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Clinical research in Europe: Who do we do all that for?

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ABSTRACT

Independent applied clinical research addresses questions which are centered on optimization of treatments and patient management. It often finds itself confronted to policies and regulations implemented more specifically with pharmaceutical research and drug development in mind but which in practice apply throughout all clinical research programs. We report herein a specific case illustrating such challenges. We question how far legal constraints overshoot their initial objectives, leading to opposite effects for which they were set up. In an era where independent evaluation of cancer treatments is becoming so critical due to complexity, duplication and costs, comprehensive and pragmatic reform of our frameworks appears critical.

1. Independent applied clinical research: does the regulator get full perspectives?

Academic medicine has always played an important role in Public health. Independent academic research attempts to address critical clinical situations and unmet needs for patient management. Large independent trials have over the years made a substantial difference to the implementation of therapeutic strategies in oncology. These have not only included new drugs, but also incorporated treatments such as surgery or radiotherapy. Important therapeutic advances have been made through the optimization and combination of existing treatment modalities. For example, pediatric oncology has reached 90 % of cure rate for certain forms of leukemia through a series of trials optimizing existing treatments [1]. Organ preservation trials have led to improved quality of life, avoiding surgery for specific stages and tumor locations [2]. Until about two decades ago, independent clinical research and commercial research aiming at developing new drugs were conducted side by side, with often limited intersection, in a regulatory and policy environment which was poorly developed. Since then, various empiric national legal and regulatory frameworks have emerged, for good reasons such as improved patient safety and privacy, but also due to the explosion of new agents and technologies being available. This, together with economic challenges in health care systems, lead to the implementation of the European Union Clinical Trials Directive (CTD) in 2004. It became immediately apparent, with the initial proposal developed by what was at that time Directorate General V, Enterprise, that the regulator had a limited view of clinical research. Indeed the CTD included provisions for developing new drugs and was immediately seen as a threat by the non-commercial sector conducting therapeutic strategy trials. The economic consequences related among others to increased regulatory burden and insurance requirements for conducting clinical research were seen at that time as an obstacle to changing practice clinical trials. The CTD helped in structuring clinical research in Europe but the side effects have been in some aspects disastrous for the European patients. The European Medicine Agency has recognized and communicated a decrease of 25 % of the volume of clinical research in Europe [3]. The implementation of the CTD resulted in an increase in regulatory and insurance costs, posing major challenges for conducting pragmatic clinical research in Europe. The Impact on Clinical Research of European Legislation was compiled in a report. The ICREL report, a multi-stakeholder analysis of the resulting European framework has carefully analyzed all the consequences of its implementation [4]. It identified the key bottlenecks to be addressed at the policy level but also helped clinical trialists to structure their efforts and find solutions to continue their activities. It required among other to develop knowledge and competences in the field of regulatory affairs and exposed trial organisers to new legal challenges.

Non-commercial sponsors had to get organized to embrace such activities for which they were not necessarily prepared. At the same time, many tried to alert against the obstacles and uncertainties that were expected to jeopardize primarily patient-centered research. Years of discussions and education of the involved stakeholders were needed to ensure that clinical research in Europe would not simply be reduced to pharmaceutical research lead by the commercial sector, ignoring the need to constantly improve multidisciplinary therapeutic strategies. It is astonishing actually today to read in the era of precision oncology that

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despite some breakthroughs in very specific clinical situations, the vast majority of new agents have limited to no impact on clinically relevant outcome, despite their high costs, on what patients expect us to address primarily i.e. duration and quality of life [5–8]. This has been actually echoed during an informal meeting of the EU Member States health and research ministers in 2018 [9], emphasizing the need of such research.

Inconsistencies immediately appeared as a result of the regulatory framework. One of them is the separation of commercial and non-commercial research, and consequently sponsors, based on the definition of what an Investigational Medicinal Product (IMP) might be. The definition which was therefore implemented describes an IMP as *"a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form"*. This, de facto, severely hampers the ability to conduct pragmatic research around dose-optimization, duration, combination with surgery or radiotherapy of licensed drugs and, hence, creates a barrier to design studies aiming at improving treatment effectiveness, including in term of decreasing health expenditures.

2. About a specific case: are patients really at the center of processes?

TOP-GEAR is randomized phase II / III trial of preoperative chemo-radiotherapy versus preoperative chemotherapy for resectable gastric cancer [10]. Its objective is straightforward: to optimize the sequence of well-established treatments, with overall survival being the primary endpoint. It is as such a typical case of an independent pragmatic trial, potentially practice-changing. The question is critical to patient management and worldwide experts decided to join forces back in 2013 to bring robust evidence to solve this question. The study is driven by an independent Australian group and has been taken up in Europe by the EORTC, a non- commercial sponsor in the EU. Twenty-two centers in six EU Member States take part in this study to recruit 620 patients, and the study is still recruiting patients at the time of this publication. This is a major worldwide enterprise that academic groups attempt to run optimally, strictly following regulations and applying risk-based approaches to control procedures and costs for a study which does not contain nor address the role of any new treatment but addresses the sequence of well-known documented therapeutic strategies. When activating the trial, EORTC proposed to run this study in Europe therefore as a non-directive trial, therefore considering that the addressed schedule does not contain any investigational agent. Though medically obvious, it was recognized that regulatory wise, the approach was debatable, though none of the tested agents or modalities is registered based on a strict use in their sequence. Labelling the study, based on a non-IMP status, was discussed with varying regulatory authorities and the trial was successfully activated in all targeted EU Member States in agreement with the assessment of EORTC. A major reason for doing so was to pragmatically avoid all possible issues related to provision, costs and constraints related to IMP management when all drugs are routinely used.

Recently, the backbone treatment has evolved and a new marketed chemotherapy schedule is now in use, having an impact on this strategic trial, without changing the initial concept, but extending the palette of available cytotoxic agents allowed for this indication. This required logically an amendment to the study to include this new regimen. While it appears that medical common sense would label as non-investigational any treatment which is known to be effective, one competent authority of an EU Member State took this opportunity to relabel the study as an IMP study, requiring then a regulatory amendment applicable throughout Europe, adding work, resources, costs and bureaucracy for no added value, nor improved safety for the patients. Not only recruitment had to be stopped in the concerned Member State, it has been requested to stop all data collection for patients within that member state, potentially exposing patients to risks. Indeed, close safety monitoring is an important aspect in all studies regardless of the investigational nature of the treatments. While we agree with the principle that there should not be two-speed research, we insist that the forms and the methods must be proportionate to the clinical situations and risks, regardless of the regulatory set up which should stimulate research instead of hampering it. The study is nevertheless continued under its initial regulatory label elsewhere in Europe, but not only the contribution of Europe will be undermined by this decision, but also some of the European citizens are not provided access based to potentially changing practice trials due to pure regulatory assessment of research, in absence of medical sense of prioritization. A formal appeal to the concerned competent authority, despite the support of worldwide scientists and medical experts failed to change this particular national regulatory decision.

3. Where are we heading to?

Europe will soon see the implementation of a newer version of the Clinical Trial Regulation (CTR). Its effects remain to be evaluated. Despite some expected benefits such as the development of the EU portal for single clinical trial application, there is no insight as whether it could address the issue of qualification of studies designed to answer questions centered on patient care as clinical trials from the moment they involve any drug, including standards of care. On the contrary, it raises the risks that all Member States could adopt the position of the most conservative, not necessarily based on medically informed criteria. It opens therefore the risks that therapeutic strategy trials may become even more challenging to perform in the European Union. Together with the already implemented General Data Protection regulation (GDPR) and the soon to come regulation for medical devices and in vitro medical devices, clinical research will need to be performed taking into account three or even four regulations for which we have already called for their inconsistencies, in the so called regulatory triangle, emerging from 3 different Directorates General : DG research, DG Justice and DG Growth [11].

Specifically in the field of oncology, even more complexity comes from other, even less harmonized pieces of legislation, such as laws on biobanks or the EURATOM directive, which is not at all specific to clinical research. The overall number of authorizations, approvals and other obligations to be met by sponsors, sites, and investigators increased to the extent that energy and funds spent into efforts to ensure documentation of compliance with various formalities may drive the attention away from what really matters: patient safety and benefit.

It is not expected that within the arena of competent authorities working in silos, voices will spontaneously emerge to position patient centered clinical benefits in the context of multiple product oriented regulations. Medical community needs to raise up to oppose silos and bureaucracy for the sake of research and therapeutic progress which may be seriously hindered otherwise.

In the end, European patients and the heath-care system are penalized by the regulatory hurdle. Fortunately, risk-adapted procedures have largely gained the wisdom of the majority without compromising the safety of patients. New technologies and the pace at which they reach market authorization, often based on small non randomized trials, plead for a continuum of drug development and pragmatic research to stimulate innovation while assessing independently in the best interest of patients and health care systems how to use these technologies. Our systems are now long overdue for reform, and should be embedding independent applied clinical research, based on appropriate forms of quality control as the knowledge develops.

Our organisation, through a European Union Manifesto developed in partnership with the E.U. Parliament [12], as well as other organisations and researchers have called for a greater independence in assessing the role of treatments [13]. It calls for new independent

mechanisms where innovation and therapeutic progress are assessed free of commercial interests in health care research programs addressing public health questions. This requires adequate and agile regulatory frameworks towards the understanding of clinical critical questions. Re-engineering clinical research from Research & Development into Access will need greater public support to independent multidisciplinary clinical research, inclusive of health technology assessments for optimized therapeutic strategy into health care.

We want herein, therefore, based on the TOP-GEAR study illustrate some of the European inconsistencies, call for urgent reform to assess interventional clinical research based on purpose, treatment modalities at investigation and medical relevance, and not necessarily through the rigid application of inappropriate frameworks.

Declaration of Competing Interest

There are no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcpo.2020.100217.

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