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How The EU Is Keeping Up With Innovation In Clinical Trials

New Guidance On Supporting Complex Clinical Trials Expected Before Summer

by Vibha Sharma

A senior EMA official says Europe has set the ball rolling on presenting a unified approach on clinical trial processes and strategic matters, and is taking steps to ensure there are no roadblocks.

Regulators in the EU are aware that the global clinical trial landscape is evolving so quickly that recent reforms introduced by the Clinical Trial Regulation (CTR) and being delivered via the new Clinical Trial Information System (CTIS) are insufficient to ensure the region remains a desirable destination for clinical research.

This is why, just days before the CTR came into effect at the end of January this year, a new ambitious EU initiative, called Accelerating Clinical Trials in the EU (ACT EU), was launched with the aim of transforming how clinical trials are initiated, designed and run, said Frank Pétavy of the European Medicines Agency.

The fact that ACT EU was "born" at around the same time as the CTR was implemented and CTIS became functional was "not a coincidence," said Pétavy, head of methodology at the EMA's Data, Analytics and Methods task force. "We had been working hard last year to make it happen" as "we thought… [the CTR and CTIS] may not be enough" for the EU to "retain its status of remaining an attractive clinical research hub globally," he added.

Pétavy was speaking at the Drug Information Association's Europe 2022 conference last month at a session that looked at various initiatives in Europe and beyond to support complex clinical trials. He explained that ACT EU would not only help track and support the successful implementation of the CTR, but facilitate, among other things, clinical trial innovation by

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supporting complex clinical trial designs and methodologies.

> *"We need to speak first with one voice in Europe" — Frank Pétavy, EMA*

ACT EU brings together for the first time three regulatory entities – the EMA, the European Commission and the EU Heads of Medicines Agencies - on the issue of clinical trials "and that's the strongest political mandate that you can imagine," said Pétavy. It will ensure that these entities are "not working in silos" but "together to transform the EU clinical research environment" in support of medical innovation and better patient outcomes, he added. (Also see "*New EU Clinical Trials Transformation Initiative Gets Underway*" - Pink Sheet, 17 Jan, 2022.)

While the CTR is focused on ensuring that the submission, assessment and supervision of trials in the EU are fully harmonized, ACT EU would help to ensure this coordinated approach is also applied to fast-evolving innovation in the clinical trial arena and to address other issues.

A topic high on this agenda is the facilitation of coordinated scientific advice to support trial authorization, marketing authorization and the medicine lifecycle. "There will be changes made to make this happen" and to "make sure that we speak to each other and there is alignment," said Pétavy.

This "doesn't mean that we need to agree all the time, but we need to have a forum for discussion and seek alignment," and ACT EU will be the vehicle for such engagement, he said. The aim is to "ensure a unified European approach for trial processes" at a "strategic level and also at international level, but we need to speak first with one voice in Europe."

Getting 'Good Vibes'

The EMA official did not want to get drawn into the debate about whether the EU had left it too late to initiate trial reforms, especially given that the CTR was initially due to be implemented in October 2018 but was delayed several times as the supporting CTIS portal was not ready. (Also see "*EU Clinical Trial System Launch Delayed To Jan 2022*" - Pink Sheet, 15 Mar, 2021.)

Pétavy noted that "sometimes things do not happen as quickly" and "then the stars align." Taking a positive view of the situation, he said there were "good vibes at the moment" as "people want to speak to each other" and "reach consensus."

To deliver the harmonization goal, the commission is already keeping a close watch on the readiness of EU countries to accept and evaluate trial applications via CTIS. Also, it has clarified that information and documents that are not part of the CTR cannot be requested in trial dossiers by member states. (Also see "*EU Clinical Trial Portal: Commission Reassures On Member States' Preparedness*" - Pink Sheet, 12 Apr, 2022.) (Also see "*EU Clinical Trial Sponsors Reassured On Member State Dossier Requirements*" - Pink Sheet, 14 Apr, 2022.)

As of mid-April, two trials had been authorized via CTIS, while another 31 trials had been submitted for approval and 366 applications were in a draft stage. (Also see "*First Clinical Trial Approved Through New EU Portal*" - Pink Sheet, 11 Apr, 2022.)

ACT EU will build on this momentum to further optimize the EU trial environment by focusing on 10 priority actions in 2022-2023, including establishing a multi-stakeholder platform. Pétavy said he was "very excited" about the cross-stakeholder platform as it is what "many of us have been waiting for many years in Europe."

Another priority is to develop guidance on topics to support clinical trial innovation, such as how to conduct complex and decentralized trials, the impact of artificial intelligence/machine learning on clinical trials, and the interface between the CTR and the EU's new In Vitro Diagnostics Regulation to offer clarity on trials involving an investigational drug coupled with an investigational companion diagnostic.

When it comes to delivering these actions, Pétavy said the "difficulty will be in prioritization" as "there's too much... to do quite quickly." However, work is "already happening and the [ACT EU] steering group has met at least once. So there will be a push to have something tangible," he added.

The EMA official was "fairly confident" that all priority actions would be delivered, but asked stakeholders to keep reminding regulators that "something concrete has to happen."

Complex Trials: Cannot Wait For Things To Settle

Supporting complex trials – eg, platform, basket, umbrella, matrix trials – is a key priority for EU regulators. Such trials are different from conventional trials as they enable researchers to address multiple clinical questions within a single study, allowing the chance to speed up research.

They permit the testing of multiple investigational drugs in one trial using an overarching master protocol and may involve setting up a framework where several hospitals and trial sites work together. "At the moment, this is probably difficult to do in Europe," Pétavy acknowledged.

Concerns about running complex trials under the CTR framework have also been voiced by the industry. While CTIS does provide the functionality to create and seek approval of such trials,

there are operational concerns about their ongoing management via the system, especially relating to handling of substantial modifications.

For some master protocol trial applications, Pétavy said he was aware that the commission was "really pushing and pulling" and "bringing together [the] member states and the EMA to find a solution" and to make such trials possible in CTIS "from a very concrete point of view." The regulators realize that "we cannot wait for two or three years until the system settles" and are keen to come up with solutions to address any urgencies.

New Q&A Document Due Soon

He noted that good progress had already been made on a key ACT EU deliverable - a new Q&A document on complex trials. "It's been very fast" because it usually takes four to five years to write guidelines but here "we tried to move as quickly as possible." Pétavy expects the Q&A document to be published before summer and said it would cover many "hot topics" relating to complex trials, such as:

- Considerations for the planning and conduct of complex clinical trials.
- Additional considerations for the design and conduct of master protocols.
- Facilitating the understanding of Bayesian approaches in complex clinical trials and regulatory decision making.
- Considerations for control data from within a complex clinical trial for regulatory purposes.
- The principles and regulatory pathways to consider when using biomarkers and biomarker assays in complex clinical trials and subsequently applying for marketing authorizations.
- Safety, rights and well-being of participants
- Balancing trial transparency with integrity, and communication between regulators, sponsors, investigators.

Industry, for its part, has high expectations from ACT EU on its ability to support complex trials. Many of the priority actions that the initiative intends to deliver "nicely fit" in with the findings of a 2021 industry workshop on accelerating the adoption of complex clinical trials in Europe, said GlaxoSmithKline's Christine Fletcher, who also spoke at the conference.

While complex trials are more commonly used in oncology, they have gained more attention during the coronavirus pandemic. Novartis's Mireille Muller said the COVID-19 pandemic had

shown that the use of “master protocols, and especially platform trials, can be really super useful to come up quite quickly with new products to treat patients.” (Also see "*Shared Control: Novel Trial Design Works In COVID, But Will Sponsors Buy In?*" - Pink Sheet, 5 Jul, 2020.)