Leading Non-Interventional Post-Authorisation Safety Studies to Success

In post-authorisation safety studies you need high data quality and compliance to fulfil requirements of regulatory authorities. Particularly with local doctors, which have limited infrastructure, such studies have a special challenge to keep timelines and match compliance criteria

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The term non-interventional study (NIS) includes observational studies or registries that are initiated by the sponsor. One subset of NIS, which is frequently required by regulatory authorities, is a non-interentional post-authorisation safety study (NI-PASS). NI-PASS comes with its own specific set of challenges, which sites – and sponsors – sometimes tend to underestimate. All parties should be aware that the safety element increases the demands for data quality, completeness, and keeping records up to date. False expectations can reduce motivation on the part of study teams, potentially endangering the success of the whole NI-PASS.

NIS vs Clinical Trials: The Site Perspective

By definition, an NIS is constrained by the limits of standard medical practice. The whole patient care setting must be in accordance with the label, and broadly reflect real-world conditions. Sites involved in an NIS, therefore, do not have to address issues, such as randomisation or study medication logistics. Similarly, the observational plan of an NIS must not ask for extra patient visits or assessments that would not be part of routine treatment. The main effort involved in an NIS is the informed consent briefing at the start and completing the electronic case report form (eCRF) after each consultation. For the sites involved, an NIS generally means significantly less work than a clinical trial.

Safety Adds Complexity

However, with an NI-PASS, site workload and engagement can be much higher. Objectives may include additionally determining, describing, and quantifying safety risks to confirm the safety profile of a drug, or assessment of the effectiveness of the risk management measures implemented (1). A common reason for the EMA to ask for real-world evidence is that treatment of patients in clinical practice is not constrained by the criteria adopted in clinical trials. Clinical trials use strict inclusion and exclusion criteria and, as a result, the patient population may significantly differ from the real-world practice. Furthermore, unexpected co-medications or off-label dosing may add to the risk.

The results of an NI-PASS may determine whether or not a marketing authorisation is upheld. Therefore, scientifically sound planning, exact implementation, documentation, and presentation of data are of paramount interest to the sponsor. An NI-PASS undoubtedly demands more work from sites than a standard NIS. For one, the eCRFs are always more complex, and extensive data cleaning is required. For another, the marketing authorisation holder commits to official timelines imposed by regulatory agencies that have to be met. Periodic safety update reports (PSURs) have to be prepared and submitted at regular intervals. Submission of PSURs, and other update reports to the regulator, can entail data snapshots as often as twice a year, thereby requiring sites to update eCRF data almost on a permanent basis. The requirement for regular reporting to the authorities also shines a brighter

spotlight on NI-PASS recruitment rates. Consequently, an NI-PASS involves more frequent contacts with the supervising clinical operations team, again resulting in additional workload for the sites. All in all, an NI-PASS requires higher site involvement. Sites with no PASS experience may, therefore, be inclined to underestimate the overall workload, as well as the time criticality of the project. If insufficient resources are allocated, or the study is delegated to inexperienced team members, it can lead to conflicting situations and low recruitment rates. To keep sites motivated, forward planning of the study, including operational aspects and giving the site a realistic estimation of the time and personnel resources needed, is imperative.

Consistent and Clear Communication With Sites Is Essential for Study Success

In an NI-PASS setting, sites are approached not only by clinical operations staff, but also by the medical science liaison (MSL) team. The MSL team is the sites' main source of information about newly available therapeutic options. MSL teams are frequently also involved in the recruitment of sites for an NI-PASS, and provide preliminary information about the study at a very early stage. The clinical operations team, which includes the specialists for the operational aspects of a trial, often enters into contact with the site only after the site has already been pre-selected. Therefore, it is important that the conditions and prerequisites for taking part in a PASS are explained thoroughly and upfront by the medical team. In the real world, sites are not always well informed about their duties and responsibilities when starting a study. This can lead to sites losing motivation or even backing out when they realise the extent of the work involved. To avoid endangering project progress by low recruitment rates or site withdrawal, it is crucial to provide a realistic outlook on the demands and challenges of a study before starting to negotiate site participation. Another important operational aspect is to select appropriate sites. Especially for PASS, where the emphasis lies more squarely on quality and solid scientific data, experience and capabilities should be the main focus when selecting suitable sites. In this process, the operational experts of the clinical operations team should have the final say.

Guiding the Site Through the Study

Even if sites are well trained on all operational aspects during the initiation phase, permanent and intensive support throughout the study is needed nonetheless. Any operational issues cropping up during the study should be resolved thoroughly and on time. Lack of adequate support will decrease patient recruitment and compromise data quality. In an NI-PASS, effective site support is more important than ever as time-critical issues have to be solved in advance of potentially necessary data snapshots and timelines have to be met. Otherwise, marketing authorisation may be at risk.

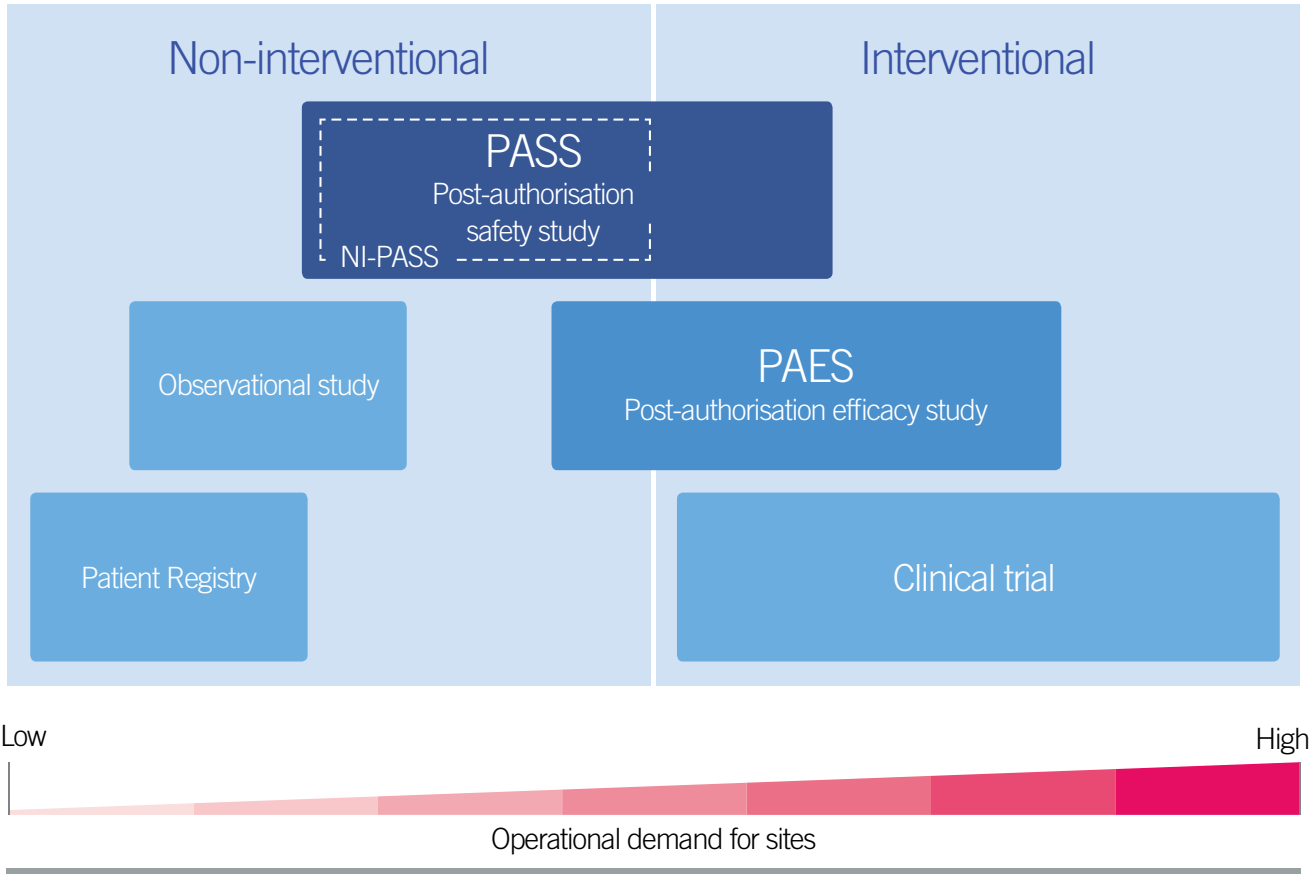

Figure 1: Interventional or non-interventional aspects of different types of studies and the operational effort involved

Cooperation of Clinical Team and Medical Liaison to Optimise Site Support

As an NI-PASS is more operationally demanding than a 'standard' NIS, close cooperation and regular communication between monitors and sites is even more important. However, there are limits in the influence that can be exerted on sites that do not comply with quality standards or are simply too busy to keep timelines. The sponsor's medical team communicates with the sites on a scientific level. Approaching sites by the MSLs can help the clinical team keep sites on track and improve data quality and compliance with the observational plan. To coordinate interaction with the sites, close communication between the clinical operations team and the MSL team is essential to keep both parties abreast of the latest developments. This will help to optimise site support. In addition to regular communication with tools such as conference calls, emails, and SharePoint, a communication platform – used for customer relationship management – would be a useful way to minimise communication gaps.

IT Solutions Could Interconnect Sites, Sponsors, and CROs to Facilitate Project Progress

A communication log accessible to the clinical and the medical team with a transparent presentation of all on-site activities can help to address shortcomings in cross-company communication. Rather than implementing stand-alone software, a practical way to establish this type of communication tool would be to add an application to the clinical trial management system (CTMS). Off-the-shelf CTMS systems, often cloud-based solutions, usually have no flexibility to add such functions without involving the IT developer team of the provider. By using a low-code CTMS system with the flexibility to add applications on the basis of existing building blocks of codes, new features of this kind can be introduced quickly and with low effort (3). To facilitate cooperation between clinical operations and MSL teams, between sponsor departments and CROs, and to provide a unique point of information for all communications about a certain project with the site, a communication log of this kind was introduced. This communication log incorporates all available sources of communication with a certain study site from sponsor and CRO systems (emails, letters, faxes, phone calls, and more) into one chronological list containing the date and time of correspondence and the subject. Every authorised team member can see if other parties contacted the site and what the conversation was about. Obstructions due to data silos and cross-company borders are removed. Information is easily accessible via website or smartphone app.

Unification of IT Systems Increases Efficacy in Cross-Company Projects

Clinical research projects involve a large number of interdisciplinary parties, many of whom work across company borders. Solutions to interconnect these parties could foster clinical research but are still in their infancy. A PASS is located at the interface between clinical research and post-marketing surveillance of a product. Good cooperation between the MSL and clinical operations team will improve interaction with sites. IT solutions that can interconnect the two parties are of special importance to optimise site support. The supervision and support of study sites by a communication log jointly used by clinical operations and MSL teams is an example of how unification of IT systems can significantly improve site operations and enhance data quality. Ultimately, such IT-based improvements can lead a project to success.

References

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