REGULATORY FOCUS

The Changing Clinical Evidence Requirements Under IVDR

By Karen Richards and Mona Dean

This article discusses the key elements of clinical requirements per the In Vitro Diagnostic Regulation (IVDR) and clinical planning. The IVDR emphasizes the need for manufacturers to demonstrate the clinical evidence for all medical devices.

Introduction

Whether a company is small or large, the idea of needing a clinical trial to demonstrate device performance can seem daunting. At the CEO level, concerns include cost, time to market and influencing the board of the market potential. At the regulatory affairs level, concerns plague the strategist over whether method comparison is enough vs demonstration of clinical utility. For the clinical affairs manager, cost containment, access to patient samples, availability of clinical trial sites, seasonal challenges and a host of other concerns are paramount.

For most companies operating in the US for any length of time, these concerns are a routine part of doing business. However, for the small start-up trying to make that first entry or for ex-US companies trying to enter the US market, these concerns are new and can be overwhelming. Many companies choose first to enter the EU market where the barriers to market entry are lower. Once on the market in Europe, revenue and experience can generate adequate capital for companies to take the dive into the US market and conduct clinical trials. That approach may be about to change.

In May 2017, the *In Vitro Diagnostic Regulation (IVDR)* was passed, superseding an earlier Directive 98/79/EC, with full application set to occur on 26 May 2022.{1,2} The new requirements are applicable to IVD products currently on the EU market; such products also will be required to produce clinical evidence data by the same timeline in order to continue being marketed in EU. One of the most significant changes resulting from the *IVDR* is the requirement for generating clinical evidence, based on proportionate to the

risk class. For companies that never before were required to conduct clinical trials or generate clinical evidence, this new requirement more similarly aligns with what is required in the US. Because of this, IVD companies planning to CE mark their first product or continue to market their existing CE-marked products may not want to wait until 2022 to transition.

Clinical Evidence Requirements

What are the clinical evidence requirements? In general, clinical evidence is required to ensure the device achieves the intended performance. Under the *IVDR*, manufacturers are required to have on file a clinical evidence report that includes scientific validity data, analytical performance data and clinical performance data, if applicable, based on the product's intended use. Unlike US requirements, the clinical evidence report is a living document, similar to risk documents and requires review and updating throughout the product's lifecycle. The Global Harmonization Task Force has issued several documents to assist manufacturers in determining what IVD clinical evidence means and how it is studied.{3-7} Clinical evidence is used to support the marketing and labeling of the IVD, including claims made about the scientific validity and performance of the device related to clinical utility. As the science changes over time, the information documented in the clinical evidence report must be updated to address assay formulation and/or performance refinements and new publications that add information about the utility of the type of device. Similarly, information obtained through these and other postmarketing surveillance activities may require that manufacturers update device labeling to remain current.

What does this mean for manufacturers? Under the *IVDR*, data collected on currently marketed products can be used to support the clinical evidence report. So companies operating a robust postmarketing surveillance program can benefit from collating this information and generating a clinical evidence report. If a company is not currently collecting this information, now is the time to begin as data collected over the next two years prior to applying for certification under the *IVDR* can be included in the clinical evidence report.

Companies seeking to place a new product in the EU market can look to the US model for what type(s) of data are necessary to demonstrate sufficient clinical performance and, more important, key building blocks for what a good clinical trial looks like.

Clinical Trial Planning

Preparation for the conduct of a clinical trial requires upfront planning and execution to ensure trial success and mitigate lengthy delays and rework. Decisions made during the planning phase are often driven by a company's corporate goals and timelines and reduced budgets that may negatively impact study conduct and data quality after a trial is well under way or even completed. It is important to create a detailed project plan, identify the key driving factors and steps to be taken during the start-up process and assign those tasks to individuals with the knowledge and skill set to accomplish them. Key driving factors include but are not limited to protocol development and finalization, site identification and feasibility, case report form design, electronic data capture build and user acceptance testing and investigational product readiness. It is also important to identify risks and have a mitigation or backup plan in place.

Having a complete and final protocol prior to initiating other trial start-up activities is important in laying a solid foundation for a successful clinical trial. Oftentimes a company wants to move forward with site identification and feasibility using a draft protocol or synopsis while the final protocol is being developed. The risk associated with this approach is that site identification and feasibility may need to be reassessed if the protocol design or logistics change significantly. Targeted patient population changes based on inclusion/exclusion criteria, amended number of patient visits or procedures to be performed, sample handling, processing and testing and storage requirements can all change. This is frustrating for both the company and sites and can cause significant delays or withdrawal of previously selected sites. Many sites are not willing to move forward into the contracting and budgeting phase without a final protocol.

Some common approaches to site identification may not always result in the best options. Companies often target sites that perform a significant number of a specific diagnostic test, prescribe a large amount of a certain medication or have faculty members who

are considered Key Opinion Leaders (KOLs) or experts in the therapeutic area. However, high volume of specific diagnostic testing does not necessarily mean a site will have direct access to the patient population for subject recruitment. Some site laboratories serve as central laboratories that receive patient samples from physician offices and clinics that are not close to the hospital/clinic. These patients may need to be excluded due to distance from the recruitment center. High prescribing does not ensure patients will meet eligibility criteria. While KOLs are great advisors, they may not necessarily have the setup to conduct trials or recruit patients. Their contributions to the success of the trials may come in a different form. Common project pitfalls are made at this stage that lead to poor study enrollment and potential lengthy project delays.

A site feasibility assessment is a critical step in the start-up pathway to determine a potential investigator and overall site-fit for the project. Developing a concise and detailed feasibility assessment tool to aid in site selection is essential. The feasibility assessment should be created specific to the protocol design, ensure all processes and logistics are mapped out in the series of questions to be answered and can achieve a clear picture of a site's ability to perform the study. It determines if the site has the appropriate facilities and equipment, patient population, resources, experience and other essentials for successful trial performance. Whenever possible, feasibility assessments should be performed both via telephone and in-person and conducted with multiple applicable site representatives. Spending the extra time at this step to ensure a site has an adequate patient population that can be recruited and retained to study completion will greatly aid patient recruitment and adherence to project timelines. Completed feasibility assessments should be evaluated individually and collectively to determine primary and backup sites.

The final protocol is needed to finalize and lock Case Report Form design. Electronic Data Capture (EDC) builds can be performed in parallel with the other start-up activities. On average, most EDC systems take eight to 12 weeks to design, build and test prior to going "live." Thorough user acceptance testing of the developed product is a critical step often overlooked or truncated. Testing from various stakeholders including site study coordinators, clinical research associates, adjudicators and others will go a long way in mitigating issues once the system is operational. Training sites on the final database design vs a test database is important for data completeness and integrity, aiding in the reduction of data queries for sites.

Trial start-up activities should coincide with the planned investigational product readiness, appropriate regulatory notifications for placement of an IP into the EU for data collection and availability to be shipped to the sites. Companies should have constant communications with their manufacturing facilities and ensure the study product is ready when the investigator meetings and/or site initiation visits are planned.

Shipping delays should be taken into consideration as well. If IP is being imported, extra time should be devoted to ensure appropriate import/export permits are obtained so there will not be any delays in customs. Utilization of companies or individuals that have specific experience handling import/export issues can aid in eliminating unexpected delays. Delays in IP availability may lead to site disinterest in the trial, concern about the IP availability for their subjects or misconceptions regarding the company's organization. Timely communications to the site regarding product availability and shipping are important in retaining site interest and internal planning.

Regardless of the type of trial to be performed (drug, device, diagnostic), successful execution of each deliverable in the start-up process will drive study quality and lead to a positive trial outcome.

Conclusion

While the *IVDR* identifies a new process and terminology for meeting the requirements in demonstrating scientific validity, analytical and clinical performance for an IVD, the best practice for generating this evidence relies on established global good clinical practices.

References

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