Orphan Drugs – Focus on clinical trials

Effective planning and conduct of clinical trials in rare diseases

By Sven Engel, CEO, SynapCon Ltd. und Thomas Ogorka, CEO, QED Clinical Services and OrphanReach Partner

6 to 8% of the European population suffers from a rare disease, which corresponds to about 27 to 36 million citizens. In addition to the approximately 7,000 known ones, approx. five rare new diseases described in the literature weekly. The global market for the treatment of rare diseases is expected to grow by 7.4% annually to a total of 127 billion USD by 2018. Despite these impressive figures, the products still have to overcome the hurdles of approval, which places some special demands on the clinical trials to be carried out.

Sven Engel

Thomas Ogorka

The number of persons available for such a project is very small – often there are only a few per country. Therefore, the cost per patient is very high, while the total cost of the study is usually lower than with conventional projects.
This is primarily due to the low number of cases, which focuses on the difficulty that each patient who is discontinued early or a delayed approval procedure causes significantly higher costs than with large-scale projects. The great interest and commitment of the organizations concerned and their supervising physicians (see box) is in addition to the financial as well as the reputational damage in the event of problems in the operational implementation more noticeable than with conventional projects.

Rare Diseases

Often there is no treatment alternative, and many sufferers hope for the rapid availability of a drug to alleviate the symptoms and delay the often-fatal course of the disease. The latter also explains the high willingness to participate in „patient registry" or "named patient" programs, as well as the active and advisory participation in clinical projects by the patient organizations. These are also what some developments are only getting off the ground – in some cases even enabling the financing of university projects.
This can lead to strong partnerships between university research, industry, and patient groups.

Planning phase gains in importance

At the cost opposite conventional projects to implement is it from there meaningful a higher effort in the planning to invest. Planning ahead helps to use resources efficiently in terms of personnel and materials and to clinically complete the study as simultaneously as possible with the participating countries/centers. Strategy and risk planning should also be worked on at the latest when the protocol is started. Cost planning without considering the possible risks does not make sense. This includes the necessary and ongoing contacts with the authorities, the planning of payer discussions on patient care (e.g., care at home), early discussions with study participants and patient organizations as well as market access considerations ("evidence-based marketing") and measures for "patient retention". Possible risks must be identified, financial implications mapped, and appropriate measures considered if they occur. The

possibility to extend or stop a project geographically, temporally or in terms of the number of cases at an early stage should be considered and also recorded financially. It should also be noted that in many countries, often emerging countries, the product must be made available free of charge to the participating patients after clinical completion of the trial until market approval. This can be associated with considerable expense.

Vendor selection

Strategic planning must be implemented in the operational set-up-. For this purpose, it seems indispensable to involve people with an extensive understanding of processes on the supplier side (CRO). In contrast to projects that involve many patients, rare diseases require tailor-made processes and additional services (see Table 1) are of crucial importance. A change of the employees involved is more difficult to compensate here.

Tab. 1: Additional Services (Sequence without wagering)
Therapy at home
Patient transport
Market access analysis
Orphan Drug Designation
Patient communication
Real World Data Collection
Prevalence data collection

Source: www.orphan-reach.com

Especially in project management and clinical monitoring, other priorities arise (see Table 2) and more extensive responsibilities have to be taken on.

Quality planning

The quality and handling of potential risks can be easily planned in the project business. This has not yet been sufficiently taken into account. The reasons for ignoring this important instrument of governance are complex. One is the frequent demand for early first patient enrollment and wrong priorities for milestone-dependent payments.

Tab. 2: Prioritization at project level		
Task	Traditional Studies	Rare Diseases
Contact with authorities	*	**
Patient Retention	**	***
Contact KOLs	*	***
Patient Registry	N/A	**
Market knowledge	*	**
Patient Organization	*	***
Project management	**	***
Clinical Monitoring	*	***

* Less priority/responsibility
** Usual Performance and Responsibility
*** Very important/high responsibility

Often a lot of money is invested to completely eliminate a tiny residual risk – money that would otherwise be better invested ("zero-risk bias"). It is advisable to involve the selected CROs in the planning activities at an early stage and to commit to the common objective in order to be able to control risks and to have the processes under control at all times.

Conclusion

As part of the funding of research projects on rare diseases, the interest, not only of biotech companies, in this branch of research has increased - abruptly – and undoubtedly for the benefit of the patients concerned.

However, traditional thinking can only be used to a limited extent to meet the special requirements of the clinical development of orphan drugs. Besides adapting the structures in one's own environment to the special requirements, the selection of suitable suppliers - especially the CRO - can not only help to reduce costs, but in extreme cases can make the difference between success and failure of an orphan drug development.