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International Workshop

The Need for Harmonisation of Clinical Trials Insurance in Europe

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Introduction

The European Clinical Trials Directive 2001/20/EC set out to harmonise clinical trials regulations across Europe, with the aim of simplifying and speeding up the process of establishing multinational clinical studies.

In the event, it is acknowledged the Directive has had the opposite effect. The way in which it was transposed into national laws has led to great variation in the rules relating to the setting up and running trials across the European Union.

Clinical trials insurance is one element that particularly highlights this variation. The requirement in the Directive that, “provision has been made for the insurance or indemnity to cover the liability of the investigator and sponsor,” has been interpreted differently in different member states, meaning that separate insurance is needed from country to country. Insuring international trials is not only more costly, it is also more bureaucratic and more complex.

In addition, this patchwork of regulation results in the ethically dubious position that patients taking part in the same trial in different countries, have different levels of insurance protection.

These issues present particular obstacles for the setting up of international investigator-driven clinical trials.

The European Commission has acknowledged these - and other shortcomings - of the way in which the Clinical Trials Directive is operating, and is currently reviewing the situation and investigating possible reforms.

It is against this background that EORTC brought together 51 representatives from insurance companies, academic sponsors, ethics committees, patients’ groups, regulators and the pharmaceutical and biotech industries, to discuss their experience and look at ways to improve the situation.

Françoise Meunier, Director General of EORTC welcomed delegates with an optimistic statement, noting there has already been much positive feedback from the Commission as it reviews the evidence and considers changes to simplify and streamline the Directive. “I have great hope that we will succeed,” she told delegates.

Now, there is a need for, “Practical suggestions on how to solve the problem of insurance for international clinical trials.” Meunier noted that EORTC has keen insights into the difficulties that the Directive presents for international clinical trials in Europe.

Academic trials account for 36 per cent of all European trials, and EORTC recruits 6,000 patients in its trials each year. But, noted Meunier, while before the Directive came into force, EORTC used to open 20 studies per year, the increase in complexity means that so

far in 2010 it has started only two. “We have to do something in Europe to maintain our ability to do international trials,” she said.

One possibility would be to establish an independent clinical trials fund for conducting investigator-driven studies across the European Union, both in cancer and other indications. This could perhaps be modelled on the recently created European Research Council, which was set up to fund excellent basic research.

Session I: Setting the current European scene

The Current European Landscape from the Academic Perspective

Denis Lacombe, Scientific Director of EORTC, elaborated on the current European landscape, as seen from EORTC’s perspective. Increasing knowledge of cell biology is providing insights that enable cancers that were previously considered to be a single type, such as breast cancer, to be broken down into sub categories. While this creates the promised of more specific, targeted treatments, it also generates a need for more international trials in order to recruit sufficient patients.

At the same time, rare types of tumours remain poorly addressed. International trials are needed to pool expertise and set up studies that are sufficiently powered.

Lacombe noted that the shift in which every cancer, in effect, becomes rare (or at least, less common), lies at the heart of changes the US National Cancer Institute is making to the way it runs clinical trials.

Reforming the rules around insuring clinical trials demands particular attention, because it leads to substantial delays, and increases complexity and costs. Over and above this, there is a high level of variability between countries. In 1995 EORTC covered all its trials with three annual insurance policies, one covering France, one Germany, the other the Rest of the World. Now it has six annual policies and 129 individual policies, a huge jump in terms of administrative overhead.

Furthermore, said Lacombe, the ethics committees which are charged with ensuring appropriate policies are in place, do not understand annual policies covering trials for their entire duration. “If it says 2010, they question if it will be valid in 2016: we explain and explain, but it is difficult to get the message across.”

The growing importance of biobanked samples as a resource for clinical research, is also compromised by the Clinical Trials Directive. In a recent case, investigators wanted to do research on material stored as part of an ongoing trial. In Austria, insurance for the original trial was still valid, but EORTC was requested to take out further insurance.

“It’s not clear why: there was no new treatment and no additional risk,” Lacombe said. Similar examples have occurred in setting up clinical trials across Europe. Insurance for follow-up is a major problem for cancer trials. In indications such as hypertension, sepsis and so on, the treatment either works or not and trials close quickly. In cancer there is long-term follow-up, often lasting many years, and insurance legislation needs to reflect the difference between treatment and follow-up.

“There is no supranational body to help, so we are stuck with national bodies,” said Lacombe, adding, “There is also a major lack of understanding by ethics committees.”

Despite the current gloomy picture, Lacombe concluded by saying, “There is plenty of hope things are moving in the right direction: we need to work with policy-makers and regulators.”

The View from the Industry

Genevieve Decoster of IT and GCP Consulting, an industry expert on clinical trials insurance, said that while the Clinical Trial Directive’s aim of ensuring trials are properly insured is good, the way it is implemented is not working. The problems are multiple:

- the level of coverage required is not defined by many member states
- some member states require the insurance provider to be a local company
- Ethics committees have different approaches and requirements from country to country
- there are very few companies which insure clinical trials
- the level of risk of individual trials is not properly evaluated
- insurance contracts may be inadequate
- in multinational studies, different countries have different requirements
- there is likely to be insufficient coverage for trials that involve more than one drug

The level of coverage demanded for each patient varies from Euro 45,000 in Greece to Euro 760,000 in France. “These amounts are changing all the time,” Decoster said. Beyond the inequity in the amounts patients in different countries might be able to claim, there are also differences in the type of cover. The UK, for example, does not have a no fault scheme. In the case of the disastrous Tegenero TGN1412 trial, in which six healthy volunteers suffered life-threatening cytokine storms, no fault was ascribed to anyone involved in running the trial, leaving victims with no one against whom to make a claim.

Decoster cited another example that had come to her attention three weeks earlier in which insurance was taken out in New York for a trial in Rumania. “That would leave patients having to go to the US to make a case,” she said.

Other inadequacies include policies covering only drug-related injuries and not trial-related injuries, and contracts that cover only what a subject’s own health insurance does not.

Then there are differences about what must be covered, so in Belgium for example, a trial of a medical device that carried no risk since it involved non-invasive imaging – was required to be insured, while in Germany it did not require cover.

In France meanwhile, the same level of coverage is required for Phase I trials with high risk, as for Phase III studies, when all safety issues are ironed out and the risk is low.

Decoster cautioned however, that while it might be good to have a single rule for insurance cover to speed up patient recruitment in global clinical trials, it is very difficult to properly evaluate risk in multi-drug trials. “Patients need to be very careful, because they would need to establish a causal relationship between one drug and the harm they have suffered,” Decoster said.

“An urgent need exists to harmonise the laws and regulations for clinical trial insurance, to better protect subjects, investigators, sponsors and all the other stakeholders,” Decoster concluded.

The Patients’ Perspective

Jan Geissler is Director of the European Cancer Patient Coalition, a body representing 300 cancer patients groups in 42 countries, which he set up to influence European health and research organisations, give patients a voice, and reduce disparity across Europe. And yet, Geissler admitted that until he began to prepare his talk for the workshop, he had little idea about the severe impact insurance is having on the conduct of clinical trials.

However, he is very clear about one thing. “We need safe and effective trials, and we need them in Europe,” he said. So it is an unfortunate paradox that the Clinical Trials Directive, put in place to protect patients and improve treatments, has had the unfortunate effect of increasing insurance premiums and reducing the number of trials.

While the Tegenero case is a searing example of what can happen when a trial goes wrong, it has to be seen in the context of around 5,000 new trials starting each year in the EU. “So if this is the only case [of a trial going wrong] to have become public, is this because of a lack of transparency about other mishaps, or a lack of accidents?” Geissler asked.

The answer, according to a straw poll of patient advocates carried out by Geissler is that, “None could [tell me] of a single trial insurance case.” One German study has shown the probability of health damage in trials is low, at 0.5 per cent, and treating this damage is mostly covered by the existing liability damage of doctors and hospitals. This raises the question, “What is it we patients are insured against?” Geissler said.

Furthermore, if the excessive demands of providing insurance cover means there are fewer trials, then the Clinical Trials Directive raises a new risk for patients: that they get no treatment.

The motto of the European Cancer Patient Coalition is “Nothing About Us – Without Us. But in the case of clinical trials insurance there is a complete lack of transparency. “We are being told ‘You are safe’ but we can’t find out what we are insured against,” said Geissler.

Research is needed to determine the real number of incidents that fall outside the range of normal events that can be expected in cancer trials, to see if these trials are over-insured, Geissler concluded.

The European Union and Clinical Trials Liability and Insurance

Stefaan Callens, Professor of Law at KU Leuven and a lawyer at the Brussels Bar, gave an overview of the different legal approaches member states have taken to the Clinical Trials Directive, noting some have a very broad view of what needs to be covered by liability rules, going so far as to demand coverage of research on an existing body of data.

In fact, there are only three articles referring to liability in the Directive as it stands at present, noted Callens. Article 3 makes insurance and indemnity of the investigator and sponsor a requirement, while Article 6 gives responsibility for ensuring this is the case to ethics committees. Article 19 meanwhile, requires the sponsor to be based in the EU.

“Ethics committees have a severe task to fulfil,” Callens said. “They are liable if they do not look at the policy in enough detail.” And it may not be enough merely to inspect the policy; ethics committees need also to consider reinsurance. “This is especially the case in large international trials,” said Callens.

While some member states have no fault liability, allowing a patient to sue without proving fault, this still takes a long time. “As soon as someone is damaged they should get compensation,” Callens said. Such a system is in place in France and was recently voted for in Belgium. Elsewhere, as in the UK, it is necessary to prove fault.

Callens emphasised that the issue of varying liability rules is being thrown into sharp relief by the Draft Directive on Patient Mobility, which will allow people to receive treatment in any member state. This highlights the need for similar liability rules to ensure patients are not disadvantaged if they are treated in certain countries, said Callens

This points to another area where the rules vary from country to country, which is where to sue the insurer, if that becomes necessary. “This could be where the patient lives, or where the trial takes place, so that is another reason why [standardised] EU rules are needed,” said Callens.

These disparities are prompting discussions on the need for a pool to pay for damage caused in trials. One factor that should be borne in mind is considering how much coverage would be needed is the movement to class actions in Europe, such as those that

are taken out in the US and Canada. However, reaching consensus at the European level on the development of such a pool might be challenging.

While there is now a powerful movement for harmonisation of rules, Callens noted that EU Competition rules present a possible barrier. Insuring clinical trials is a specialist field in which very few companies are active. Any agreement over pricing policies could be construed as a cartel.

In summary, Callens said, insurance is a stark example of the different ways in which member states have implemented the Clinical Trials Directive in their national statutes. There is now a chorus of voices calling for harmonisation, and the promise of political action. The Belgian Government has said it wants to take measures to stimulate pharmaceutical innovation as part of its current EU Presidency and the European Medicines Agency has similar ambitions in its Roadmap 2015 strategy.

Clinical Trials Insurance – National Case Studies

Different national positions on clinical trials insurance were then examined in more depth, in four presentations covering France, Italy, the UK and Germany

In France, the Huriet-Sérusclat Act of 1988 created specific civil liability, guaranteeing indemnification of study participants. “Only the sponsors are liable, therefore if injured sue the sponsor,” said **Thomas Roche, Avocat, Roche and Associates**.

While there is a presumption of fault by a sponsor, the victim needs to provide evidence of the injury suffered and show there is a causal link between the injury and participation in the study. There is a time limit of ten years on making a claim, apart from exceptional cases where there is an accusation of violence or torture.

France has a single body, the Tribunal de Grande Instance, which is solely responsible for dealing with clinical trials insurance claims. In contesting a claim, a sponsor needs to show there was no fault committed before, during or after a trial by the sponsor, the investigators, or any other stakeholder. In the event that a sponsor is found not to be liable France has a public fund, Office National d’indemnification des Accidents Medicaux, that pays compensation to victims.

If the sponsor is found liable, victims are paid through the civil liability cover. However, it is then open to the sponsor to take action against CROs, investigators, or other stakeholders. For this reason, all those involved in clinical trials need separate liability insurance.

Sponsors also need to be careful about the length of coverage of any policy, since they are liable for up to ten years after the research ends, which is defined as the date when the last patient in the trial receives the final treatment.

“The purpose of the law is to protect the patient. If there is an injury, the insurer [of the sponsor] has to pay, but afterwards has recourse to find fault with other stakeholders,” Roche concluded.

In Italy, a new law on minimum requirements for insurance in clinical trials came into effect in March 2010, replacing the existing legislation that was failing to protect patients, with variability of cover from one part of the country to another. **Silvio Garattini of the Mario Negri Instituto di Ricerche Farmacologiche** outlined the new law, which specifies there must be a specific insurance certificate for each study. These policies must provide cover for all damages, including any accidental damage.

The damage can have occurred up to two years after a trial, and claims can be made up to three years the trial. However, the length of cover may be extended, for example in oncology trials, paediatric studies and gene therapy trials, where it is accepted that it may take more time for any damage to come to light.

Patients must be informed about the level and limits of liability when giving consent to take part in a trial.

Garattini noted there are significant consequences of the new law for academic not-for-profit studies. Most hospitals are defining not-for-profit in a more restricted way than before, to reduce the number of studies that are eligible for support from local funds. In some cases, only a fixed number of studies can get coverage from local insurance, for example, there may be a limit of ten trials per year, to limit the amount hospitals have to pay for their insurance cover. “This is leading to competition between studies [within one institution] to get coverage,” Garattini said.

In the case of multi-centre independent studies that are coordinated by independent institutions, the sponsor has to provide the insurance at all sites.

Overall, the legal changes in Italy are having a positive effect on patients’ safety and rights. But, said Garattini, both old and new laws are being applied too rigidly to Phase IV studies of marketed drugs. “It’s not rational; most Phase IV drugs are part of a current medical prescription.”

Time is needed before the new law is bedded down and the overall effect becomes evident, but Garattini says he is concerned. “It has created an imbalance between the industry and academic trials, and there is a possibility it will kill off not-for-profit research.

Finally, Garattini proposed a three tier risk classification of clinical trials.

Category 1 – high risk – Trials on non-EU registered products, with an extra risk assessment for first in man, or for novel constructs, for example, cell therapies

Category 2 – medium risk – Trials on marketed products in new indications

Category 3 – low risk – Trials on marketed products in licensed applications.

Brendan Lavery, who is responsible for oversight of the governance of trials at Birmingham University, began by noting there is no specific UK legislation defining the insurance requirements for a clinical trial.

However, ethics committees are required to consider both indemnity – that is a promise to compensate a claim – and to ensure that the insurance will enable a sponsor to meet the indemnity. In the case of commercial trials the National Health Service (NHS) Trust where the study takes place has to make sure indemnity is in place.

The UK does have a compensation scheme, the Clinical Negligence System for Trusts. In 2010/2011 this expects to pay out GBP 778 million, [to cover claims in England, not the UK as a whole]. However, most claims are for negligence in obstetrics, and it is not clear how many, if any, claims are for damage caused in clinical trials.

Birmingham University acts as sponsor of non-commercial trials. In that role it must provide indemnity for the design and management of a trial, with the NHS providing indemnity for the conduct of a trial. Things become more complicated when the university acts as sponsor of a trial with international sites. “We need to be well up on regulations in other countries; the legal requirements often change and insurance often has to be taken out with an insurer based in the host country,” Lavery said.

While Birmingham University sponsors trials outside the UK currently, insurance costs are rising and “the model is not sustainable,” Lavery said.

Overall, Lavery said, the current legal situation raises many questions for UK academic sponsors, including what insurance is needed; is cover needed for negligence (given the existence of the NHS compensation fund); who is really responsible - and therefore liable - for trial design given there are often multiple authors; can NHS sponsors take out insurance; can academic sponsors in the UK share costs with counterparts elsewhere.

By contrast, in Germany, sponsors are required by the German Drug Law (AMG) and the Medical Device Law (MPG) to provide no fault insurance coverage for all subjects. While coverage must extend to Euro 500,000 per patient, the compensation is for material loss only, there is no compensation for pain or suffering. “This is despite the fact that patients often believe this is what they are covered for,” said **Inga Rossion of SDGC, the Study Centre of the German Surgical Society, in Heidelberg.**

One problem sponsors encounter in Germany is that there are few insurance companies providing cover for clinical trials. This means there is a lack of competition and can make it difficult to get cover. Since a framework agreement on contracts was disbanded in 2004, the cost of insurance has risen.

In 2005, new risk categories were introduced that set a fixed price per patient for low risk trials and intermediate risk trials. However, in higher risks trials, a category that encompasses 80 per cent of trials in oncology, there is an individual calculation for each trial.

Rossion described examples where this is leading the level of cover to be inappropriate. For example, in a paediatric trial of children being treated for brain tumours, the premium was Euro 500 per patient, leading to a total insurance bill of Euro 90,000. However, the risk calculation was based on the high risk attaching to brain surgery. “But if a child not in the trial had a brain tumour, an operation is needed,” Rossion noted.

The response to this was for the German Cancer Society to set up an annual contract for oncology trials with a range of premiums that better reflect the risk. Now, said Rossion, premiums may be affordable, but there is a bottleneck because trials that have already been reviewed once, must be reviewed again to assess risk.

Another example of the inflexibility of the German system is provided by the Crash 2 trial, which investigated the use of an antifibrinolytic agent in trauma patients with significant haemorrhage. This trial was sponsored by the London School of Hygiene and Tropical Medicine, which had indemnity insurance. However, this did not satisfy the German law. It proved impossible to find a German insurer at an affordable price, and as a result there were no German sites in the trial, which included 20,211 patients in 274 centres in 40 countries. The study concluded that administering a clotting agent to trauma victims with severe bleeding would save 100,000 lives a year globally.

In a response to this, German universities have made a similar move to the German Cancer Society and established yearly insurance contracts. The system involves risk assessments, and Rossion says there is a lack of clarity on this procedure. “You never know in advance how risk will be assessed – it’s like a black box,” she said.

According to Rossion, the example of Germany highlights the need for EU-wide agreement on criteria for risk assessment. Multinational contracts should be available and there should be a choice of insurance company. These and other requirements were set out in the recommendations, drawn up after the first meeting of the Vienna Initiative to Save European Academic Research (VISEAR) in May 2005, but as yet there has been no action.

Work is in hand to improve the German system for investigator initiated trials. “A lot has happened, but so far there are no results,” Rossion said. A working group made recommendations for an overhaul of the system but failed to agree new risk categories. The matter has been passed over to the German Research Council. There is political pressure for action, but, “this leaves a lot of possibilities not to act,” said Rossion.

Session II: Bottlenecks that need to be addressed

Ethics Committees

Christiane Druml of the Ethics Committee of the Medical University of Vienna, highlighted that at a time when the number of trials carried out worldwide is going up, the number carried out in Europe has remained constant. This is despite the fact that the Clinical Trials directive was intended to boost the number of studies taking place in Europe.

As discussed above, many of the changes that are needed were highlighted in the VISEAR recommendations. “One still sees the same problems five years later,” Druml said. There is still a lack of an EU-wide agreement on the criteria for study risk assessment. The principle of strict liability is applied whether a trial involves aspirin or a new cytotoxic, and regardless of whether the patient gets an active drug.

At its most extreme, this leads to insurance cover being required for studies that do not involve any treatment. As an example, Druml cited a study evaluating nutrition in intensive care units. “When Belgium asked for insurance cover I thought there must be a misunderstanding: why would it be necessary? Investigators were only writing down what nutrition was given.”

Druml also drew attention to the need for ethics committees to have formal training, and for the creation of EU standards for how ethics committees should operate. In addition, she believes ethics committees should be informed of any claims. “Ethics committees decide on insurance certificates, we should get this feedback,” Druml said.

“There is a need to figure out the particularities among member states and move to the creation of a Single European Union Clinical Research Area,” Druml concluded.

Risk Assessment Parameters: the risk-based approach

“It should all have been so different: the 2001 Clinical Trials Directive was meant to be about harmonisation and getting [insurance of clinical trials] to work efficiently across borders,” said **Chris Tait, European Life Science Manager, Chubb Insurance Company of Europe SE**. “It has not worked out like that.”

There remains much variation in how clinical trials are insured in Europe. Does there need to be a general insurance policy or a policy for each trial? Does the policy need to be taken out with a local insurance company? How much cover must the policy provide? What should the insurance certificate look like?

There should be a distinction between clinical trials involving patients with life threatening disease and trials involving healthy volunteers as study participants. The level of risk is not comparable. Specific risk assessments approach should therefore be considered.

“How do insurers deal with this? How do they know what to do?” asked Tait. The overhead of dealing with all this variation is often compounded because the last thing anyone thinks of when they are setting up a study is the insurance policy.

While companies that specialise in insuring clinical trials may have their own – consistent - approach to assessing risk, there are always variables that must be accommodated, such as continual changes in the fine details of a trial, for example, an alteration to patient numbers, or a change in the investigators. Given a requirement to provide ethics committees with a specific certificate, insurance companies are often left chasing moving targets.

In terms of the clinical trials landscape in Europe as a whole, this means there are often delays in finalising the insurance certificate. Ethics committees are not insurance experts and yet are placed in the invidious position of having to ensure the insurance is appropriate and sufficient. The difficulties of navigating the widely varying requirements means there is now a shortage of companies providing clinical trials insurance in Europe. In the end, Tait said, “Insurance becomes a negative factor when deciding whether to stage trials in Europe, or go elsewhere.”

Insurers are responding by the use of more sophisticated systems for issuing certificates that are able to assimilate any changes very quickly, and are continually reviewing the amount of coverage available for any one clinical trial.

Reinsurance - A Reinsurer’s approach to clinical trials insurance

Insurance is not a tangible commodity, and so it is very important to understand what is covered and what is not. “You have to see the risks that are involved,” said **Burkhardt Swik, who manages the German Probandencover (Pharmapool) at the reinsurance company Munich RE**. Insurance of clinical trials is perceived to be expensive because there are not that many claims. “Instead you should see it from the value of having cover in place,” Swik said.

The Probandenpool has an 80 per cent share of the market in Germany, dealing with 1,000 submissions to reinsure clinical trials each year. “We charge Euro 4 million for all the coverage we give, which is not a lot,” said Swik. Munich RE is able to provide cover at the low rate because it has very efficient internal administration systems, processing 95 per cent of quotes within 24 hours.

Insurance only comes into play when something goes wrong in a clinical trial. In one such example, in the US, subjects in a melanoma cancer vaccine trial at the University of Oklahoma Health Sciences Center (OHSC) filed a suit against individual members of the Institutional Review Board after the trial was stopped following an independent audit. Amongst other concerns, this raised the issue of whether individuals were covered by the OHSC’s institutional liability insurance.

Change should be built on the central principle that clinical trial regulation is there for the benefit of the patient or subject of a trial. There should be no need to prove liability. Instead, there should be comprehensive protection with specific cover for specific injuries, as in motor insurance.

“Patients should only need to show a causal link between being in a trial and the damage they sustained,” Swik, noting even that could be difficult to do.

“The fact is that patients want compensation. They don’t want to find out who did something wrong, they want to get the money quickly,” he concluded.

Round Table: How to improve the insurance framework for international clinical research in Europe

With discussions on reforms to the Directive now in progress, EORTC brought together experts from across Europe to discuss the need for changes to liability insurance for clinical trials, an area that has been greatly complicated as requirements related to the Directive, and where there is urgent need for reform.

Following a series of presentations, setting the scene and highlighting the bottlenecks in the system of insuring clinical trials currently, (covered in the main report) a roundtable discussion followed, to come up with practical proposals and action points.

The Guiding Principle

In the face of widely varying national regulations and mainly requirements by Ethics committee, it was agreed there should be one guiding principle for reform: that the needs of subjects and patients are paramount. As Jan Geissler of the European Patient Coalition put it, “Nothing about us without us.”

The question then becomes: What should the European Clinical Trial insurance scene look like in an ideal world, with the perspective of the patient in mind; if a patient experiences harm, what recourse should he or she have?

The way to approach the solution is to:

- put the patient first
- protect the patient in the easiest way
- do this in a harmonised way across Europe

The delegates approached this from two angles, considering how they and their peers could apply their own knowledge, expertise and contacts to start to get change and improvements from the bottom up, working with current legislation. Second, they proposed legislative changes that are needed to improve the Directive and national laws.

Action Points and Recommendations

1. Training for Ethics Committees

It is widely considered that risk aversion on the part of Ethics Committees is the source of many of the difficulties that arise currently. In their assessment of a trial Committees are required to ensure appropriate insurance is in place. However, their members are not experts in insurance and indemnity. This is leading them to call for broader insurance coverage than is necessary. Guidance and training on insurance risks for members of Committees would help them overcome this understandable conservatism.

2. Information and Education for patients

Patients and patient advocacy groups must be given full information about treatments. They need an explanation of what will happen if something goes wrong, an understanding of how often it does, and information on who to contact if they have a problem. This would prevent misplaced anxiety, improve patient recruitment, and make it possible to demonstrate to Ethics Committees that patients understand the risks.

3. Consider changes to informed consent documents

Patients have to sign these to say they understand the treatment and agree to receive it. But because consent forms are written to protect all stakeholders, it can be hard for patients to read and understand these documents.

4. European Commission research to find out how often claims occur.

There is a general feeling that clinical trials are over-insured, but there is no data on the number of claims to confirm this. As Silvio Garattini of Institute Mario Negri, Italy put it, “We need to know the size of the problem.” He, for one, believes the number of cases where claims are made to be very few. “In Italy we couldn’t find one,” he told delegates.

It was suggested there could be an “honesty call” asking insurers how much they have paid out, to make it possible to model likely losses.

Apart from making it possible to estimate the size of the risk, an understanding of the claims that have been made would inform moves to have certain types of trial excluded from the scope of the indemnity requirement in the Clinical Trials Directive.

5. Create an international framework to streamline the claims process

Some countries have no-fault compensation systems, which mean it is not necessary to prove liability. Maybe this should be a general rule for clinical trials insurance policies. The aim should be three-fold: to harmonise, streamline and simplify

6. Establish a system for rehabilitation in the event of injury in an international clinical trial

This would have to dual benefit of ensuring a patient gets the best remedial treatment, and could reduce risk because it would reduce the size of any claim

8. Establish a central national body in each EU member state to provide insurance cover for all and deal with claims

This would be a single national point of call for patients to go for compensation. While each country would have its own body, they would operate according to the same rules in the case of international trials. Such bodies would assess damages and pay out on a no fault basis, solving the problem from the patient's perspective and then working out who was liable to pay any compensation. The model here is car insurance. The car gets fixed and back on the road and then the respective insurance companies decide on liability and who pays what.

Such a body would also address one of the key inequalities in the system as it stands, which is that patients in the same trial have different indemnity rights in different countries.

One suggestion was that this would cover academic trials only. Another suggestion was of a three tier system in which large pharmaceutical companies pay their own way, biotechs pool their risk and academic trials are covered by a public fund. Given the belief that there are not many claims, such a system would not be too expensive. It was suggested the pool could be modelled on Germany's Probandenpool, or on the system of shared risk that operates in Scandinavian countries. This option has to be carefully considered.

Although it was recognised that it may at times be difficult to make the distinction, it was proposed that such a body would deal with claims arising from international trials only, as is the case with the Scandinavian pool.

Such a pool would require some level of fine-tuned risk assessment to ensure the level of cover was appropriate, as described in point nine below.

It was acknowledged that this raises the question of whether compensation is provided from the public purse, or if insurance companies would still be involved. Similar changes in the rules in the Netherlands and France caused insurance companies to withdraw from the market. However, mutual organisations subsequently sprang up to fill the gap.

A working party in the UK examining the consequences of the Tegenero TGN1412 case has concluded it would be necessary to have third party indemnity for a publicly-funded compensation scheme. There is an important distinction to be made here however, between the Tegenero trial, where the subjects were healthy volunteers and the majority of cancer trials, in which patients are treated. It was suggested that there should be separate laws applying to these two categories of subject.

It was noted that ultimately confidence in setting up a pool comes down to having confidence in the likely amount of losses, underlining the need for claims data.

9. Reform the criteria for trials that require insurance

Different trials have different levels of risk. At present this is not reflected in the indemnity requirements of the Clinical Trials Directive. A first in human trial with a novel construct, versus a Phase IV comparing patients' reactions to marketed drugs that they are being treated with already, illustrates one set of extremes; a paediatric trial where any damage could last a lifetime, versus a trial in patients with advanced cancer and a low life expectancy, is another.

At the same time the increasing use of biobank resources such as blood samples, DNA or other tissues means that more research requires the approval of Ethics Committee, and is thus becoming subject to insurance requirements, even though no new treatment is involved.

If the criteria were to be changed, exclusions could then be agreed. It was noted that just one exclusion – of insuring patients in Phase IV trials would mean 50 per cent of academic trials no longer need insurance cover. While having no cover at all may not be appropriate, it should certainly be possible to reduce the level of cover for Phase IV trials

10. Harmonise liability across Europe

At present there are different levels and types of liability in place to protect study participants, and there is a need to harmonise the rules across Europe. A comparison would be the harmonised system for product liability introduced in 1985.

Given a harmonisation of liability, it would be easier to harmonise insurance cover.

11. Rethink Liability

Currently, in many EU countries liability insurance is taken out to cover the possibility that anyone does something wrong. In the tragic case of Tegenero's TGN1412 Phase I trial in which six subjects suffered life-threatening cytokine storms, the subsequent investigation found no evidence of malpractice. As a result, those affected have found it hard to get full compensation, because no one is liable.

This raises the question of whether this type of liability insurance is appropriate to protect subjects. Indeed, there is an argument that other stakeholders are overprotected and as a result patients are not properly protected.

It is also the case that while the Clinical Trials Directive says there has to be indemnity, it does not specify that this is provided via insurance.

12. Set an EU definition of risk and agree risk categories

Better risk assessment lies at the heart of solving the insurance problem. Such assessments need to be based on standard EU definitions of risk. At the same time a

harmonised approach to risk could form the basis for agreeing exclusions or for reducing the level of cover so that it is in line with the real level of risk, for example in Phase IV clinical trials, thus reducing the size of the overall problem.

However, it was accepted that perceptions of risk differ from country to country.

Given an EU definition of risk it becomes possible to agree risk categories. Delegates made the following suggestion:

- a. All trials before marketing authorisation
- b. All trials outside the label
- c. All trials within the label

It is recognised that there are different levels of risk in categories a and b, which would need to be assessed.

Conclusion

EORTC will set up a single working group, reflecting all stakeholders, to advise DG Health and Consumers as it mulls changes to the Clinical Trials Directive.

The group will formulate these recommendations and action points into a proposal. The group's deliberations will be guided by the requirement to put the patient first and make the coverage equivalent to the risk.

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