Combined Studies Under the New EU Clinical Trial Regulation

The key aims of the new EU Clinical Trial Regulation 536/2014, which is currently planned for implementation in mid-2019, are to boost clinical research in the European Union (EU).

Its major impact will be a new authorisation process which will involve a single submission via the EMA portal, with a two-step approval procedure: the first step assessing the scientific portion; and the second assessing the local requirements of the application file.

The Regulation has mainly been developed to improve the competitiveness of the EU in late-phase clinical research, however early-phase clinical research (Phase I/IIa) has several specificities which are not covered by the new Regulation 536/2014, potentially introducing additional challenges.

Combined Studies

There is a growing tendency to obtain a first indication of efficacy early on in a drug's development. This has led to so-called 'combined' studies, where the single ascending dose (SAD) and multiple ascending dose (MAD) part in healthy volunteers (HV) is supplemented by a patient cohort, in which a limited number of patients are included to make a first assessment of the efficacy of the drug. These data are used to make early go/no-go decisions and to support the design of Phase II trials.

In the EU, the HV part of such studies is often conducted in countries with competitive Phase I timelines and a well-developed clinical research infrastructure, such as Belgium or the UK.

One of the complexities of these studies is that they may require treatment-naive patients. Depending on the indication, these can be difficult to find in Western Europe, but more easily in Eastern Europe countries. The problem is that clinical trial authorisation (CTA) approval timelines in Eastern European member states are much longer than those where the HV part of the study will be conducted, ranging from 60 to 90 days, depending on the country.

Under the current Directive 2001/20/EC, this is not an issue as each country individually approves the study, so it is possible to start the HV part quickly in a country with short Phase I timelines, and by the time the countries where the patient part will be undertaken have approved the trial, the HV part has been finished, and the trial can proceed to the patient part. This makes the EU a competitive region to perform such studies, combining quick study start with good patient recruitment.

Under Regulation 536/2014, this will no longer be possible, as the full trial will be approved at the same time for all the countries. It will, therefore, be impossible to take advantage of countries with short approval timelines to start the study, while the study is still under review in the countries where the patients will be included, but which have longer CTA approval timelines. Under the new Regulation, the approval will be available between 60 and 106 days after submission, which is much longer than the 15 days' approval for the HV part that is available under current national law under Directive 2001/20.

The upshot is that this will reduce the EU's competitiveness to perform these trials. The risk is that sponsors will conduct the HV part as a single-centre study in the EU (taking advantage of the short timelines some MS would still offer for such studies), but will conduct the patient part outside the EU, or decide to perform the full study outside the EU. However, the Regulation does leave room for manoeuvre. It is indeed possible to submit a combined proof of concept (PoC) protocol as a single-country study in the country where the HV part will be conducted. As the trial is approved, a sponsor can start the study, and then add the 'patient part' countries as additional countries. Adding these will take between 52 and 83 days under the new Regulation, depending on the length of validation and the questions. This will allow sponsors to maintain the current advantage of being able to start such a study quickly.

However, this can entail some risk, as although it is allowed under the Regulation, it is not within the "spirit" of it. An applicant choosing this approach could run the risk that the member state being added as an additional country might not be agreeable to the trial, as they would have to accept the conclusion of the assessment of part I, despite the fact that they would be responsible for the full patient part.

When choosing this strategy, it would be advisable to discuss this upfront with the concerned member state.

Figure 1 shows a combined FIH/PoC study conducted in three countries, Belgium (HV), Romania and Poland (patients). Three scenarios are presented: the first gives the approval timelines and

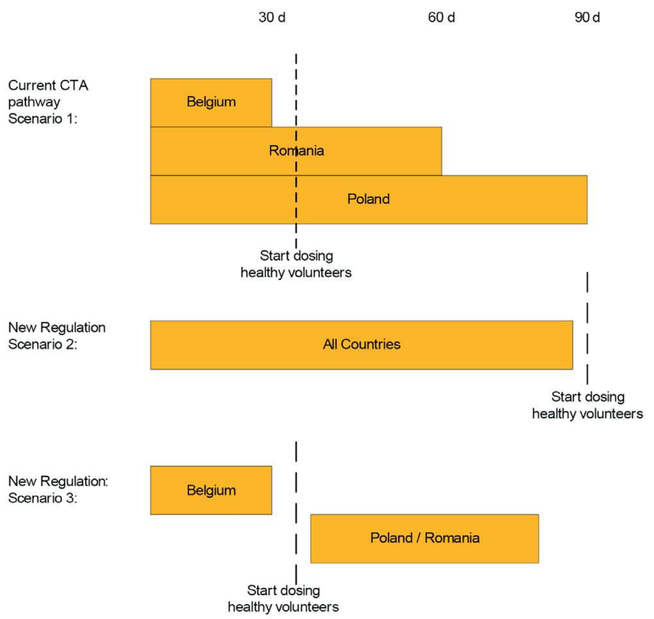

Figure 1: Approval timelines for combined protocol with patient proof of concept part

the date of the start of the study (as first-patient-first-visit) under the current Directive; the second scenario does the same but under the new Regulation, when all countries are included in the initial application; and the third scenario gives the approval timelines and study start when Belgium is included in the initial application, and Poland and Romania are the additional countries.

Conclusion

While the new Regulation 532/2014 will be beneficial for larger late-phase trials, it might have a negative impact on the performance of combined studies, where it could delay the start-up timelines. However, from a regulatory viewpoint, the choice of country in which to conduct Phase I studies is not only dependent on timelines but also on a good infrastructure for scientific advice.

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