trial.

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While the insurers present were not favourable towards the idea of the Regulation mandating such national indemnity mechanisms – in particular the Danish system – it is fair to say that the unanimous opinion of academic researchers seeking to hold clinical trials in Europe is that the present indemnity system is not fit for purpose. Simply put, it fails to put patients first, it cannot and does not assure every European patient equally well, it places obstacles and costs in the way of holding clinical trials, and it denies patients from smaller or poorer countries in Europe the opportunity to take part in clinical trials.

_In other words, academic researchers clearly favour keeping Article 73 as proposed by the Commission and Parliament._

4.4. “No Fault” works best for patients

Everyone at the workshop favoured “no fault” indemnification procedures so that patients seeking to make a claim need prove only that the damage is related to the trial and occurred because of it, not that a particular individual or individuals had been at fault. No fault, said Ruth Ladenstein, reflecting feeling at the workshop, provides more predictable care and support to patients, more consistent coverage of all injured people, is more efficient in terms of cost, supports risk management by encouraging professionals to learn from their mistakes (rather than feel penalised), and encourages more complete reporting of adverse events and outcomes.

Such a scheme can be based on the concept of “avoidability” (whether or not an injury would have been prevented by best practice) rather than on the concept of “negligence”. It delivers benefits all round, to patients, to clinical science, and through them to society as a whole. This, said Ruth Ladenstein, is why its funding should be a societal responsibility, rather than one that falls on the trial sponsor.

4.5. Europe needs harmonisation

The indemnification system should be harmonised across Europe. This aim may be too ambitious. It was not evident to anyone – academics and insurers alike – that the Council’s proposed amendments introduced any harmonisation in insurance requirements beyond stating that insurance should exist. This is a major concern.

4.6. Guidelines will be needed

The draft Regulation calls for a national indemnification with no fee where the trial is not intended to lead to a request for marketing authorisation for a medicinal product. So far, so simple (and to the academic world, so necessary and acceptable). Where the trial does aim for a marketing authorisation, the draft calls for insurance to be on a not-for-profit basis, taking into account the risk of the trial, the potential damage, and the likelihood of damage. These concepts are far from simple.

It is certainly not clear how not-for profit might be defined in practice, nor how traditional insurance companies might appreciate working on a not-for-profit basis. Further, as Katelijne De Nys from UZ Leuven, Belgium, made clear in her presentation, risk is a complex issue. There are many types of trials – from purely observational trials (some countries require insurance for these, others not) to ones involving surgical interventions. Some trials enlist healthy volunteers, others terminally ill patients. To cope with this complexity she suggested risk-based monitoring, based on algorithms or questionnaires. Such risk categorisation performed by sponsors and assessed by ethics committees and competent authorities during the study approval procedure could also be the basis for definition of the required indemnity coverage and related insurance fee. But first of all guidelines are required to enable a common approach to risk assessment in European clinical studies.

Much of the workshop was spent clarifying the background behind concerns over indemnity insurance. Those considerations are presented in greater detail below.
5. Background 1: Academic-initiated innovation is suffering

If the aim of the Clinical Trials Directive of 2001 was to make Europe a more attractive place in which to perform clinical trials – and through that more attractive as a research region for the pharmaceutical industry – then as far as academic research is concerned has not been an obvious success since it entered into force in 2004.

The first consequence of the Directive, as Ruth Ladenstein explained, was a slump of 25 per cent in the number of clinical trials, particularly affecting multinational clinical trials. In the UK, the number of academic trials fell by half. Since then some of the ground has been made up, but it is still difficult, time-consuming and costly to mount a clinical trial in more than one country.

That matters because Europe needs objective, neutral research, particularly on optimising treatments for health, safety, efficacy and cost. There is a public responsibility to enable such research to be carried out independently of industry.

It also matters because in many conditions individual Member States will not have sufficient patients to base a clinical trial within just one country. So if Europe is to establish a level playing field where all Member States can, in practice, have the same opportunities for their populations to take part in clinical development, it cannot do it without easing the path for multinational trials. The workshop heard, for example, from Anastassia Negrouk how for many years exorbitant insurance costs in the Czech Republic had excluded Czech patients from multicentre trials for rare cancers.

And if Europe will not do these trials, there are large populations outside Europe where it can seem much cheaper to do clinical research. Such a clinical research drain impacts adversely on other clinical research investment in Europe and in the long term erodes the Union’s competitive advantages in this key area.

Of course, a number of factors have interacted to create an unattractive landscape for academic clinical research in Europe. But undoubtedly one of the key issues is the cost of insurance. This varies hugely – by orders of magnitude – according to which Member State, and which condition (see Background 2 for detailed examples).

The insurers present disputed the idea that there was market failure. Burkhardt Swik argued strongly that insurance schemes worked well, that national indemnity mechanisms would lead to taxpayers subsidising industry trials and the loss of the insurers’ core competencies of risk assessment and efficient claims handling. Valérie Mot, from Belgian insurer Mot-Dehon & Partners, said that state enterprises are always less efficient, more costly and less innovative than private solutions. But while discussion was cordial, it is fair to say that the academic community represented at the workshop was unconvinced by such arguments – particularly in the light of the presentations showing the high cost and variability of insurance around Europe and the difficulties in finding appropriate insurance policies for trials involving different types of intervention.

6. Background 2: The insurance market is failing academic clinical research in Europe

The workshop heard compelling evidence from Germany, Denmark, Sweden, Spain, the UK, and other countries, of the extent of this variation and its impact on the costs of running a clinical trial. These can vary from €24 per participant in an academic trial (a flat rate) in Sweden to €710 per patient in Finland in a neuroblastoma trial for a drug in early development.

In one international trial comparing treatments for children and adolescents with acute lymphoblastic leukaemia, insurance – for the same trial and the same protocols – cost €11 per patient in the Czech Republic and €221 per patient in Germany. Burkhardt Swik, of German Pharmapool, explained that German law requires insurance to cover all events in a trial, not just proven negligence, and suggested that this adds to insurance costs.
Insa Bruns from the Central Office of the KKS-Network, Germany’s paediatric cancer network, went through a series of astonishing cost burdens, in particular for in Germany so-called “Category C” trials, considered to be of high risk. These showed not only high costs but huge variability. Different trials with the same study medication, the same indication, the same patient population, etc., had insurance costs varying from €82 per patient to €473 per patient.

Worse, the cost of insurance in countries such as Germany appears to have skyrocketed since 2004. So insurance costs were €480 per patient in a stem cell transplantation trial in 2013, while the same trial costed €35 per patient in 2005. On top of this, German academic sponsors have to pay insurance for all patients screened for possible trial inclusion (and at that point not yet exposed to any treatment), whether or not they are then actually included in the trial.

The result: graphics showing the distribution of insurance costs in Germany resemble the Swiss Alps rather than the “level playing field” that is so generally desired in Europe.

But where national schemes have been implemented, costs are dramatically lower. Sweden, referenced above, has both state coverage for academic institutions and an industry-funded scheme. Denmark has a state compensation scheme that covers all trials, commercial and non-commercial.

An interesting observation on the possible influence of state mechanisms on the monopoly position of insurers came from Jean-Paul Deslypere of Aesculap CRO, Singapore. When that country’s only two insurance companies increased their rates by many times, making investigator-initiated trials unaffordable, the government stepped in, setting aside money for a compensation fund. “Then the insurance companies were much more reasonable,” he said.

7. Background 3: Patients are not clear about what will be indemnified, by whom, and how

The whole idea of indemnity insurance is that the patient will be compensated for any harm caused by the trial, over and above what their condition and its standard treatment might cause. For this to work, it has to be clear what will be indemnified, by whom, and how the patient might seek indemnification.

Report after report at the meeting demonstrated that there is no harmonisation across Europe. Apart from the nationally centralised mechanisms such as exist in Denmark and Sweden, mechanisms – and transparency – tend to vary. The implications of this for the process of informed consent are seriously troubling.

Nor is it clear across Europe what needs to be proved to obtain indemnification. “No fault” schemes are the norm in Germany, France, Belgium and Spain, according to one academic survey. The position in Italy and the Netherlands is not clear, and in the UK can vary according to whether the trial is Phase 1 or later. In Spain, “no fault” operates during the trial and in the first year after the trial ends, explained Cristina Avendaño Solá of the Hospital Universitario Puerta de Hierro, Spain. So in this, too, European patients cannot expect equal treatment.

“No fault” was backed by Karin Meissner, Global Head of Group Insurance at F. Hoffman-La Roche, Switzerland. She called for a Europe-wide right for patients to claim against an insurance company rather than have to claim against a hospital or medical professional.

It is not at all clear what injuries might be excluded from compensation. Věra Strnadová, from the Forum of Czech Ethics Committees, recounted the tale of one multinational trial she had seen. It listed 200 adverse drug reactions that were excluded from insurance, ranging from nausea to hepatitis and renal failure. “Is such an insurance meaningful?” she asked. “Not for patients, I think.” Cristina Avendaño Solá reported on a big debate currently ongoing in Spain on whether exclusions should be allowed, and if so under what conditions. The debate was triggered after a patient who suffered heart muscle damage had their claim rejected because the condition was listed as a possible adverse reaction in the consent form.
It's clearly a complex issue. Ruth Ladenstein suggested that indemnification should bear some relation to the context: if you get treatment for cancer and your hair falls out, that might be seen as normal; if you take a headache pill and the same thing happens, you might reasonably expect some kind of compensation. Either way, as Burkhardt Swik said, it cannot be right to diminish coverage with a list of 200 side effects, though clearly minor side effects should be excluded from coverage. But, he said, the rationale of compensation must be clear, as well as the degree of evidence required.

One of the potential advantages of a "no fault" approach is that patients can get compensation swiftly while insurers and sponsors work out – in the background – where responsibility lies. During the workshop the analogy was frequently drawn with car insurance, where most payments for damage come before insurers have allocated responsibility between the two drivers, for example.

A final comment, from Anastassia Negrouk of the EORTC: “For many of my 13 years at the EORTC I’ve been trying to understand these insurance issues. It's impossible. Even for me, working here for so many years, it is still a huge challenge. I wonder what patients make of it all.”

8. Background 4: Pan-European insurance is a long way off

The ideal – and an ideal for industry delegates at the workshop as well as academic delegates – would be "one policy for all Europe", as Karin Meissner put it. That ideal seems a distant dream. It seems that the closest is the kind of arrangement, outlined by Ruth Ladenstein, whereby a large insurance company will arrange for identical cover in each country taking part in a trial. “So we know that all patients are covered to the same extent,” she said, but adding, “But we pay differently per country.”

This seems to be a deep-seated problem, with no easy solutions. Mark Clements, from the UK’s University Mutual Association, who has a background in global broking, explained that even when you issue cover for the whole of Europe, most insurers would want you to have a local policy “because of the language issues and the comfort people have with the local legal system”.

Although UK coverage can be organised “with relatively modest quotes”, he said, as soon as you get to international trials you find few insurance companies interested in covering the risk. Burkhardt Swik agreed. The problem is that there are just 5,000 clinical trials in Europe each year, spread around 27 countries: “not a lot per country,” he said. Germany, he reckoned, had just 10 to 15 companies interested in insuring trials. Noting that the draft Regulation does not seek to harmonise insurance, he said that it should concentrate on harmonising insurance requirements rather than insurance systems.

For the academics, the point is not harmonising insurance, but controlling costs and ensuring equitable treatment for all patients in Europe, irrespective of which country they live in.

9. Background 5: Lessons from the pharmaceutical industry

Large pharmaceutical companies obviously have a great deal of experience with insurance issues in many countries. So it was interesting to hear how they operate.

First, cost does not appear to be a great consideration, even though – as the European Commission has reported – insurance fees for industry sponsors have increased by 800 per cent since 2001. But there are no free lunches. “I’m pretty sure that sooner or later it gets into the cost of drugs,” said Anastassia Negrouk. Perhaps the larger a company is, the easier it is to work around the problem of insurance. As Karin Meissner from Roche explained, the Swiss company simply confirms with the relevant authorities that it has the resources to cover any claims (effectively covering its own insurance).

Second, reputation matters. Eric Fumière, Corporate Insurance Director at UCB, Belgium, said the company has an interest in dealing with claims swiftly, before any possible adverse coverage in the media. It passes any claims from patients straight to a committee of specialists. If the committee thinks compensation is justified, the company indemnifies the patient directly within weeks. “Then we start talking to the insurance company to...
see whether they will indemnify us,” he said, adding, “I understand it is more difficult for academic institutions to do this.” The essence of this arrangement – that to be compensated patients should have only to show damage resulting from the trial, not prove who caused it – is precisely what academics, patient organisations and ethics committees would like to see applied throughout Europe.

• This report was produced by the rapporteur, Peter Wrobel, of Clarity in Science Communication, UK, who takes full responsibility for this summary of the messages and spirit of the workshop.

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