Clinical trial conduct is demanding and rigorous, especially in orphan indications where patient populations are small. Even well-qualified, specifically selected Contract Research Organisations (CROs) can struggle to deliver studies in line with Sponsor expectations. The clinical trial pathway is complex and fraught with pitfalls that can manifest themselves to service providers who lack understanding or who fail to undertake the additional planning necessary to complete successfully clinical studies in more complex disease areas. Lack of consideration can result in delays in regulatory or ethics submissions, poor patient recruitment, concerns with data integrity and poorly motivated study and site staff.

If some or all of these issues occur, the question arises as to whether the current CRO is capable of delivering in-line with Sponsor expectations. Should a failing study be transitioned to another CRO – either completely or partially? How and when is it best to make this decision? In this guide, we answer these questions and provide a handy checklist and advice on the best way to ensure a timely, cost-efficient and seamless transition to a new CRO.

**Contract Research Organisations**

Biopharmaceutical companies choose from a wide variety of CROs: global, regional, niche or therapy-oriented. Internal teams within Biopharmaceutical companies select CROs using a “due diligence”, vendor selection process that is robust and assesses a range of factors in potential CROs: qualifications, experience, past performance, geographic coverage, timelines and services provided.

**Why transition a trial?**

Failing clinical trials can result in delays in programme milestones and decision points, delays in submissions, increases in costs for the Sponsor and, ultimately, lack of treatment options for patients awaiting treatment. Trials conducted in patients with rare diseases may experience problems with patient recruitment and retention. The scarcity of rare disease patients and their generally young age negatively impact subject recruitment. Given that some marketing applications for orphan indications include data from only a few dozen patients, the contribution of every single patient is crucial.

The decision to transition a trial is based on two factors. First, is the current CRO performing at such a low level that the Sponsor must conclude that the trial will not be delivered satisfactorily by the current provider? Second, is there the belief that a replacement CRO has the breadth of skills and capabilities to turn the trial around and deliver within the required specifications? In short, does the Sponsor stay and make changes—or swap to another provider?

**Before transitioning a trial**

From the outset of the study, the Sponsor should maintain continuous evaluation of the CRO's performance in a fair and objective manner to allow timely intervention on any issue that might
arise. In collaboration with the CRO, the Sponsor should evaluate the current health of the trial by reviewing relevant operational, financial and regulatory information. For a failing trial, this analysis identifies where resources will be best utilised to bring the trial back on track and allows for the development of an efficient trial transition strategy.

The decision to stay with the current CRO or to transition is lengthy and difficult. Many factors likely to impact on trial cost, timelines and delivery must be considered. The Sponsor should carefully consider known and potential risks and benefits of the current and future CRO.

Any decision to maintain the current CRO or switch provider should be made using a scientific approach. Our checklist (Appendix 1) provides a basis for assessing a current CRO in terms of regulatory activities, communication, team dynamics, quality and study conduct. Before using the checklist, it is beneficial to discuss what satisfaction level would be required either to stay with the current provider or to seek a new CRO.

Selecting a team that can rescue your trial

The ability to rescue a trial is the domain of a select group of CROs and is unlikely to simply reflect the size per se of the organisation. In many cases the challenges to be overcome will be highly specific. The Sponsor must identify a suitable replacement CRO, perhaps one with an approach that can address the current challenges of the ongoing trial. A blend of expertise and lessons learned from previous CRO selection will guide the decision. Some of the best indicators of potential success are a track record of successfully managing clinical trials in small patient populations, global reach, rapid response and provision of a service that is flexible and tailored to the situation.

How to transition a trial

Momentum

The key to an efficient trial transition is to maintain momentum; stagnation is one of the biggest fears for Sponsors transitioning a trial. Having made the definitive decision to move to another CRO, the Sponsor must ensure the transfer of tasks between CROs. A meticulous risk management plan should be developed and implemented to mitigate any potential risks related to transition and thereafter, such as loss of information during transition, potential delays in particular trial activities and handover delays.

Communication

Transparent and honest communication is a vital element to achieve successful and efficient transition. Before any transition activities start, the Sponsor should inform the current CRO of their decision and the reasons for making it. The relationship with the current CRO should be managed professionally, and they should be requested to support transition activities in the best interest of the trial. Any financial obligations between the Sponsor and current CRO should be agreed as soon as possible.

Cooperation

Success is dependent on cooperation between the two CROs. The Sponsor should seek and obtain the commitment of the outgoing CRO to ease the transition of activities. Complete details of transition meetings and timelines should be communicated by the replacement CRO to the outgoing CRO in consultation with the Sponsor. Every effort should be made to collect as much historical information about the trial as possible.
Important and urgent areas of training and familiarisation should be identified, and lessons learned during the trial should be communicated to the new CRO team members. This information is critical to the incoming project team. Although most information transfer occurs during the transition period, it cannot be guaranteed that all the necessary information from the outgoing CRO will be communicated during the transition. The replacement CRO should be prepared for this circumstance and plan accordingly.

Oversight
In a rescue situation, there must be appropriate management level oversight and governance. Careful assessment of the trial and deployment of an experienced and qualified team will help the Sponsor to bring the trial back on track. A governance committee should be formed, with adequate representation from the Sponsor and CRO, for high-level review of the trial and for the discussion of protocol issues, operational issues, project status, progress, issue escalation and quality of deliverables.

Implementation
Once the root cause of the problems that have affected the trial has been identified, the team must implement the transition plan, which should have as part of its design the necessary corrective manoeuvres. The transition and rescue plan should be structured in such a manner that all functional areas involved in the transition are covered, and the project team should incorporate all of the critical aspects that relate to transition. The key areas of focus in a transition and rescue plan are:

- Transition risk management
- Training and trial familiarisation for the new team members
- Identification of roles and responsibilities

The exact transition activities will vary based on the timing of the transition and the trial stage. There must be adequate representation from both CROs in the transition team to cover these key functional service areas. Appendix 2 provides an expansive list of functional service areas and the corresponding transition activities.

Budget
The budget for the trial will most likely be compromised if timelines and milestone delivery are not met. As a general rule, the smaller the scope of the trial the less impact costs will have. For larger trials one possible solution could be a partial transition of tasks. Alternatively, a more cost-effective ‘niche’ CRO with trial transition expertise may be the right choice to take on the rescue. Adequate resources must be available to manage the transition, its associated costs and ongoing tasks.

The Sponsor should ensure that the outgoing CRO performs the contracted activities as agreed until the point of handover. The Sponsor may want to retain some of the services of the outgoing CRO, and it is therefore important to define the scope of each of the functional service areas. This avoids duplication of effort, delays and/or additional unforeseen costs.
Final Thoughts

One should not underestimate the rigours of the transition pathway activities (summarised in Figure 1). When performed with an experienced partner, however, transition can positively impact the trial. Frustration and wasted effort can be eliminated, allowing room for positive thinking and motivation. With careful planning, an objective approach and cooperation from all parties, it is possible to rescue a trial.

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### Appendix 1

**Checklist for evaluating a Contract Research Organisation**

#### Regulatory Activities
- ✔ How satisfied are you with the feasibility process (selection of sites/countries)?
- ✔ How satisfied are you with the regulatory/ethics process (on-time submissions/response to questions)?
- ✔ How well was the process of obtaining import and export licenses/warehousing handled?
- ✔ Did the CRO have a clear understanding of the regulatory/ethics process in the various countries?

#### Communication
- ✔ Does the Project team respond in a timely manner to requests?
- ✔ Are Trial status reports/spreadsheets available to you on a regular basis?
- ✔ Are issues generally resolved to the Sponsor’s satisfaction?
- ✔ Has escalation of issues to CRO management been successful in overcoming issues?
- ✔ Does the CRO come to the Sponsor with solutions to problems?

#### Team Dynamics
- ✔ Is the Project Manager proactive?
- ✔ Has there been high turnover of trial personnel?
- ✔ Are the CRAs experienced enough to motivate the sites?
- ✔ Have any of the sites complained about the assigned CRA?
- ✔ Has the training of personnel been handled satisfactorily?

#### Quality
- ✔ Were plans/manuals developed on time and to a high standard (maximum two reviews)?
- ✔ Are you satisfied with the quality of the documents?
- ✔ Is the Trial Master File inspection ready?
- ✔ Are there concerns with site monitoring and quality of the data?

#### Study Conduct
- ✔ Does the CRO take ownership of the tasks delegated to them?
- ✔ Have data queries been answered satisfactorily?
- ✔ Are there issues with Data Management services?
- ✔ Are there issues with the Safety services provided?
- ✔ Are there any issues with other functional services?
- ✔ Is predicted recruitment to actual recruitment on target and in the CRO’s control?
- ✔ Do you feel the CRO is in control of the trial, or has the Sponsor had to micro-manage the CRO?
- ✔ Compared to other CROs you have used, how would rate the current CRO overall?
- ✔ How honest and transparent is the CRO?

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**Key**

1. Not satisfied
2. Slightly satisfied
3. Moderately satisfied
4. Very satisfied
5. Completely satisfied

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CRA: clinical research associate; CRO: contract research organisation
### Appendix 2  
**Key functional service areas and associated transition elements in a rescue trial**

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<tr>
<th>Functional Service Area</th>
<th>Key Transition Elements</th>
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| **Site Selection**           | **Validated - Efficient - Unbiased - Feasible:**  
|                              | Objective assessment of existing countries and sites  
|                              | Identification of additional and back-up countries and sites with expertise and high recruitment potential  
|                              | Selection of countries and sites with fast trial start-up  |
| **Regulatory and Ethics**    | **Pertinent questions:**  
|                              | Existing EC and RA submissions and approvals obtained?  
|                              | Status of ongoing submissions?  
|                              | Submission requirements for the remaining or additional sites/countries?  
|                              | Timely completion of required documents?  
|                              | Country- and site-level RA requirements for the change of CRO?  
|                              | Change of CRO considered a substantial amendment, or is notification of RA sufficient?  
|                              | Timelines for the approval/notification of CRO change to RA and EC?  
|                              | Next steps and action plan?  
|                              | Local and central expertise on board to successfully manage regulatory, import and export issues in challenging countries?  
|                              | Insurance and indemnity documents need revision because of CRO change?  
|                              | Replacement CRO required to serve as a legal representative (countries where the Sponsor does not have a legal presence)?  |
| **Investigational Product Management** | **Actions required:**  
|                              | Identify country specific requirements for import of trial medications  
|                              | Determine if CRO change affects the import license, labelling requirements etc.  
|                              | Collect information relating to country- and site-level, drug shipments and accountability to better equip the replacement CRO to manage the investigational product-related matters  |
| **Site Management**          | **Tasks to undertake:**  
|                              | Work closely with the previous CRO to ensure a good transition on- and off-site  
|                              | Ensure sites are adequately supported and highly motivated during transition  
|                              | Manage relationship with sites  
|                              | Perform on-site handover visits at identified sites, and plan motivational visits as needed  
|                              | Complete transition plan/checklist for each site  
|                              | Confirm if amendment to site contracts are required for the replacement CRO  
|                              | Establish previous financial status of site payments, and check that trackers are current  
|                              | Obtain access for CRAs and project team members to various trial electronic systems  
|                              | Have complete overview of site status (on-going major concerns, source document verification, recruitment plan and processes etc.)  |
| **Clinical Project Management** | **Project management team:**  
|                              | Provides central leadership of the transition effort  
|                              | Coordinates all transition activities and ensures efficient functional level transition  
|                              | Provides transition status updates to Sponsor on a weekly basis  
|                              | Amends/creates various trial plans and manuals (Project Plan, Risk Management Plan, Recruitment and Retention Plan, Reference Manuals etc.)  
|                              | Establishes appropriate communication and escalation channels for the transition process  
|                              | Works closely with stakeholders of various departments (Clinical operations, Biometrics, Safety etc.)  |
| **Document Management**      | **Review and QC checks of:**  
|                              | • Existing trial documents (drug release documents, EC/RA approvals, etc.)  
|                              | • Country-and site-level TMF (identify and collect missing documents)  
|                              | Work closely with Sponsor and agree on TMF transfer and management approach  
|                              | Adapt forms where necessary to the replacement CRO’s SOPs  |
| **Other Functions – Biometrics, Safety, Medical Monitoring** | **Other important issues:**  
|                              | Identification of a Lead to manage the tasks associated with each functional area  
|                              | Central coordination and reporting to project management team  |

CRA: clinical research associate; CRO: contract research organisation; EC: ethics committee; RA: regulatory authority; SOP: standard operating procedure; TMF: Trial Master Files; QC: quality control