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Regulatory issues for clinical trials at EORTC: the way forward

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Abstract

Since the Declaration of Helsinki, the performance of clinical trials is subject to ethical and gradually also legal requirements. As the EORTC is performing clinical trials in more then 30 countries, it gained expertise in the field of Regulatory Affairs of all those countries. This paper intends to address the general approach with regard to European Regulatory Affairs. Furthermore, it is focusing on the role of the EORTC at the level of the competent regulatory authorities. As recently things are moving and changing on a European level, it describes the perception of the current and future European regulatory framework, and last, but not least, it is explained in what respect the achievements of the EORTC could be of benefit to society when defining their cancer treatment policies.

Keywords: Clinical Trial Regulatory Affairs; European policy

EORTC has been involved for many years in European regulatory affairs at several levels. The most relevant ones are its role in establishing with the regulators 'state of the art' methodology for drug development and its role in advocating for independent research when European policies relating to the activation and conduct of clinical trials are proposed. This paper focuses on these two major areas of activities.

1. Regulatory affairs and drug development: the role of EORTC

Not only is clinical research practice rapidly changing, but also cancer research is faced with a multiplicity of new approaches and new agents with new mechanism of actions. The methodology for clinical trials and the way the outcome of new treatments is being evaluated are being challenged. New ways are to be found to bring innovative drugs with innovative mechanisms of action to the patients. Indeed, new technologies and breakthroughs from molecular biology allow scientists to create agents with a scientifically sound development, but clinical research has to face the challenge of developing appropriate clinical trials endpoints to change trial design and a lot of work still has to be done in that respect. In addition, these new technologies—whether they come from the laboratories or from the imaging field—will enable clinical investigators to better define the targeted population who may benefit from certain treatment, and to establish strict guidelines for tailor-made treatment approaches for the ultimate user of a treatment and for the targeted patient population. From this approach, the health management and reimbursement policies of our societies are expected to benefit directly. The EORTC has been for many years working in cooperation with the European Medicine Evaluation Agency (EMEA) and has contributed to the current European procedures in order to define 'state of the art' methodology and all related issues to cancer clinicals trials design and end-points.

Cancer clinical research is living a very exciting time in terms of new discoveries and potential openings for new fields and new areas of treatment. The challenges to methodology for clinical trials and evaluation of the outcome of new treatments come at a time where the European regulatory framework will be completely reviewed due to the implementation of the new clinical trials Directive [1]. Europe should significantly contribute to these developments, but health authorities and various agencies will be facing the challenge of major scientific openings to coincide with new unfolding European procedures. Therefore, all key players of the competent authorities in Europe, as well as national and

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international organisations (such as the EORTC), should realise the societal responsibility of independent clinical research networks sustained by methodologists and experts covering all aspects of modern clinical research.

The EORTC (through its network of clinical investigators and its Data Center) has both the expertise and the availability for such methodological challenges and regulatory awareness. Indeed, the scientific revolution will impose that competent authorities obtain an exact picture of the most adequate and 'state of the art' clinical trial methodology in order to register new molecules and/or new treatment strategies. Assessing the outcome of a new treatment will definitely change the way clinical research is performed and evaluated. Building *ad-hoc* networks will no longer be sufficient to strive forward. Promoting a new approach will require that networks, having developed a specific expertise, should be involved as partners to ensure the adequacy and the relevance of the addressed question, as well as the tools that need to be put together to answer the question. Indeed, competent authorities could benefit from the support of such expertise to allow new candidate drugs to move forward in their development. Ideally, the involvement of experts should not only be asked for at the time of granting authorisation for a new treatment, but also in the process of optimising such new treatments in therapeutic strategies. Moreover, rationalisation of the economical aspects of health can only be sustained by a close cooperation between the scientists and the competent authorities.

That is why organisations like EORTC constitute for our societies a unique opportunity for cooperation with healthcare providers in order to streamline the availability of drugs that cancer patients really need, while protecting the citizens by maintaining healthy a national reimbursement system.

This new type of close cooperation between competent authorities and experts can only be achieved if Europe is equipped with two major features: the first is an adequate legal framework which allows both rapid and effective new drug development, but also academic research establishing 'state-of-the-art' strategies; the second is the availability of an adequate support for independent research. Indeed, academic research should be performed to the highest scientific standards and according to the principles of Good Clinical Practice. Cancer clinical trials are often a multinational effort and as EORTC studies are being preformed in more than 30 countries, it constitutes an unique observation point on all different procedures and treatment options for the same disease type in different healthcare environments.

Close interaction between research organisations like the EORTC and competent authorities would contribute to an efficient European system. This would also be beneficial to the industry in general, including large numbers of small companies which are newcomers in the field of cancer drug development. Indeed, there is an absolute need for a private–public partnership to help drug developers in making scientifically good and economically sound decisions and this must include the competent authorities side-by-side with the scientific networks. Ultimately, it would also protect patients from entering trials that will not be of any benefit to them or to society.

During the last 40 years, the EORTC has contributed to the improvement of treatment of cancer patients and over the last 5 years a Regulatory Affairs Unit has expanded to fulfil all of the legal requirements of European regulation that are relevant to clinical trials. All EORTC studies are conducted according to the ICH Good Clinical Practice Guidelines.

2. The EORTC Regulatory Affairs Unit (RAU): internal procedures and European policy activities

The ultimate goal of the EORTC is to ensure that relevant scientific questions to optimise current therapeutic strategies are correctly addressed since the regulatory framework under which the EORTC trials have to be conducted may constitute a limiting factor. The EORTC RAU has structured its activities in two main directions. The first is to implement mechanisms not only to ensure compliance of any clinical trial with national requirements wherever trials are conducted, but also to allow a rapid adaptation to constantly evolving regulations and requirements from the competent authorities. The second is to be a partner acting prospectively in the development of European policies due to its position offering a unique European insight with the ultimate goal of supporting policy makers in their challenging missions. There are tremendous opportunities for leading European investigators to maintain a high level of competitiveness. This can only be secured if Europe has an optimum and efficient regulatory network which will enable investigators to take on board new clinical approaches guaranteeing, therefore, their exposure to constantly challenging scientific situations and ensuring that Europe also remains attractive to high-quality pharmaceutical research.

2.1. Mechanisms for implementation of regulatory affairs at the EORTC

For most EORTC studies, the EORTC is the legal sponsor and has to ensure that for each participating centre all pertinent regulations are being fulfilled. As the EORTC is active in more than 30 countries in Europe, this implies also that the EORTC Regulatory Affairs Unit is dealing with more than 30 different national sets

of regulation relating to clinical trials. The pace at which a study can be initiated in a certain country will, of course, depend on the applicable national regulations and on the working procedures of the competent authorities. Apart from this, as science is progressing, the existing regulations are also being constantly adapted. Besides the increasing complexity of the regulatory process, a similar trend can be seen at the level of the ethical review procedure. Accordingly, the EORTC RAU has established strict procedures to ensure that EORTC staff are always updated with any changes in such a way that EORTC trials are fully compliant with the evolving regulations. This mechanism is ensured by various activities at several levels. The staff at the RAU has established specific contact with the competent authorities in countries where the EORTC operates. Changes to procedures are communicated to the EORTC personnel through mandatory meetings which are made compulsory at the time of initiating a trial and when applicable to ongoing trials by general announcements and communication to the scientific teams. Actions taken are then followed up country by country and centre by centre according to predefined monitoring timelines which determine the deadlines by which the actions must be implemented. This applies to all regulatory issues including the management of Serious Adverse Events in cooperation with the EORTC safety desk [2]. Table 1 summarises the varying European Member States legislations.

The EORTC has made regulatory issues a priority for a number of years [3]. However, EORTC has been a pioneer in Europe in raising the issue of insurance for clinical trials by alerting early on the enormous discrepancies between European Member States. Starting as early as 1993, the EORTC has committed itself to fully understand all the practical steps for insuring clinical trials. Symposia have been organised by the EORTC (DIA Workshop, December 1998) which subsequently described all these issues [4]. Despite some improvements, insuring clinical trials remains an obscure field for many personnel involved in clinical research. Cost assessment of the medical risk for research remains extremely variable amongst Member States and the lack of understanding of insurance matters for clinical research obviously puts not only ethics committees and investigators, but also authorities, in such a position that it results in unreasonable requests that may threaten the performance of clinical trials. The EORTC has investigated in depth the various legal systems, as well as the national systems of insurance. This information obtained by EORTC survey is available to policymakers and may contribute to a better understanding on the functioning of the different national regulatory procedures. Table 2 highlights the major features of the clinical research insurance in the European Member States which have such requirements.

2.2. Potential role for independent organisation to general policy implementation

Being a pan-European academic research organisation, the EORTC is in a privileged position to highlight inconsistencies and to ensure that the specificity of academic clinical research is appropriately taken into account by competent authorities. Close interaction at

Table 1
Highlight of some differences in legislation for trial activation

Country	Authorities	Term
Belgium	No obligation to notify	Not applicable
The Netherlands	No obligation to notify	Not applicable
France	Notification	Not applicable
Portugal	Notification	Not applicable
Germany	Notification in order to obtain Vorlagenummer	7 days/5 months (radiotherapy) for Vorlagenummer
Denmark	Authorisation	30 days or more
Greece	Authorisation	30 days or more
Luxembourg	Receipt of notification	30 days
Austria	Notification	35 days after notification after authorisation
United Kingdom	Authorisation	21 or 35 days
Sweden	Authorisation	40 days
Finland	Notification	60 days after notification
Italy	Judgement of notoriety[a]	60 days after application[a]
Spain	Authorisation	60 days
Ireland	Authorisation[a]	80 days

[a] In practice, it takes approximately 30 days.

the national level is necessary, as well as with European Institutions preparing Directives and Guidelines. This interaction implies an interactive relationship with different Directorate Generals of the European Commission (DG Entreprise, DG Research, DG Internal Market (Data Protection) and DG Public Health and Consumer Protection), the European Medicines Evaluation Agency and with the European Parliament. Beside this, the RAU is also involved in the legal aspects related to the development of a tissue bank project, requiring an appropriate ethical and legal framework for tissue research and tumour bank. All the expertise developed over the years by independent organisations like the EORTC is explained by their quest for an appropriate balance for the continuation and upgrade of their activities to the benefit of patients and international scientific community, while adapting to the regulations by applying the most pragmatic approach possible. Innovation and pragmatism has given to such organisations an excellent grasp on which policy makers could build with the ultimate goal of full cooperation between academics, pharmaceutical industry and regulators. This last activity also feeds directly into the EORTC activities for drug development described in Section 1.

3. The challenges of the future European regulatory framework and EORTC achievements

Regulations and derived procedures have increased globally and this can be partly explained by the great progress of science in the last 10 years. While there is no doubt that any regulation with a clear benefit to the quality of research and/or safeguarding of patient's interests is an asset, policy makers should consider adopting regulations that are not merely conceived for drug development, but that also take into account the whole scientific environment and the specificity of 'academic' clinical research, particularly for clinical trials aiming at establishing state-of-the-art strategies with registered drugs. There is still a lot that can and should be realised on a European level, particularly given that many trials are now conducted on an international scale.

Beside the participating patients, who definitely have a better outcome compared with patients who are not participating in a clinical trial, society will also benefit from the study results. Academic clinical research that establishes 'state-of-the-art' treatments, besides making an important contribution to progress in medicine, also has a purpose in the field of education. It promotes dissemination of up-to-date information to all participating

Table 2
Insurance indemnities in European Member States

Territories	Indemnity	In EURO	Insured	Period
Austria	ASH 5 000 000 per victim	363 364.00	Sponsor, investigators, all persons involved in the trial	Period of the trial plus 3 years
	ASH 35 000 000 per protocol	2 543 549.00		
	ASH 50 000 000 per year of insurance	3 633 642.00		
France	FFR 5 000 000 per victim	762 245.00	Sponsor, investigators, all persons involved in the trial	Period of the trial plus 10 years
	FFR 30 000 000 per protocol	4 573 471.00		
	FFR 50 000 000 per year of insurance	7 622 451.00		
Germany	DM 1 000 000 per victim	511 292.00	Sponsor and investigators	Period of the trial plus 3 years
	DM 50 000 000 per year of insurance	25 564 594.00		
	Per protocol:	Per protocol:		
	DM 10 000 000 up to 1000 subjects	5 112 919.00		
	DM 20 000 000 from 1000 to 3000 subjects	10 225 838.00		
	DM 30 000 000 for more than 3000 subjects	15 338 756.00		
Greece	GDR 15 000 000 per victim	44 449.00	Sponsor, investigators, all persons involved in the trial	Period of the trial plus 3 years
	GDR 150 000 000 per protocol	444 497.00		
	GDR 700 000 000 per year of insurance	2 074 320.00		
Italy	LIT 2 000 000 000 per victim	1 000 000.00	Sponsor, investigators, all persons involved in the trial	Period of the trial plus 2 years
	LIT 15 000 000 000 per protocol	10 000 000.00		
	per year of insurance	15 000 000.00		
Spain	SP 30 000 000 per victim	180 304.00	Sponsor, investigators, all persons involved in the trial	Period of the trial (plus 1 year claims possible 2 years)
	SP 300 000 000 per protocol	1 803 036.00		
	SP 500 000 000 per year of insurance	3 005 061.00		
The Netherlands	NLG 1 000 000 per victim	453 780.00	Sponsor, investigators, all persons involved in the trial	Period of the trial plus 5 years
	NLG 15 000 000 per protocol	6 806 703.00		
	NLG 20 000 000 per year of insurance	9 075 604.00		

centres on the best treatments available, but it also facilitates the rapid dissemination of the study results through the established academic network of investigators. Furthermore, health insurance systems will benefit from the study results, allowing them to define optimal ways to allocate their resources. All these facts point in a single direction, that all of the expertise in Europe must be utilised. All parties involved in clinical research can only benefit from global evaluations which take into account the full scientific environment. Academic clinical research can contribute largely to the establishment of an optimised European framework which will need constant re-evaluation due to all the innovative medical approaches resulting from the evolving discoveries.

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