Aspects to contemplate when selecting a CRO for rare disease trials

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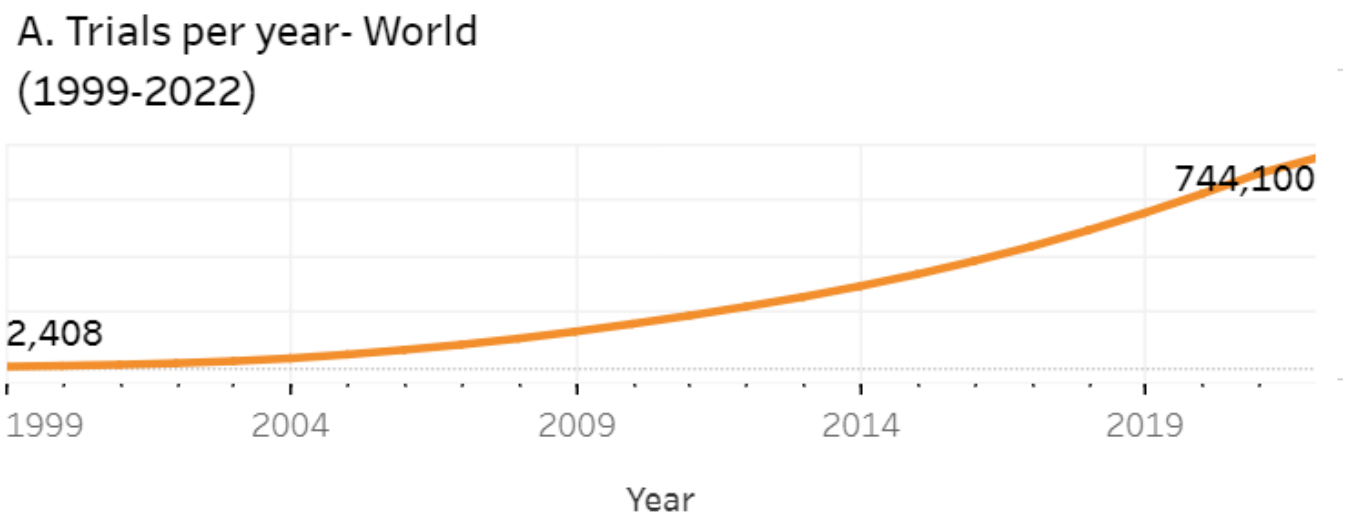
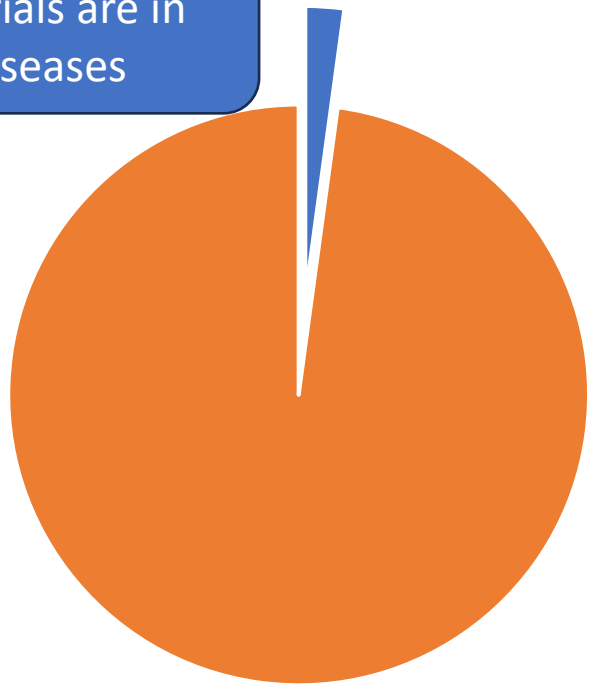
Questions this presentation will (try to) answer

- Does possessing therapeutic expertise remain imperative in choosing a CRO for a rare disease inquiry?
- Evaluating the advantages of niche specialized CROs versus expansive multinational CROs
- Extra hurdles in the CRO selection procedure arise when addressing ultra-rare diseases, where CROs may lack familiarity with the condition
- Discussing the merits and drawbacks of engaging a comprehensive service CRO for your rare disease examination versus collaborating with various vendors across the study

Amount of clinical trials worldwide has increased by 310x over the past 25 years



16’000 out of the 744’000 trials are in Rare Diseases



[Number of trial registrations by location, disease, phase of development, age and sex of trial participants (1999-2022) (who.int)]

[Rare Diseases: an FAQ Overview on the Global Clinical Trial Landscape| Novotech CRO (novotech-cro.com)]

72% of all clinical trials are outsourced to a CRO

https://vial.com/blog/articles/how-many-clinical-trials-are-run-by-cros/?https://vial.com/blog/articles/how-many-clinical-trials-are-run-by-cros/?utm_source=organic

Key challenges when conducting trials in Rare Diseases: think **SPECIAL**!

1. **S**ites and HCPs with expertise in rare diseases are limited
2. **P**atient population is (very) small
3. **E**nding trial early: patient retention for clinical trials
4. **C**hildren in rare disease tr**ial**s

Sites and HCPs with expertise in rare diseases are limited

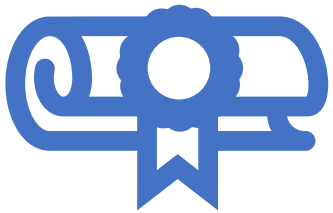
Investigator quote

"Almost nobody except the sites actually understand the patients"

Briel et al. Trials (2021) 22:844

Limited amount of HCPs and sites

78.8% of patients affected by rare diseases have not received proper care because of limited training of health care professionals in this field[1]



Limited interest in clinical research: the average age at first independent federal grant (R01) for an MD is **44 yrs**[2]

[1]Estudio sobre situación de Necesidades Sociosanitarias de las personas con Enfermedades Raras en España Estudio ENSERio; [2]Statland et al, Neurology, 2012

Questions for CRO

Has the CRO conducted one or more trial(s) in the same disease?

- If not, have they conducted one or more trial(s) in the same therapeutic area, in a rare disease?
- Did they conduct this/these trial(s) <2 years ago?

Can the CRO demonstrate that they have an existing network in the disease/therapeutic area (with HCPs, scientific societies, patient advocacy groups)?

What is the CRO's plan to reach out to sites? (emails, calls, leverage existing network)

- When planning site outreach with the CRO, sponsors should not forget that their own network in the TA is probably stronger than the CRO's network!

Case study 1: Lost control of the project timeline because of insufficient network

- Phase 2 trial in a Rare Disease
- Significant challenges to identify sites, leading to delays in starting the trial
- *Root causes identified*:
  - CRO did not have the necessary network in the Therapeutic Area.
  - Sponsor underestimated the importance of this network, and relied too heavily on the CRO.
- *Corrective action:*
  - Sponsor and CRO worked hand-in-hand to engage with investigators (in-person conferences & meetings, identification of study champions, …)

Patient population is (very) small

(Very) small patient population

A disease is deemed to be rare if it affects ≤5/10’000 people.

7,000-8,000 rare diseases have been identified worldwide

https://www.bag.admin.ch/bag/en/home/krankheiten/krankheiten-im-ueberblick/viele-seltene-krankheiten.html

Questions for CRO

Can the CRO provide examples of how they dealt with small patient populations in the recent past (<2 years ago)

- What was undertaken to identify patients?

Does the CRO have a large enough (global) footprint to reach out to multiple sites?

Ending trial early: patient retention for clinical trials

Patient retention: why do patients leave trials?

Results of a recent study revealed that 19% of paediatric trials were discontinued early, with patient accrual difficulty (37%) as the most common reason for discontinuation.

Main reasons patients gave for dropping out of the clinical trials were

lack of time	lengthy travel distance	technical complications with study procedures	too many doctor appointments	family concerns

[Rare Disease Clinical Trials | Challenges & Solutions | Congenius]

Questions for CRO

Does the CRO have success stories in achieving patient retention?

What are the strategies used by the CRO to increase patient retention, eg

- White glove service (eg eliminate out-of-pocket expenses, transportation for patients who live far away from the study sites)
- Advice on clinical study protocol/schedule of assessments to limit the amount and burden of visits
- Consider broader windows for study visits (eg ±3 days rather than ±1 day)
- Home health visits
- Dialogue with patient advocacy organizations

Children in rare disease trials

Rare diseases and paediatric clinical trials

of rare diseases affect children

Specific challenges:

- Geographical dispersion
- Phenotypic diversity
- Lack of validated outcomes
- No precedent for drug development
- Ethical considerations for children

"What Is a Rare Disease? – Rare Disease Day 2022." Rare Disease Day®, www.rarediseaseday.org/ what-is-a-rare-disease/.

Questions for CRO

Does the CRO have recent examples of trials conducted in children with a rare disease?

Can the CRO describe specific challenges they encountered, and how they were overcome?

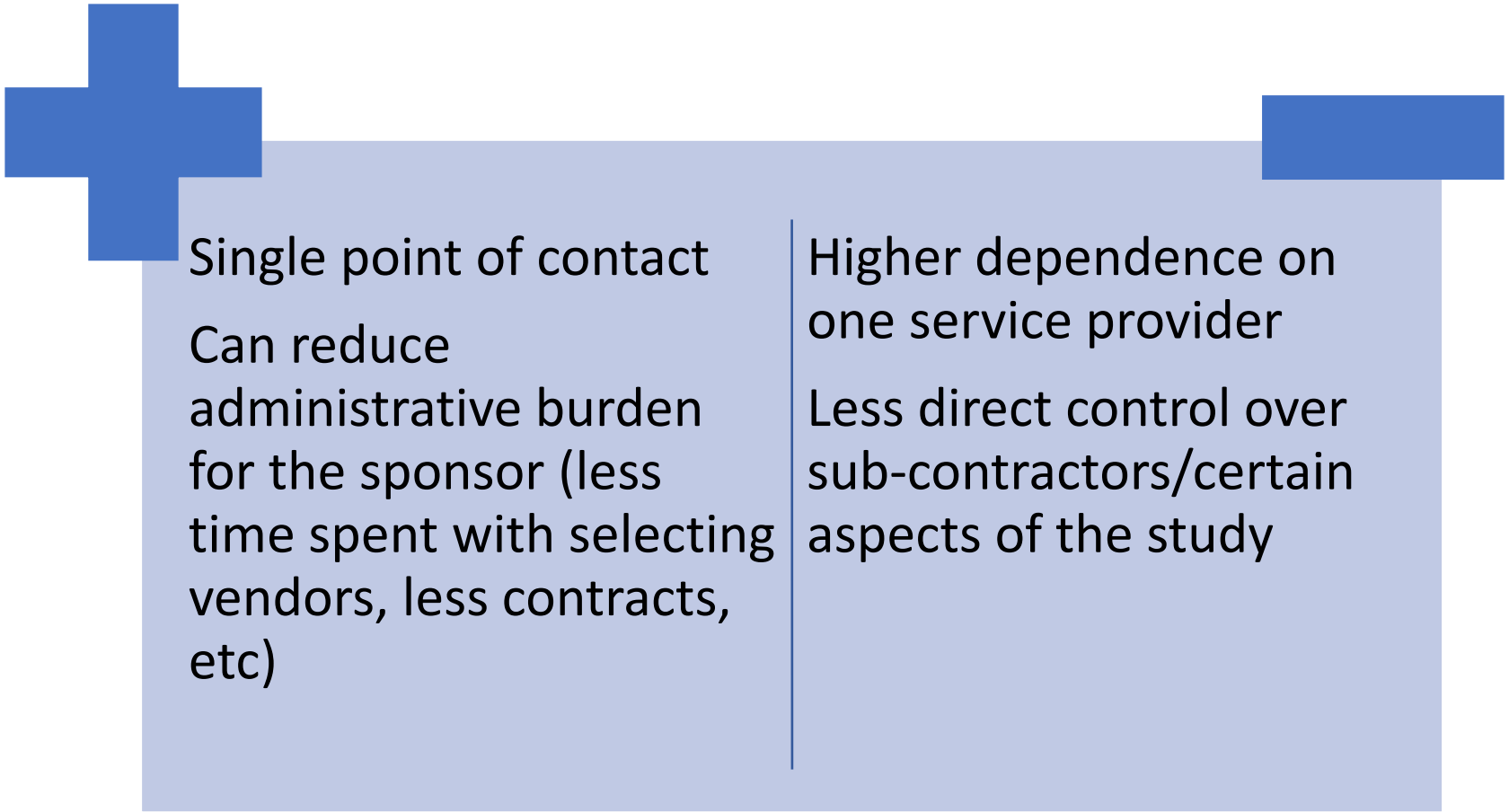
Case study 2: High staff turnover at CRO resulting in loss of expertise in pediatric trials

- Phase 3 trial in a Rare Disease
- CRO claimed significant expertise in pediatric trials
- Staff turn-over at CRO led to loss in key experts in pediatric trials
- *Root causes identified*:
  - Number of in-house experts at CRO was too small
- *Corrective action:*
  - Ad hoc external consultant was hired
  - Sponsor identified internal expert to support

Evaluating the advantages of niche specialized CROs versus expansive multinational CROs

	Niche specialized CRO	Expansive multinational CRO
Sites and HCPs with expertise in rare diseases are limited	Can have excellent network in selected diseases	Good network in a broader variety of diseases
Patient population is (very) small	Leverage network (including patient advocacy organizations) in selected diseases	Usually, their global footprint is larger
Ending trial early: patient retention for clinical trials	Good understanding of very specific patient populations	Can leverage experience from a broad variety of trials
Children in rare disease trials	Experience of senior associates at CRO can be very valuable	Have often conducted a significant amount of pediatric trials

Merits and drawbacks of comprehensive service CRO versus various vendors



Summary and conclusions

Key questions	Recommendations
Does possessing therapeutic expertise remain imperative in choosing a CRO for a rare disease inquiry?	YES, absolutely
Evaluating the advantages of niche specialized CROs versus expansive multinational CROs	Selection of the right CRO depends on needs, nature of trial, study size, etc
Extra hurdles in the CRO selection procedure arise when addressing ultra-rare diseases, where CROs may lack familiarity with the condition	Think SPECial
Discussing the merits and drawbacks of engaging a comprehensive service CRO for your rare disease examination versus collaborating with various vendors across the study	Putting all eggs in one basket can be risky