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The EMA's Peter Arlett looks back on two years of the Accelerating Clinical Trials in the European Union (ACT EU) initiative which aims to improve the environment for clinical trials in the EU by transforming how trials are initiated, designed, and run. In conversation following DIA Europe 2024 in Brussels, Arlett also highlights the impact of the DARWIN EU real-world evidence (RWE) programme in its two years of existence as more data partners are added and studies conducted.

Two years on from its implementation, what impact has ACT EU had on invigorating the EU clinical research environment?

After two years, we have made great progress towards the broad goal of ACT EU: better and more impactful clinical trials in Europe.

Firstly, we have brought the complex web of regulatory actors at both the member state and European level together. We have also launched a Multi-Stakeholder Platform Advisory Board which brings together about 50 different stakeholders from patients to academia and commercial sponsors. There, they can discuss their priorities for invigorating the research environment and making clinical trials more impactful more generally.

This year is the last in the transition to the Clinical Trials Regulation (CTR) (2022-2025), meaning we are almost at the finish line of the transition. Any change has the potential to be painful, with people needing to be trained to work differently, but the progress has been impressive.

The Clinical Trial Information System (CTIS) that was launched in 2022 had challenges at the beginning but is now working *much* better, with high volumes of clinical trial applications being processed through it. A big advantage of this system is that sponsors only need to submit a single application to the IT system for a clinical trial that could potentially run across every EU member state.

Additionally, also under the auspices of ACT EU, we have rolled out some important guidelines on decentralised clinical trials. Prior to this paper, released last year, regulators had not given clear guidance on managing the benefits of decentralised trials (such as accessibility for patients) with its challenges (such as maintaining data integrity and less face-to-face patient supervision).

Finally, we have made major progress in bringing together scientific advice from both the European and national levels on R&D programme design. Eventually, this will mean that sponsors will receive responses to requests for scientific advice from both EMA's Committee for Medicinal Products for Human Use (CHMP) and the Heads of Medicines Agencies (HMA) Clinical Trials Coordination Group (CTCG) concurrently. We will be launching some combined advice pilots under the ACT EU umbrella by May this year, which will represent an important and concrete step towards decomplexifying clinical trials.

What type of trial sponsors stand to benefit most from these regulatory upgrades?

Commercial sponsors, as historically, there has been a significant skew towards these sponsors in multinational clinical trials, and this remains today. Having said that, we are going to be launching various support programmes and initiatives to support non-commercial clinical trials. This is vitally important, as was shown in the COVID-19 pandemic where, apart from vaccine studies, most of the other studies (therapeutics and repurposing) were done by academia. We need to continue to support academia to ensure that their trials are bigger and more impactful going forward.

By the end of January 2025, any ongoing trials under the previous legislation, the Clinical Trials Directive (CTD), will need to be transitioned to CTIS to follow the CTR regime. Given the initial teething problems that CTIS faced, how ready are stakeholders

across the European ecosystem for this impending cut-off?

There are a maximum of 5,000 ongoing trials under the Clinical Trials Directive which will need to be transitioned to CTIS. We have already authorised 900 of these through CTIS and are ready to authorise the remainder. I would like to issue a call to arms for sponsors to get those applications into CTIS, because the EU Regulatory Network is ready to receive them. We have published guidance and an expedited procedure is in place, but processing takes time. It can take up to three months to process the applications, so if they all come in in November and December 2024, things will get very tight.

Have clinical trial numbers in Europe risen since ACT EU was passed?

There have been approximately 2,500 clinical trial applications since the launch of CTIS in January 2022 and we are authorising about 300 clinical trials per month. These numbers have remained largely the same over the past decade, with the COVID-19 period complicating the analysis for a couple of years.

The problem statement is not, as has been reported in some quarters, that European clinical trials are declining. It is that they are not growing, as they have been in the US, for example. The EU has extremely strong hospitals, hospital networks, and academia: all the ingredients needed for conducting outstanding clinical trials. Moreover, historically, Europe has been the engineroom of global clinical trials, but we haven’t seen the growth. This means that we need to foster this growth in clinical trial numbers, size, and level of innovation.

Some big positives beyond trial numbers are already apparent. Primarily, EMA internal analysis shows that the number of Member States per commercial multinational clinical trial is higher under the CTR than it was under the CTD. This is almost certainly because under the CTR sponsors can apply to multiple Member States with one application. This holds a lot of promise in terms of more, larger multinational clinical trials, whether in two or 27 member states.

Does EMA have any preference in terms of the kinds of clinical trials it is hoping to attract to Europe?

Different stakeholders will have different answers to this question. A patient association representing patients with a particular rare disease would ask for really well-designed clinical trials

around that rare disease. The oncology community might want a big clinical trial focused on optimising the various cancer medicines that are already authorised. A pharma company might want rapid recruitment for a Phase II or III trial of their new investigative medicine.

From EMA's perspective, we want to put in place the ingredients to support whatever type of clinical trial a sponsor wants. This includes those utilising innovative methods or decentralised elements, with the overall goal of collectively invigorating the clinical research environment in Europe.

The COVID experience continues to loom large for regulators across the world and ACT EU includes a focus on clinical trials in health emergencies. To what extent is Europe better prepared today to tackle the next pandemic in terms of fast, efficient, cross-border clinical trials than it was in 2020?

We've come a long way. In terms of clinical trials during COVID, we were too slow and too small in Europe. None of the clinical trials that led to the authorization of the COVID vaccines rolled out in 2020 and 2021 were held in the EU, which was telling. Additionally, there were many clinical trials registered in Europe for repurposing therapeutics but, in general, they were too small to be impactful. Moreover, the big clinical trials that were planned took an exceptionally long time to get off the ground.

To address this, we have rolled out several initiatives. In June 2023 EMA co-hosted a highly successful public workshop with the European Commission's DG Research and DG Sante. The morning session focused on regulatory hurdles and what we can do to improve and speed up the authorisation of clinical trials, while the afternoon looked at infrastructure and funding for fighting public health emergencies.

We're not at our destination yet but we've made significant progress. One example is the Guidance on Regulatory Flexibility for Clinical Trial Applications in Public Emergencies. This Guidance minimises the number of documents that need to be submitted in a health emergency, ensures we have an agile scientific advice offering service, and reinforces the role of EMA's Emergency Task Force (ETF) which brings together regulators with ethics bodies and other stakeholder to ensure that the advice is easily implemented. Bringing together ethics bodies, which tend to sit at a national level, will really speed up the rollout of big multinational clinical trials and reduce the time needed to consult with multiple national level stakeholders. While the ultimate responsibility for ethics decisions will remain at a national level, this is clearly a concrete step forward,

Finally, upgrades on the clinical trial infrastructure and funding side have been embraced at the Commission level, actively supported by EMA. There are interesting discussions ongoing around establishing ‘ever warm’ clinical trial networks for better preparedness and response to public health emergencies. The EC is also talking about creating a coordination mechanism so that with advice from EMA, they can pick products to be subject of clinical trials and gain direct funding fast in the event of an emerging public health emergency. All in all, we still have headroom for improvement, but step by step we are working through the problems that exist to ensure that we are faster in future.

When we spoke to EMA Executive Director Emer Cooke last year, she told us that while the DARWIN EU real-world evidence (RWE) programme only completed four studies in 2022, there were plans for between ten to 15 in 2023, and around 150 per year from 2025. Have these milestones been met and what have been the challenges faced in scaling up this initiative?

DARWIN EU promises to be a great success. It is growing and delivering clinical evidence via real-world data studies. In terms of data partners, we had ten in the first year, we now have 20, with plans for 30 by the end of 2024 and 40 by the end of 2025. The current 20 data partners represent 130 million *active patients* who are continually contributing data, making this a massive and powerful system already.

So far, we have completed 14 studies, with 11 ongoing and the potential to initiate up to 70 additional studies this year, which is in line with our planning. This could vary if we focus on more complicated studies. From 2025, we are contracted to a ceiling of 140 studies, which is an absolute game changer. As far as I’m aware, no other organisation in the world has ever done RWE studies in those kinds of numbers before.

We are going to be able to do this thanks to a few secret ingredients. The first is the use of a Common Data Model. The data partners and datasets we are onboarding are converted into a common structure with mapped terminologies, meaning that computer script can be run through the entire dataset despite the original data source being in different formats. Researchers can then upscale in terms of the number of data sources rather quickly. For example, this means that if a study happened last year using a particular protocol with three data sources, this same study could potentially be replicated this year within a matter of weeks through another ten data sources.

Currently, we are looking at a whole array of different types of studies and questions. We can look at disease epidemiology, understanding who gets a particular disease, their age, gender distribution, their symptoms or mortality, how they are treated, the pathway in terms of therapeutics, and the natural population with a disease compared to the clinical trial population. This allows us to understand the external validity and relevance of the clinical trial results to the general population or the general population with that disease.

We can also do causality studies: looking at associations between particular medical events and exposure to medicines. This is very well established in the drug safety area and has been done for over 30 years but is still relatively new in terms of efficacy and effectiveness. For example, there were some promising vaccine effectiveness studies using DARWIN conducted during COVID because high levels of testing meant that there were a lot of records of infection. Naturally, there is a huge interest from the industry in RWE effectiveness studies, but from a scientific point of view, this is the area where we need to go most cautiously given that it is less well-established than the drug safety area.

How would you define a “complicated” RWE study?

Firstly, complexity can be defined by whether something has been done before. For example, if we have done a study of the natural history of multiple myeloma, written the protocol, identified data sources, and learned from doing, then repeating a study like that would be quite straightforward. Within DARWIN we call these “routine repeat studies.” Another example was one of the studies we completed last year, looking at drug utilisation of antibiotics. This is particularly relevant in monitoring for antimicrobial resistance (AMR) as these were antibiotics on the WHO’s watch list of antibiotics for concern. We were able to look at how the antibiotics are being prescribed and what they have been prescribed for. Now we have done that and established protocols, as we onboard new data partners, potentially every year, we can repeat that study and look at trends in prescribing over time. This is interesting from both a public health policy and AMR prevention perspective.

An additional complexity element is simply the methodological complexity of the question. Looking at the example of efficacy and effectiveness, one of the reasons that we rely on randomised controlled trials is that the randomisation process deals with bias which is the core strength of the methodology. For real-world data studies there is no randomisation. This means that for effectiveness studies very granular data on the patient and treatment is needed, all of which must

be balanced to address potential bias, creating greater complexity. On the other hand, descriptive observational studies using real-world data, for example, in disease epidemiology or drug utilisation, tend to be much more straightforward.

What kinds of organisations and institutions have signed up as data partners for DARWIN EU thus far?

Institutions from 13 different countries have signed up thus far. They are bringing a mixture of GP datasets, hospital data sets, and a couple of registries. For example, we now have the Netherlands Cancer Registry on board, as well as their integrated primary care information dataset.

An exciting newly onboarded data partner is the French Health Data Hub, which has access to the entire insurance dataset of France. This is going to be an enormously important source of data going forward as, certainly outside of France, it has been little researched. DARWIN EU's ability to research this data will open up tons of opportunities for questions about medicines, regulation, and public health policy.

The Nordic health registries – particularly those of Norway, Denmark, and Finland – are of great quality. While the individual countries' populations are not as big as those of countries like France, if we are able to do studies across the different registries, then we will be able to generate extraordinarily rich and informative evidence. This has already been shown through the COVID-19 vaccine effectiveness studies which included the Nordic health registries, making this an extremely exciting region from a data-sourcing perspective.

I notice that the UK is also a partner, even post-Brexit. Is that unusual?

Some of the UK's data sources are truly excellent, and we decided that science and public health should be driving our decisions. We therefore talk about "European" rather than "EU" data sources. The inclusion of the UK has brought scientific benefits.

The UK's Clinical Practice Research Datalink, run by the MHRA, is of excellent quality and probably the most studied electronic health record dataset in the world. We have also recently onboarded the UK Biobank which will allow us to link genomics data to clinical records and clinical outcomes, which is quite exciting and cutting-edge.

How do you hope to expand the DARWIN EU network even further, both in terms of geography and types of data partners?

On the DARWIN EU website, there is an open call for data partners, where interested institutions can send in some basic information about their dataset. Another important evolution has been the very recent launch of an HMA/EMA catalogue of real-world data sources (https://catalogues.ema.europa.eu/). This is a big deal and is an all-singing-all-dancing catalogue which takes fingerprints of the datasets and allows data to be discoverable. This catalogue has only just been launched and there are only 200 or so datasets on there right now, but over time we will be reaching out to different stakeholders with the aim of including thousands of datasets. That means that the data will then be discoverable (some refer to 'findable'), allowing researchers to look at certain metadata around aspects of quality, representativeness, and so on. That is also helpful to us as EMA in selecting future data partners.

Ultimately, we are making choices on data partners based on the questions we get. For example, around 50 percent of all new marketing authorisation applications coming through EMA are in oncology, meaning that we want to make sure we have good data on patients with cancer and cancer treatments. Another area where we are getting a lot of questions is paediatric use. EMA's Paediatric Committee has a difficult job of deciding which products developed for adults should also be developed in children, and if so what the clinical trials or evidence package should look like. Therefore, that might drive a preference to onboard datasets that include paediatric data, ultimately helping the Paediatric Committee better answer these challenging questions.

Do you have a final message for PharmaBoardroom's industry-focused audience on behalf of EMA?

We are in the business of excellent clinical evidence. EMA wants to partner with stakeholders, including those from industry, to drive up the quality of evidence that supports the decisions of regulators, HTA bodies, and payers. Bigger, better, and more impactful clinical trials are one part of this while enabling the use and establishing the value of RWE is another. That is our vision, and we are on track to achieve it.

The industry should work with us to pursue ever better evidence on medicines. This will potentially lead to earlier authorisation of medicines and optimisation of their use. The industry will benefit, but most importantly public health and patients will too.

Photo Credit: European Medicines Agency

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