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Diverging EU health regulations: The urgent need for co ordination and convergence

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ABSTRACT

At the time of mayor breakthroughs in knowledge of molecular biology leading to change in design and conduct of innovative clinical research, there is a clear need for optimal co-operation at the EU level as well as with each Member States. The current legal framework for health research is developed and revised by several DGs dealing with clinical trials, data protection, in-vitro diagnostic tests and biomarkers. Also medical devices and advanced therapy directive / regulation have to be taken into consideration, all within a single trial/study. Such fragmentation of legal framework and national laws lead to several inconsistencies, wasting time and scarce resources of sponsors, whether academic or pharmaceutical industry and all involved parties are facing the complexity of current clinical research. Could we consider a single stop-shop for such initiative? Competitivity of European research is at stake and comprehensive coordination between all partners is crucial for the benefit of European citizens.

With the rapid development of new technologies and the massive call for personalized treatments, the biomarkers, gene signatures and other advances in diagnostic development became of the utmost importance in the field of oncology.

There is a strong call for both, drug and diagnostics to be developed in parallel, with IVD entering clinical testing (and so practically being part of the same trial) [1–6]; this approach has been recently supported by FDA with its draft guidelines for co-development of IVDs and drugs [7].

On the other hand, McKinsey report 2013 [8] suggests that the regulatory environment is not keeping up with rapid technological advances and therefore slows down the capacity of researchers to radically move towards such co-developments; the report also cautions the success of personalized medicines and optimal biomarker development is dependent on the successful coordination and drug-ivd co-development capacity from organizational and regulatory perspectives.

Back in 2012, the EU issued three key draft regulations critical to the field of healthcare research in EU. Namely, clinical trials regulation (CTR [9]), in vitro diagnostics regulation (IVDR [10]) and data protection regulation (DPR [11]; though this last one is a general regulation and not specific to research).

As exposed above, in the field of cancer, in the era of personalized medicines, the rise of biomarkers based clinical trials, perfomed internationally to access molecularly defined patient populations in the EU would fall simultaneously under the CTR and IVDR with the additional need to comply simultaneously with the general data protection regulation, thus emphasizing the importance of smooth coordination between all these regulations.

Several examples of trials at the edge of three regulations can be given. The EORTC MINDACT [12] trial is an interventional trial from the perspective of IVD and does fall under the scope of CTR and DPR (see Fig. 1).

Another illustrative example is NCI-MATCH trial (though not conducted in EU) which represents well the efficient trial designs (Fig. 2). NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) is a clinical trial that analyzes patients' tumors to determine whether they contain gene abnormalities for which a targeted drug exists (that is, "actionable mutations") and assigns treatment based on the abnormality. NCI-MATCH seeks to determine whether treating cancers according to their molecular abnormalities will show evidence of effectiveness.

Each treatment in NCI-MATCH will be used in a unique arm, or substudy, of the trial. Currently 24 treatment arms are open and enrolling patients. Unfortunately, within the current and likely future framework, it is highly unlikely such a design would ever be approved as pan-EU trial, which may impact on the competitiveness of EU.

CTR is a great example of open multi-stakeholder dialogue. Indeed, during discussions on the text and throughout the ongoing implementation phase, multiple events brought all together involved

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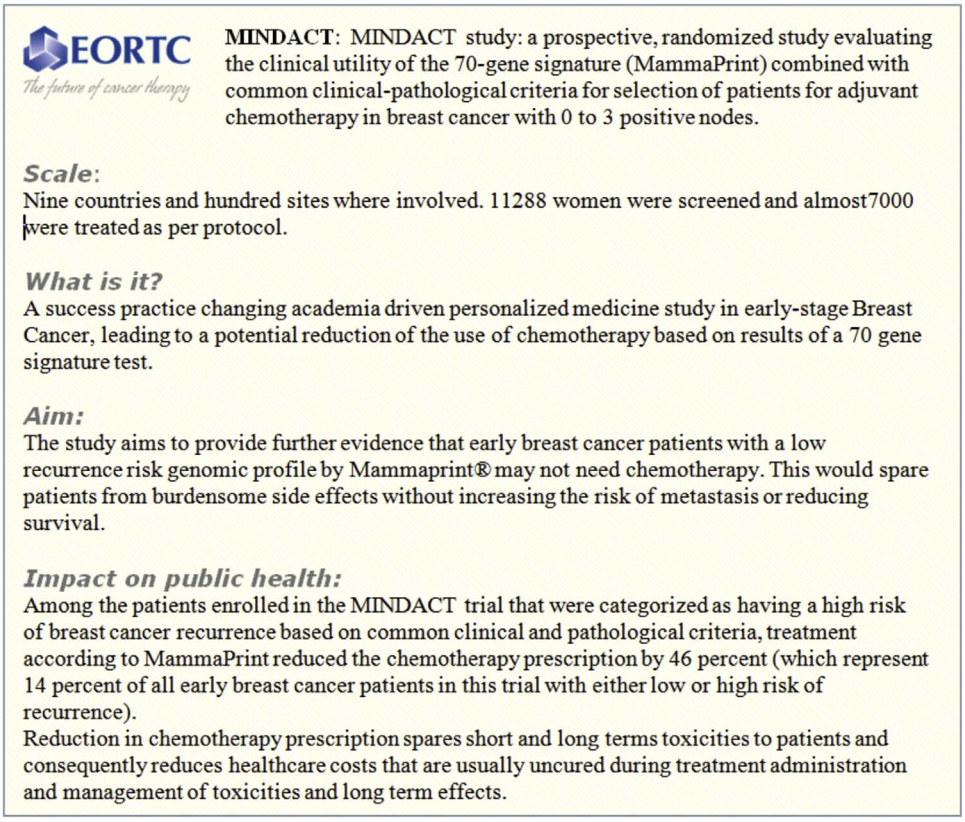

Fig. 1. MINDACT Study.

stakeholders, stimulating productive detailed discussions that ended up by finding acceptable solutions to most of the identified issues. Specifically, teams from the commission and EMA were very receptive to listen to detailed descriptions of practical issues sometimes less relevant to the higher level text of the regulation itself, but essential to ensure the appropriate implementation.

CTR is currently under implementation and the overall collaboration with all parties is excellent. However, when CTR was discussed and the functionalities of the EU portal debated, very little was known about efficient trial designs and adaptive designs. Today, the scientific community has more experiences and pilot projects being done to be able to project how these will fit into the new system. It can be therefore anticipated that new regulations would not meet the needs of these trials (i.e. 95 days amendment approval timelines of the clinical trials regulation are far too long for trials with designs such Bayesian or MUMs). EORTC believes some specific discussions shall take place around this subject; probably within the already existing working groups (though this subject is currently not yet part of the agenda).

The IVDR and DPR unfortunately did not benefit from this enlarged and close collaboration. Moreover, as the hree regulations are developed by different DGs (Fig. 3) with somehow divergent priorities, the way these regulations currently come-up together is clearly sub-optimal, revealing numbers of contradictions and issues arising specifically from their cumulative application (annex 1).

1. Specific issues related to the data protection regulation

DPR being a general regulation, the academic community has been from the very start concerned by the lack of recognition of specificities of health research. These concerns were partially addressed by the formulation of possible exemptions suggested by the regulation. However, the implementation of most of these possible exemptions in the field of research are being delegated to individual member states (such as, thus entirely compromising the harmonizing value of the regulation. Some argued that this situation makes the realities of health research unchanged, as such heterogeneity of environment is already

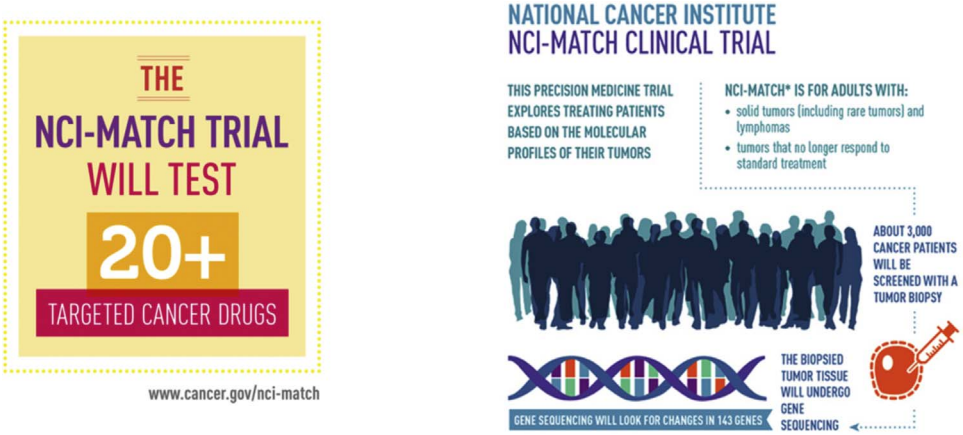

Fig. 2. The NCI MATCH Trial.