Pink Sheet
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Not A Smooth Ride: How One Of The First Studies Navigated The EU Clinical Trial Portal

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by Vibha Sharma | @ScripRegVibha | vibha.sharma@informa.com

Executive Summary

From grappling with a never-ending list of conflicting national requirements to dealing with numerous technical issues, a research project manager at Norway's Oslo University Hospital talks about the hiccups faced by their multinational COVID-19 platform trial that was among the first studies submitted for approval under the EU Clinical Trial Regulation.

FITTING A PLATFORM TRIAL INTO CTIS WAS COMPLICATED *Source: Shutterstock*

The experience of submitting one of the first studies to the EU Clinical Trial Information System (CTIS), which became operational earlier this year to support the provisions of the Clinical Trial Regulation (CTR), was described with mixed emotions by an academic sponsor at a webinar organized by the European Medicines Agency.

"We know that our trial is a nightmare," Thale Patrick-Brown of the Oslo University Hospital said about EU-SolidAct, an adaptive platform trial for evaluating treatments in hospitalized patients with COVID-19.

"But thanks to constructive feedback" from regulators "we were still able to meet all the requirements" of the CTR without the huge resources of big pharma, said Patrick-Brown, who is trial manager for EU-SolidAct. She was speaking at a virtual webinar organized by the EMA on 1 July to discuss stakeholder experience with CTIS.

EU-SolidAct was initiated under the Clinical Trial Directive, which has been replaced with the CTR. To shift EU-SolidAct to the new framework, information on the trial was re-submitted to CTIS. Although a transition trial is not re-assessed, all documents are checked by the member states concerned to ensure they meet the provisions of the CTR. (Also see "Straightforward But Technical: Transferring Existing Studies To EU Clinical Trial Portal" - Pink Sheet, 26 Jul, 2022.)

Reflections And Experiences With CTIS

The European Medicines Agency's webinar on the Clinical Trials Information System that went live in January 2022 gave trial sponsors and EU member states the opportunity to discuss their experiences with the CTIS so far. Other *Pink Sheet* articles from the webinar are:

- Sponsors Urged To 'Push Back' On EU Country-Specific Clinical Trial Requirements
- EU Rejects Calls To Extend Clinical Trial Regulation Transition Period
- CTIS: EU Member States Seek Advance 'Warning' On Lead Assessor Requests
- So Far So Good: EU Member States On 'Limited' Experience With Clinical Trial Portal
- Straightforward But Technical: Transferring Existing Studies To EU Clinical Trial Portal

Shifting EU-SolidAct to the CTR was not easy because "we are a very large trial with a lot of [study] centers" and the transition process needed a "lot of coordination," explained Patrick-Brown. The trial spans 14 EU member states involving 102 trial sites, and there are plans to extend it to Romania, Switzerland and Turkey.

When preparing EU-SolidAct's dossier in accordance with the CTR, the study team encountered problems in complying with disparate member state-specific requirements as well as making sense of how to structure study data in CTIS given the trial's complex design.

"27 support tickets [were] submitted by me alone and there were more from my team" – Thale Patrick-Brown, trial manager for EU-SolidAct

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There were a lot of technical challenges too. “27 support tickets [were] submitted by me alone and there were more from my team,” Patrick-Brown said, adding that many of these tickets were closed before a resolution was reached. “We also had three false starts due to unsolvable problems” and the trial application had to be entirely recreated in the system, she said.

On the experience of submitting information into CTIS, Patrick-Brown said the system was “rather unforgiving.” Although it “standardizes things,” it “doesn't allow us to have a lot of variation or deviation” and needs workarounds, which means “we have to think outside of the box to fix a lot of the problems,” she noted.

However, the system also has its positive aspects, said Patrick-Brown. “As Norwegians, we are pretty happy to share everything with everyone all the time” and the transparency provisions in the CTR have enabled sharing of trial documents on the CTIS public site, she noted.

But this transparency is also a “bit of an issue” as personal and commercially confidential data has to redacted from documents before they can be made public, she said. “On the whole, it's been very positive” and “we also liked that there is a full audit trail” of documents posted online.

EMA Survey On Critical Hurdles

The European Medicines Agency has launched a survey to gather feedback on the critical hurdles that sponsors perceive or experience when submitting a study application under the Clinical Trial Regulation.

Industry associations as well as sponsors who have submitted a trial application under the CTR (whether it was authorized, rejected, withdrawn or lapsed) have been invited to respond to the survey, the agency announced in the July edition of its monthly CT newsletter.

Endless List Of National Requirements

One of the first hurdles faced by Patrick-Brown’s team in shifting EU-SolidAct to the CTR was complying with different, and “sometimes inconsistent,” member state-specific requirements. “I can't think of one country that has been the same as another country at this point,” she noted.

Trial applications to CTIS involve submitting a two-part dossier, a pan-European part I on scientific and medicinal product requirements, and part II on national and patient-level requirements. Patrick-Brown said the “national requirements are quite high” so many new documents are required. This resulted in the need for:

> “A lot of signatures” and while some member states accept electronic signatures, others do not, said Patrick-Brown.
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> Better coordination as some countries have developed their own new templates and “they won't allow [sponsors to use] a central template,” she added.
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> Keeping track of “inconsistent” national requirements. Some countries asked for a signed agreement between the sponsor and study site before the trial was approved. Patrick-Brown said this was “quite unusual because generally you don't sign that agreement with the site until after the trial is approved.” Also, some countries asked for a copy of the annotated electronic case report form, some required statements from the data protection officer (appointed under the EU General Data Protection Regulation), but others did not. “It just goes on and on... The list is endless,” she noted.

Platform Design Created Issues

The platform design of EU-SolidAct made its transition to the CTR more complicated. Platform trials are characterized by a "shared framework" that allows for the investigation of multiple investigational medicinal products (IMPs) in a continuous manner, with different IMPs "entering" and "leaving" the platform at different times based on pre-specified decision rules. Such trials have an overarching master protocol with multiple sub-protocols.

Patrick-Brown noted that CTIS "wasn't designed to take care of platform trials" so when creating the initial study application in the system "we were a little bit unsure what to do." The way CTIS is set up means that each upcoming study arm in the shared framework has to be entered as a brand new trial, she explained.

In practice this means:

> In most countries, "we have to pay [the] full fees for every arm that we add... and that's actually very expensive" and a "real problem" for academic sponsors, said Patrick-Brown.
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> Redoing "all of the documents every time we start a new arm," which involves "wrangling" with 600+ documents, she noted. Moreover, all these documents undergo the entire examination/validation process again which "wastes a lot of time where docs are straight duplicates of already approved documents."
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> Deciding "where on Earth do you put the master protocol and how do you refer to it" in sub-protocols. For EU-SolidAct, "we've had problems with this already" as "it's not immediately clear to some of the ethics committees where certain documents are," she said.

EU-SolidAct's initial arm is investigating the impact of Eli Lilly's rheumatoid arthritis drug Olumiant (baricitinib) in immunocompromised COVID-19 patients. Another arm of the trial (AXL-SolidAct), to investigate BerGenBio's AXL inhibitor bemcentinib in treating moderate COVID-19 infection, was submitted as a separate trial in CTIS.

Some of the issues raised by Patrick-Brown relating to platform trials were addressed in an EU-wide guidance, issued in June, on the scientific and operational aspects of undertaking complex clinical trials under the CTR. (Also see "EU Offers Advice On Running Complex Clinical Trials Under CTR" - Pink Sheet, 10 Jun, 2022.)

Technical Challenges

Based on her experience with working in CTIS, Patrick-Brown has some tips for sponsors planning to create a new trial application in the system. Have all documents and information in one place "ready to go" just in case "you have to start again" else it can be a "logistical nightmare."

Also, she highlighted some "outstanding issues" still plaguing the system that sponsors should be mindful of:

> Adding trial sites to the EMA's Organization Management Service (OMS) that supports regulatory activities throughout the EU. "It is quite an onerous process" so "make sure that all your sites are entered into the OMS and that you know their number prior to starting" the application, said Patrick-Brown. For EU-SolidAct, this issue "became a logistical nightmare" as around 50% of the 102 study centers were not registered, but "luckily, we got some help... from the EMA," she said.
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> It is difficult to work on country-specific requests for information (RFIs) in parallel. RFIs are issued by member states seeking more information on the trial, but the system allows only one person at a time to work on RFIs. "It means that you need to have really good coordination" within the team to respond to RFIs within stipulated deadlines, she explained.
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> Documents uploaded by the sponsor, regulators or ethics committee may not show up on the other side.

> This can be addressed by sending screenshots and asking the helpdesk to fix the "viewing rights" of the person who cannot see the document.
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> It is not possible to "put dates in the past even for transitional trials that are already running," she said.

For the helpdesk to be able to assist with an issue, Patrick-Brown suggested providing as much information as possible in the ticket, including the time, date, username, web browser, screenshots and the embedded codes "if you know how to grab them" and to "be prepared to reopen the tickets," if need be.

She suggested CTIS users flag up even minor issues as it "might be the tip of the iceberg." As a "former coder myself, I feel for these guys - this is a tough situation. So any help you can give them is probably really great" and "everybody is very open to wanting to help," she said of the EMA, which maintains CTIS.