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The New European Regulation on Clinical Trials

My topic is the New European Regulation on Clinical Trials. I think this regulation is not only interesting for the twenty-eight member states that compose the European Union, but I truly believe that it is interesting for all of you, for the entire world, for two main reasons. First of all, it confirms a new model of policy for clinical trials. Secondly, it goes in totally different direction of the one that has been pursued for the majority of the countries. I was totally forgetting that I have here in my head.

I will start by going through very briefly the first European initiatives, mainly to point out that it is a coherent path that goes from the very beginning until today. Then, I will go to consider the proposal of the regulation. This is very important to understand: the proposal comes from the European Commission, and this proposal was made in 2012. This proposal was very controversial, especially in what concerns the ethical issues. Later, we have the regulation on clinical trials that was approved last April, so it is brand new; the regulation also addresses, of course, two main ethical issues the ethics committees in the informed consent.

Why? Because you could ask me, don't you go straight to the regulation and you start by talking about the proposal? The proposal was two years ago —yes, that's true—, but the proposal, which was very controversial —in my view— does reflect the real perspective, the real intention of the European Commission in what concerns clinical trials.

I don't think that it was surpassed, it remains, and it is persistent and if we have any doubts about that, by considering the whole path, since the very beginning until today, we will see there is a coherent project here. It really deserves attention the proposal of the Commission.

The first European initiative, there was one directive in 1965, a second one in 1975, these two directives were not really dedicated to clinical trials, but they did create a framework for clinical trials in Europe. Then, the directive of 2001, which is still enforced, was really

dedicated to clinical trials and it presented a very extensive and detailed ethical requirements.

We can say, in a very general way, that these three directives did draw a path, a very coherent one that became clear each step of the way. It's just like a project that unfolds. There are major orientations in these three directives. The first one is harmonization. If you read the directive of 2001, recital one, you see that the harmonization is quite clear there. Approximation of the laws of the member States are also there, uniform rules on the compilation of those years including their presentation. Harmonization is the word of order.

There is another main direction in these directives: centralization. Centralization, we read in a single opinion for each member State. You see, if we talk about centralization in Europe, this goes in a totally different direction of what we see in the other countries, because we are talking about one Institutional Review Board (IRB) in each country. We are talking about one single position, approval or refusal in each country.

What we saw in Europe until 2001, what we see now in the rest of the world is several IRBs, one IRB in each healthcare facility.

Ethically speaking, I would say that these first European initiatives do have very strong ethical concerns, specially the directive. I will point out some of them here: reinforce quality in safety, the ethical principles, protection of rights with risk assessment, better protection for persons who are incapable of giving legal consents. It's also in the directive of 2001 that ethics committees are established in a compulsory way for an approval of clinical trial, but, again, one for each member State.

Very important it is also to introduce the obligation of insurance. These are the three directives, the one that is still enforced, and now we move on to the proposal of a regulation.

The 3 UE Directives deepen the ethical concerns (and Directive 2001/20/CE):

- *Strengthen the protection of rights, safety and well-being of trial subjects* (risks assessment; data protection; persons who are incapable of giving legal consent to clinical trials receive special protection);

- *Establish ethics committees that, notwithstanding their number, will produce a single opinion for Member States* (in order to achieve an uniform position and increase the speed of the process);
- Introduce the obligation of insurance or indemnity to cover the liability of the investigator and sponsor.

Just a change of directive towards regulation, we see immediately that the harmonization is becoming stronger, because a directive can be changed in each member state; a regulation imposed itself as it is, so there is no change whatsoever.

In what concerns the proposal, the one that was made by the European Commission in 2012, we see that the harmonization becomes stronger. We have here again a single administrative decision by the member State concerned, but we have one single position for all European Union.

We asked for harmonization and also for simplification. Simplification, for instance, single entry, one application dossier, single submission, single safety reports, for twenty-eight member states. We can go a little further and see that besides harmonization and simplification we have also facilitation. Facilitation of procedures and I draw your attention, for instance, for the possibility of not reporting adverse events.

If the protocol provides already this possibility, reduced timelines for authorization and possibility of tacit authorization of clinical trials, so everything becomes quite easy. Again, centralization; but here we have a little something: not only centralization of procedures that were already placed in the directives, but we have —and this is very important— we have decentralization in what concerns ethical review and insurance, two major topics of ethical concerns. They are not centralized anymore, they become decentralized, and the proposal does not even refer to them as compulsory.

Ethical procedures are said —by the proponents of these regulations— to be linked and impossible to harmonize; therefore, either they fall out of the proposal; yes, they did, or they become a responsible for the member States as they now are in the new regulation. It's very difficult to understand this kind of arguments

because, of course, it is possible to have some kind of harmonization in ethical issues, Europe has the charter of fundamental rights; we have many international and legal documents, we have standards for minimal ethics, so harmonization is possible.

Even if it wasn't, we would ask —insurance is not possible either to harmonize? That is a very interesting question. If it not possible to harmonize, if it becomes a responsibility for the State member, then I would ask, we can have two European citizens that are under the very same clinical trial, that can suffer the same injuries, but if they are in two different member states, they receive different compensation. This is something that we have to look in more detail.

Of course, that this picture can be easily understood if we read the exposition introduction of the proposal. Where it is that? The number of the applications for clinical trials in Europe, between 2007 and 2011, fell 25%. Yet, costs for conducting clinical trials have increased; staff has doubled, increase of administrative costs, insurance has increased 800%, and the average of the clinical trial has increased 90%.

This is not the only thing that we read in the introduction of the proposal. We also read which the objectives are, they ensure attractiveness of the EU for contracting clinical trials, and establishing and functioning the internal market regards clinical trials and medicinal products for human use. That is, clinical trials are seen now as an economic sector and the engine of economic development.

No one really wants the sponsors prefer to outsource their clinical trials towards countries having less strict laws. The European Union really wants to make the European Union as attractive as possible. While the majority of the world's countries are reducing the number of clinical trials, the EU wants to increase their number. While the majority of the world's countries are committed to more strict rules, the EU wants to soften the clinical trial rules and to become more attractive.

Well, from the ethical point of view, the proposal presents two major problems. Ethics committees are no longer considered; informed consent is not very well developed, and it presents a brand new possibility of skipping informed consent in emergency situations. This was the proposal. The proposal was revealed by the European Parliament, by the European Council, and now we go very fast to my third and last point that is the regulation.

Indeed, in this regulation it was possible to make some important revisions, because it constituted that the European Commission's proposal neglected a significant part of the most relevant bioethical reflection of the last years, namely, in what concerns ethics committees and the strong requirements for informed consent.

The European Regulation proposal raises serious ethical concerns:

- *Ethics Committees,* which are no longer considered compulsory neither their advice needed prior to authorization (ethical aspects relate, in particular, to the need to obtain informed consent from the subject or the legal representative);
- *Informed consent,* especially the brand new possibility of skipping informed consent in emergency situations.

Now I will show you what is in the regulation that was approved last April, and that will come enforced in 2016, but it was totally absent from the proposal. I think that it speaks by itself: definition of an ethics committee was totally absent.

The European Commission's proposal neglected a significant part of the most relevant bioethical reflection of the last past years.

On the other hand, the Trilogue Agreement succeeded to introduce the right measures that follow from the wide ethical consensus on the present issue, namely in what concerns:

- Need for ethics committees; and
- Strong requirements for Informed Consent.

Here, member States are the only responsible to organize the enforcement of the ethics committees, it is now in the regulation and at least gives member states this possibility. Research projects should be reviewed; it was not, it is now. Ethical review from ethics committees prior requirement; it was not, it is now. Ethics committees advise binding. We cannot forget that this was deleted in the proposal. It is now, fortunately, in the regulation. Ethical and scientific quality; this is what concerns ethical committees.

In what concerns ethics committees

- *Definition of an ethics committee* (Article 2, 11);
- *Member States are the only responsible to organise the involvement of the ethics committees* (Recital18);
- *Research projects should be reviewed from the ethical point of view before being conducted* (R29);
- *Ethical review, from ethics committees, becomes a prior requirement for a clinical trial authorization* (A4);
- *Ethics committee advice is binding* (A8, 4; A14, 10; A19, 2c; A20, 7; A23, 4);
- *There are ethical and scientific quality requirements for good clinical practice* (A2, 30).

Let's move on to informed consent. I believe that the new regulation now in what concerns informed consent has tripled the size of the articles of informed consent. Now the regulation presents a very good overall statement about informed consent. The more complete that I know, but it was not so. Everything that I am about to show you now it was totally absent from the proposal: information in a prior interview in a clear language, opportunity to ask questions, time to consider the decision, consideration of specific situations, among others.

These specific situations that can affect free decision-making, economically and socially disadvantaged groups; all these details are now considered, with additional requirements in case of minors, incapacitated subjects, minimal burden, knowing your influence including that of financial nature, and there is more to come, special attention paid to the information needs of individual subjects, confirmation that information was understood and this is very rare to see and I am glad that it is now in the regulation; detailed specification of daily information, involvement of a minor capable of assenting; of course, clinical trials on incapacitated subjects and minors; enlargement of the vulnerable populations, explicitly considered such as pregnant and breast-feeding women and others, and here, on the other slide, we talk about military, prisoners and also, well, additional safeguards for clinical trials in emergency situations. This is something that for me is still open as a major problem.

Sometimes, people tell me: "well, if we really need from the medical point of view to have the possibility of engaging clinical trials in

emergency situations, and in this case, we do not have time, there is no possibility to ask for informed consent."

I proposed at the European Parliament that the same system that we have now in organ donation with the possibility of opting out would be also applicable in these cases. That is, we would have national registration for people that would not want to engage in a clinical trial in an emergency situation. This was totally neglected. It means that for every European citizen that goes in an emergency situation, he can become a subject of a clinical trial under specific situations and the specific requirements, it is true, that are much tougher now than they were in the proposal of the Commission.

In conclusion, the proposal of the European Commission was duly reviewed, but remains a very important indicator for the future steps in what concerns clinical trials. The EU regulation will have strong implications, I believe, in the rest of the world, because it will become enforced in 2016 for twenty-eight member States. It's impossible not to have an impact in the rest of the world. I believe that it can strengthen a similar orientation already existing in the USA. There are lots of papers about how different IRBs in the states issue different opinions about the very same clinical trial. That puts a question that, of course, the new European regulation answers.

I believe that reducing the number of the cities that clinical trials in South America, in Africa, because for Europe now clinical trials are a question of economic development.

Europeans want to have more and more clinical trials in Europe, so it is a question for them of competing with the other parts of the world. I believe if it succeeds the number of clinical trials can decrease in other parts of the world. Some current discussions, very hot discussions in what concerns placebo, or double standards, will lose somehow their importance if this regulation has the implication that I foresee.

Of course, it is also a question of proliferation of IRBs in these regions. Since now, in the European Union we have just one single decision for the entire twenty-eight member states.

My very last word. Well, that is the very last. Let me got to the other one. I believe that it does inaugurate a new paradigm in the clinical trials' history. First, it was science, the major value before the Second World War. After the Second World War, ethics was the most important

perspective for clinical trials and now it seems that market will be the most important one.