32nd Workshop of the
EURORDIS Round Table of Companies (ERTC)

Get ready for imminent changes!
The impact of the EU regulatory network strategy 2020-2025 on the development of orphan medicines in a rapidly evolving healthcare environment

Preamble

This report aims to reflect the discussion amongst attendees and panellists of the meeting, rather than to record the subject matter from each presentation. As could be expected, this includes some counter-opinions and some off-topic comments, neither of which should be taken to represent the views of EURORDIS. We have, however, tried to propose actions that might be helpful in bridging any divide.

Session 1:
Working on science and innovation to reach patients and address unmet medical needs.

Discussion and key questions
Key themes were the difficulty of obtaining joint parallel advice from HTA and EMA and a request for greater patient involvement at all stages of the process, especially in the development of outcome measures or Drug Development Tools (DDTs). Apparent conflicts between regulatory and HTA assessments and some solutions were proposed to address these, including having HTA representatives as observers in regulatory decision meetings. The fragmented nature of HTA in Europe was recognised as a major barrier to this understanding, however.

Closer international cooperation and a move towards harmonisation with FDA policies was considered desirable and a strong trend of attendees urging lessons learned from the rapid response to the COVID crisis to be evaluated and implemented where possible.

Session 2:
Transforming medicines regulation: data analytics and methods

Discussion and key questions
There was some complaint from attendees about the exclusion of industry from much of the discussion that impacts their work. Where industry *is* included, it is normally with observer status only and this is wasteful use of a valuable resource. Industry could input into the analytical methodologies under consideration by EMA and contribute to the debate on new techniques.

The relatively new standing of ERNs was highlighted as being a missed opportunity so far, with these networks having the potential to be substantial and reliable sources of data to support

regulatory and HTA decision making. Some frustration was expressed from industry at the current lack of any mechanism for them to engage with ERNs.

On a more general level there was considerable frustration and confusion regarding issues of data management and integration, especially across borders. Inevitably GDPR was raised as a major barrier by some participants, while some actually suggested that properly understood and implemented, it could actually be a facilitator to effective data sharing.

Session 3:

Clinical Trials workstream at EMA: Regulation and Clinical Trials Information System (CTIS)

Discussion and key questions

All Member States took part in the development of the CTIS, a regulation from which no Member State can disengage, and EURORDIS witnessed their engagement at CTIS meetings. The EMA has made substantial efforts to inform and provide training regarding CTIS, but within the resources and the remit under which they operate. This regulation represents great change, and as such there is a transition period of one year for those involved to learn how to use it. All users are therefore encouraged to make use of the transition period in order to ensure that everyone receives adequate training and support. The CTIS will only succeed if all stakeholders rapidly learn how to use it.

The new regulation was described by some participants as being process-driven and designed to make management and control of CTs more efficient and streamlined. This regulation was proposed to make Europe more attractive in terms of clinical trials and to simplify the process to obtain the authorisation to conduct a trial, and to simplify all procedures when a change in the conduct of the trial is needed. There will be one-stop-shop to submit all necessary documents rather than to each Member State separately. Ethical divergence across the member states was highlighted as one of the difficulties in compiling a common application for all.

The changes were suggested to be particularly challenging to SME companies and to academia, most of whom lack understanding and familiarity with regulatory authorities. One suggestion (from an academic) went so far as to describe academics as being illiterate regarding the regulatory process.

Session 4:

ICH GCP Renovation, Decentralized Clinical Trials and Outcomes of Adaptive Clinical Trials

Discussion and key questions

Revision of ICHE6

Suggestions included a more systematised use of Community Advisory Boards (CABs) in early stages of trial design and considerable concern and debate around various aspects of informed consent – electronic and dynamic consent risk creating confusion and introducing new and less obvious bias in participation; excessive safety reporting which paradoxically reduces patient safety by obscuring the picture; informed consent increasingly becoming uninformed consent (one patient was reported as being on their 11th iteration of informed consent, each one being completely different to the one that preceded it, with the inevitable result it is signed without reading).

The burden of administration means that smaller enterprises and academia cannot comply with the requirements without support from Clinical Research Organisations (CROs). In the case of academia specifically, this effectively means that many avenues of research are closed off in the absence of its being feasible or even legal to engage industry support for their work (eg ERNs are severely restricted in this respect). There are new opportunities for ICH provisions to consider flexibility to consider sophisticated use of trial data, such as combining and interrogating placebo data.

Adaptive designs in clinical trials

The industry view was that adaptive trials are maturing and becoming more accepted, having demonstrated their value on a number of occasions. Terminology was becoming confused but essentially the key benefits are increased flexibility and efficiency in trial management, with both patients and investigators benefiting from this. For patients, a key benefit is the reduced need for placebo enrolment, especially for platform trials. This was evidenced by their use during the COVID pandemic, with the FDA calling for increased use of adaptive design as a consequence of that success.

The reimbursement viewpoint was inevitably more nuanced. Attendees were less convinced that adaptive design itself really aided the decision process – "difference between because and despite!" From a methodological view the benefits are obvious and real; from a regulatory view they present challenges, but from an HTA view they can be "almost dangerous." Evidence required for robust decisions must never be compromised in the interests of efficiency.

There is bias toward "clean" confirmation of a research question, which is not always possible with adaptive designs. A further problem is the issue of communication – HTA rarely sees the whole picture and is expected to trust applicants' and regulators' diligence. It was admitted, however, that HTAs can be quite unpredictable, and it is impossible to speak for the body as a whole as there will always be national differences in approach. However, it was claimed that there is nothing worse than for an HTA body to reject an application due to poor documentation as opposed to an ineffective treatment. The difference between a failed trial and failed drug needs further examination.

Recommended Actions

Several important issues were raised over the two days which merit further discussion, either at future ERTC workshops or perhaps via dedicated task forces established to commence a dialogue for that purpose. It is clear that all stakeholders should be involved in this process, whatever form it may take, as far as possible: industry, regulators, HTA agencies, clinicians and patients (not in order of priority; all are needed). Some of these are highlighted below:

1. ***Data sharing and GDPR***
   Confusion over the operation of GDPR is the norm, rather than the exception, with little doubt that, real or imagined, there are real and significant barriers resulting from different interpretations of EU rules on data privacy as well as national predilections and regulation. If we are to take full advantage of the opportunities that new analytical tools presented to us, this confusion needs to be lifted, and urgently.

2. ***Conflicts between HTA and Regulatory decisions***
   This was a recurrent theme throughout the two days and there is a sense that this problem is increasing rather than decreasing, despite the many initiatives designed to counter the trend. The uncoordinated nature of the HTA landscape is a barrier to be overcome but also the absence from much of the dialogue of three key stakeholders – patients, clinicians and industry – needs to be addressed for progress to be achieved. Communication is recognisably poor and as a result inter-agency confidence is a casualty for which we all pay the price.

3. ***Education and training opportunities over regulatory affairs generally and CTIS specifically***
   This is already addressed via several programmes, but in an increasingly complex healthcare environment, efforts need to be augmented substantially.
   For CTIS, a comprehensive training programme for Member States, sponsors and CROs is in place. See here: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme.

4. ***The need to establish specific programmes to engage ERNs in regulatory processes***
   ERNs are a relatively new concept and still in their infancy. They are also underfunded and suffer from an evolving rulebook – they are still unable to engage with industry due to their founding constitution and this severely limits the scope of their operations. They are also completely absent from regulatory and reimbursement processes, which is a serious waste of a resource that has enormous potential to contribute to better decisions.

5. ***Adaptive/hybrid trial designs and the use of new statistical methods***
   Without action on point 2 to address the lack of trust and confidence between agencies, a move towards greater complexity in trial design and interpretation is fraught with difficulty. Yet these new opportunities offer enormous prospects of improved and more streamlined decision making and, ultimately, better decisions. Failing to address these would represent extreme negligence.