Finding the Right Contract Research Organisation (CRO) in Rare Disease

Developing a New Medicine

Only about 6% of people with rare disease currently have a treatment for their condition1 and after an average of 7 years navigating the diagnostic odyssey, some patients receive a diagnosis and then enter a life of symptom control and support, but not necessarily therapy 2. This needs to change.

To develop a new therapy a drug or device must go through a multi-stage process of clinical development. Here, the benefits and risks of potential new treatments are tested in non-clinical and clinical trials that build together into a program of understanding together in the form of a research package to deliver the component pieces of evidence (Figure 1).

The Research Package

Non-Clinical Research	This is the research that happens before a human ever takes the drug. The aim is to explore how to tackle the condition at a cellular level, select the best potential drug, and predict side effects so that they can be monitored and managed when people first take the medicine.
Phase One	Small trials usually involving healthy volunteers. The aim is to characterise what the drug does to the body, what the body does to the drug (most of us are pretty good at getting rid of unwanted things from our system), as well as finding out which dose might be best.
Phase Two	A moderate number of patients receieve the potential drug and are monitored. Researchers look at early signs that the medicine may be of benefit, as well as characterising and managing side effects.
Phase Three	This is the largest study and is designed to test the balance of beneifts and side effects for the population receiving the potential treatment. This is the ultimate test of 'does it work?'

Figure 1. The standard approach to building a clinical trial program.

It can be seen that developing a new treatment is a long process that involves multiple trials before enough evidence is gathered to fully understand the balance of benefits and side effects that patients can expect.

As many will have seen in the news with the Covid vaccine trials – large numbers are usually needed to be able to reliably characterise a therapy and characterise it quickly 3. A rare disease though is – by its very nature – rare and with that comes several inherent challenges.

This leaves the rare disease community with a unique problem – a desperate need for new treatments, along with the challenge of delivering robust research when there is only a small number of available people, spread around the world, who can actually take part in trials to make those treatments reality 4.

Conversely, this can sometimes lead to people receiving multiple invitations to join clinical trials by several sponsors who are competing for the same cohort of patients.

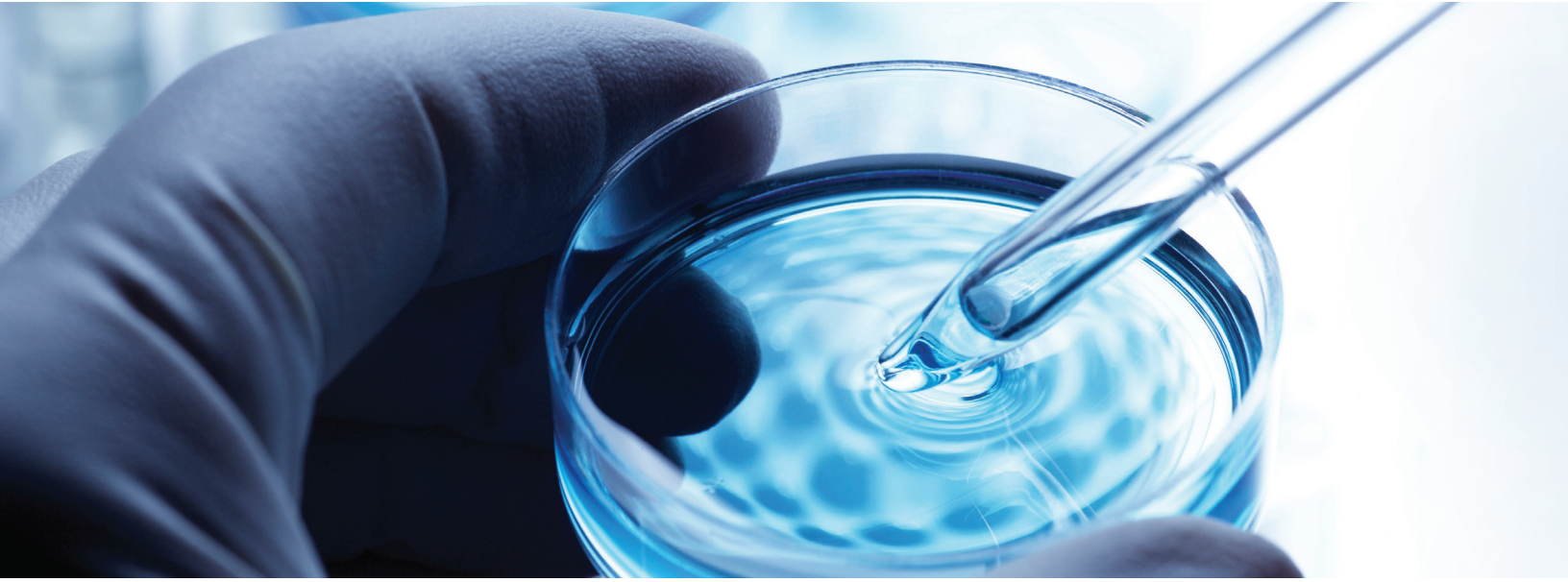
Contract Research Organisations (CROs)

Running good clinical trials within the rare disease community requires a unique skillset. There are many groups who need to collaborate to successfully run trials as shown in Figure 2. The CRO is a team of people who form a 'delivery engine' – sitting between, and partnering with, all groups to ensure a trial is delivered to the highest standards, and in a way that is meaningful and respectful to all those involved. They have two simple remits: Make it happen. Do it well.

Figure 1. The main groups of people who come together to deliver clinical trials

For sponsors, selection of the right CRO to develop their orphan drug is crucial to the delivery of a successful clinical trial6. Plus, the future of the potential medicine for rare disease patients is entirely dependent upon the quality of the trials that are run.

Choosing the right CRO is therefore a fundamentally important step towards success and one that should be undertaken carefully. We discuss what might impact upon this decision-making process below based upon published literature, white papers, and our own experience and that of our clients.



Selecting the Right Partner

Experience

As already discussed, the challenges of delivering clinical trials within the rare disease community are unique 5. A CRO delivering this research must have a strong track record, understanding of the environment that the trial is working within, and the skills to manage problems proactively and with efficiency and positivity. A successful trial is built upon the quality of the relationships, agile nature of delivery and knowledge of the ecosystem involved. It is therefore essential for each CRO team member to have experience and understanding of delivering research in the rare disease community environment so that issues can be predicted, proactively overcome, and any unforeseen circumstances can be handled promptly when they arise.

A positive and efficient partnership can be achieved if CRO team members use their expertise and experience to see beyond the brief – be responsive to questions, and proactive enough to spot opportunities – using their experience to solve problems that may arise as rare disease trials reach out into patient's real world.

Key questions to ask: What is the experience and capability within the specifific project team the CRO proposes? What is the CRO's track record in delivering trials in rare disease?

Sponsor-CRO Company Alignment

Optimal sponsor-CRO partnerships become long-term relationships built on a foundation of trust. For a sponsor to engage and rely on a CRO, both companies must have compatible aims, aligned values, and the same standards and ethos. Both should routinely uphold the same high standards in both work output and behaviour.

When this is working well, colleagues from both companies know and understand each other and enjoy working together with mutual respect – they become a team. This has been summarised beautifully in the past by one of our sponsors who simply said: "We're in it together".

Key questions to ask: What are the CRO's mission, aims and values? How do they align with our own approach?

Capabilities

There are many different aspects to a clinical study that need to be project managed and delivered seamlessly and to time. For example, checking that all the data are gathered correctly (monitoring), payments made, documents sent to relevant authorities (such as summary reports outlining trial progress and the evolving safety profile). To efficiently and calmly juggle all these tasks, the CRO needs both the people and systems to be able to efficiently project manage and reliably deliver to time.

People

Having people with the right experience and capabilities to be able to deliver reliably is essential. However, in rare conditions where the challenges are so unique, having that extra speciality to complement the sponsor's own knowledge can make all the difference. We've seen anecdotally, for example, regulatory submissions being brought forward based on the recommendation of a CRO. Beyond the team's experience are also the networks of vendors that a high-quality specialist CRO builds.

These established and trusted partners that a CRO provides gives extra flexibility and responsiveness if a challenge is met so that the trial can continue without incurring unnecessary delays.

Systems

This encompasses both the processes and IT systems. All processes, programmes and operating systems used by the CRO should be linked up to create efficient, secure working environments and effective project management with good optimal oversight and care.

Key questions : Is the full range of capabilities in the proposed project team? Do the CRO's systems support effifficient project management of the entire trial and all associated delivery tasks? Can the CRO provide examples of the flflexibility needed to navigate the logistical complexities of orphan drug trials?

Customer Service

For delivery of a high-standard trial, the CRO cannot just passively respond to questions from the sponsor. Instead, they should be a proactive and engaged partner to the sponsor study team, with a direct and strong working relationship built between team members. The CRO should be always available and proactively driving the trial. Engaging with their partners in the sponsor team with consistent, responsive and transparent communication. This ensures that problems can be rapidly solved together, and that thoughts, ideas, and proposals can be openly shared and discussed. Although it may sound obvious, a high standard of partnership like this takes time, commitment, and dedication to your project. Not every CRO has enough experienced people to be able to resource such a project-focussed, personalised approach and it's worthwhile trying to understand the realities of the customer service experience.

Key questions : Will the team be dedicated to your project or will they be stretched across numerous trials? What is the CRO's approach to allocating experienced and junior staffff, and what are their key focuses and priorities within service delivery as a company?

Interactions with Research Sites

Research sites are on the front-line of trial delivery – they are focussed first and foremost on the support of patients in their care, whilst also ensuring that the correct data are gathered, and the study delivered, as planned. This is a lot to manage, and in rare disease conditions the patients and families who are often experts at managing the condition clinically may not be experts in all the clinical trial peculiarities that need to be completed. For this reason, the CRO needs to be able to monitor, support, and build a relationship with the research sites in trials. A positive and helpful relationship between sites and the CRO monitor (who checks that trial information is gathered accurately and on time) is essential to ensuring that staff within the site remain productive and positive, despite all the activities that they are juggling. The people in the CRO working with the site, particularly the clinical monitors, are also likely to be the primary representatives of the larger study team and the sponsor acting as the sponsor's "ambassador". Therefore, having capable trial specialists, who enjoy and specialise in helping rare disease sites repeatedly deliver is likely to also have a big impact on the sponsor's reputation and relationship with sites in the future.

Key questions to ask: What site-level feedback has the CRO received from rare disease experts in the past?

Patient Focus

Rare diseases generally bring huge quality of life impacts and burdens on patients and their families7,8,9. Therefore, when trying to attract patients to take part in the trial, not only does a CRO need to find out who and where they are located, but they need to be able to deliver the trial in a way that ensures people can take part. Strong and established links between the CRO and rare disease patient communities are critical to ensure that a patient's thoughts and ideas can be included in the trial delivery approach, as well as being able to reach and give the option of trial participation to those with the disease. After all, many rare disease patients only hear about research and trials via the patient organisations and so active, early engagement with these groups by the CRO is essential for the trial's success.

> "We found out about the clinical trials ourselves after the death via the internet, [the] trial was being run in [the] hospital [where our son was being treated] but they didn't tell us about it."
>
> Relative of a patient (deceased) who had haemophagocylic lymphohistiocytosis10.

> "The only information about research and trials that I have gained is through the Myasthenia Gravis Association UK, which I only found out about by accident when researching my condition, myself on the internet."
>
> Patient, ocular myasthenia gravis10.

Key questions to ask: Does the CRO actively engage with patient organisations early on and throughout the development process?

Conclusion

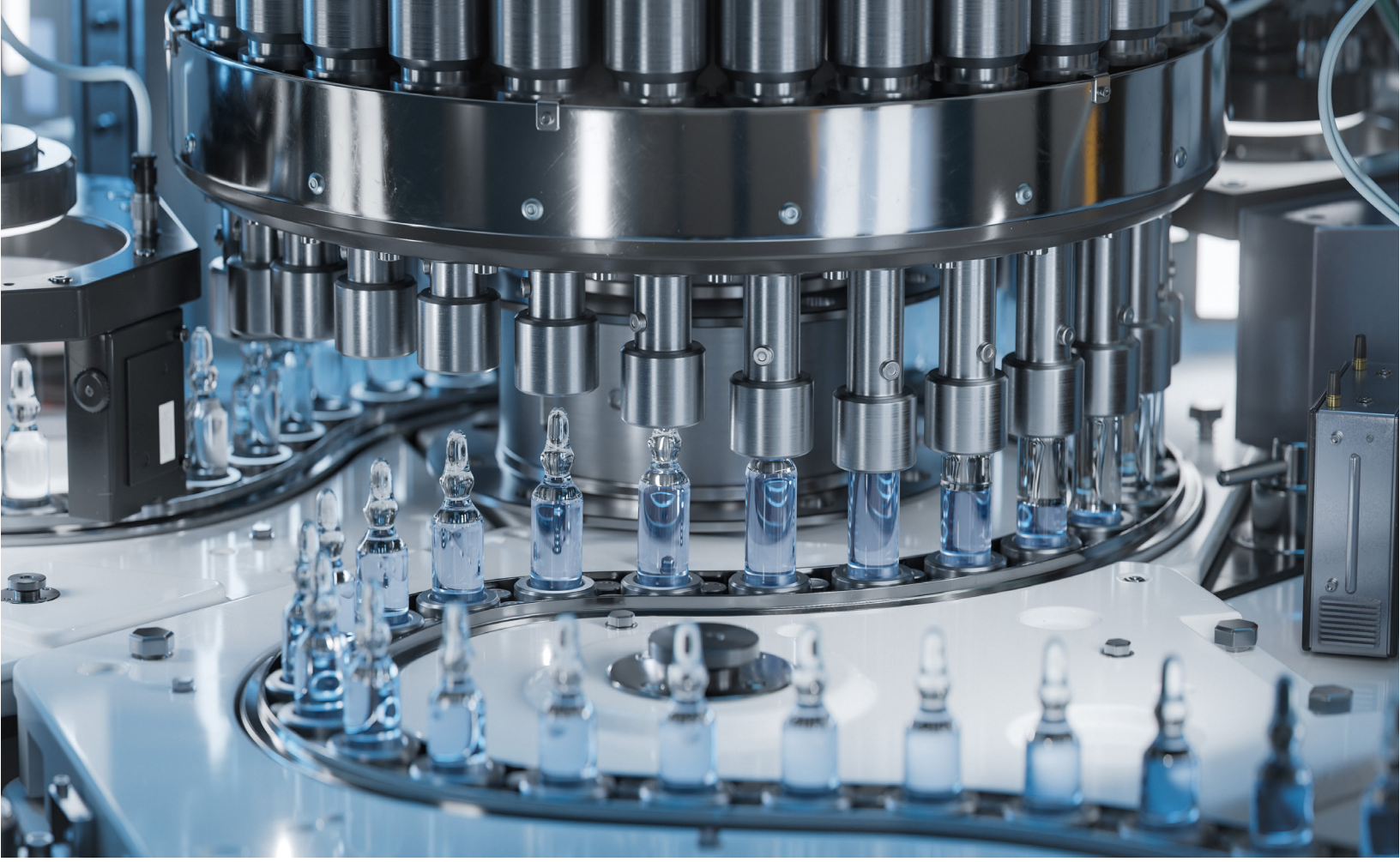
Clinical trials in rare disease are unique. Although there is an urgent need for new therapies for those living with rare disease, the people who could take part in trials

are very few and thinly spread around the globe. This makes both the design and delivery of the trials in rare diseases challenging and unless experienced teams are delivering them, highly problematic. CROs sit between decision-makers such as trial sponsors, regulators, patients, and research sites, and they project manage the whole trial-ecosystem to ensure that everyone pulls together to deliver. This makes it critically important for sponsors to select the right CRO for them – the one who has the same vision, who partners, supports, and can enhance their research.

Through highlighting the points above, we hope we have highlighted the importance of addressing such critical questions early in the CRO-selection process.

Our aim is simple – we want the rare disease community to access more therapies. For that to happen, every sponsor needs to engage a team who will work alongside them to achieve success.

Together we will make it happen.



References

1. https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12500
2. https://jamanetwork.com/journals/jamapediatrics/article-abstract/2767278
3. https://www.npr.org/2020/09/22/915749201/why-coronavirus-vaccine-trials-need-large- numbers-of-volunteers?t=1615328333730
4. https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.a.38413
5. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2645-0.
6. https://www.pharmaceuticalonline.com/doc/cro-management-why-sponsors-dont-do-0001
7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6110620/
8. https://link.springer.com/article/10.1186/s13023-017-0631-3
9. http://ajmc.s3.amazonaws.com/_media/_pdf/AJMC_A755_05_2017_hATTR_Article01.pdf
10. https://www.raredisease.org.uk/media/1594/rduk-family-report.pdf

For additional information on our global feasibility services, please email
info@emmes.com

Date Published: 09/21/2023 | Emmes- Finding the Right CRO in Rare Disease- V:01

Emmes