Table 1. EU Clinical Trial Regulation changes to address limitations in existing Clinical Trial Directive.

Issues/ limitations of the existing Directive	**Changes in the new regulation to counteract these limitations**
Reduction in the number and/or delay in the initiation of noncommercial investigator-driven trials including the ones investigating marketed medicinal products.	Clearer definition for investigator-driven trials conducted using marketed, authorized medicinal products which will be subjected to less stringent requirements (low-intervention trials).
Several regulatory authorities are required to approve a multi-state clinical trial leading to a large amount of associated paperwork and costs.	The sponsor is required to submit a single application dossier for all Concerned Member States within the EU, where the sponsor is intending to carry out a multicenter, multi-state clinical trial.
Different set of forms in different EU member states are required for obtaining a clinical trial approval.	The application dossier will follow a harmonized format and will be submitted through a single web-based portal (the EU portal).
Variable approval timelines and divergent assessments of clinical trial applications submitted by sponsors to different Member States	All member states will have to follow the specific timelines and procedures for Part I and II assessment of clinical trial applications set out in the Regulation.
Reporting of all suspected serious adverse events, regardless of whether they are caused by the investigational drug or by the underlying disease, separately to all competent authorities and ethics committees.	Sponsors are required to submit their suspected unexpected serious adverse reactions (SUSARs), annual safety reports and other relevant adverse events that influence the benefit-risk balance of the trial, directly to an extended module of the EudraVigilance system.
Difficulty of obtaining a legal representative to give informed consent in clinical trials being conducted in emergency situations (e.g., sudden life-threatening conditions).	Simplified consent requirements are provided for conducting clinical trials on vulnerable populations, including incapacitated subjects and in emergency situations.
A single sponsor is responsible for a multicenter trial, which is considered a major challenge for academic sponsors.	Multicenter clinical trials may have more than one sponsor, defined as co-sponsors, sharing the responsibilities among them.