ERICA

European Rare Disease Research Coordination and Support Action

Designing and conducting clinical trials in rare diseases

What industries expect for partnering with clinical sites

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European Commission

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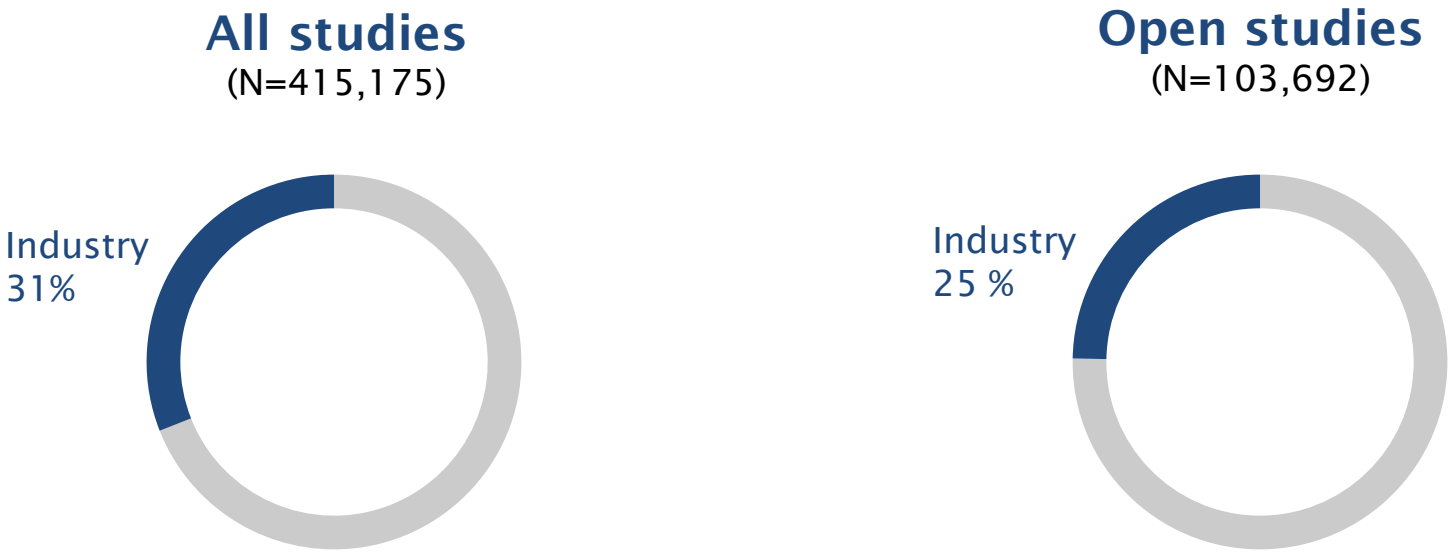
European Reference Networks

Proportion of clinical trials sponsored by industry



Source: Clinicaltrials.gov

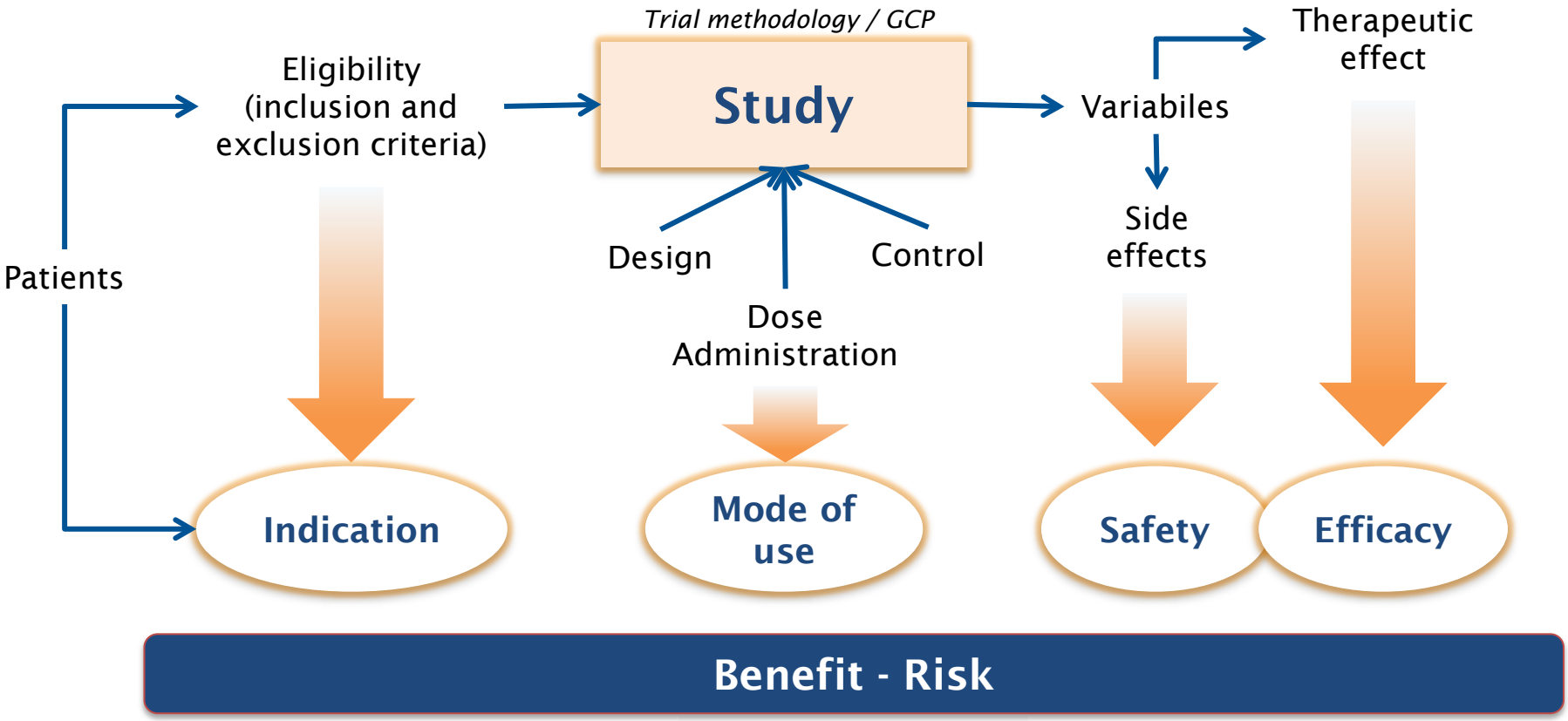
Academic VS industry trials

ACADEMIC TRIALS		INDUSTRIAL TRIALS
Research Question		Exploration / Verification
(usually) Known drug		(usually) Investigational drug
Targeting peer-review publication		Targeting auditable CSR/TMF
«Good enough» quality		Full GCP compliance
Data truthfulness		Data quality and integrity

VS

Sponsorship obligations

Conceptual structure of pivotal clinical studies



Why drug development for these diseases is so difficult?

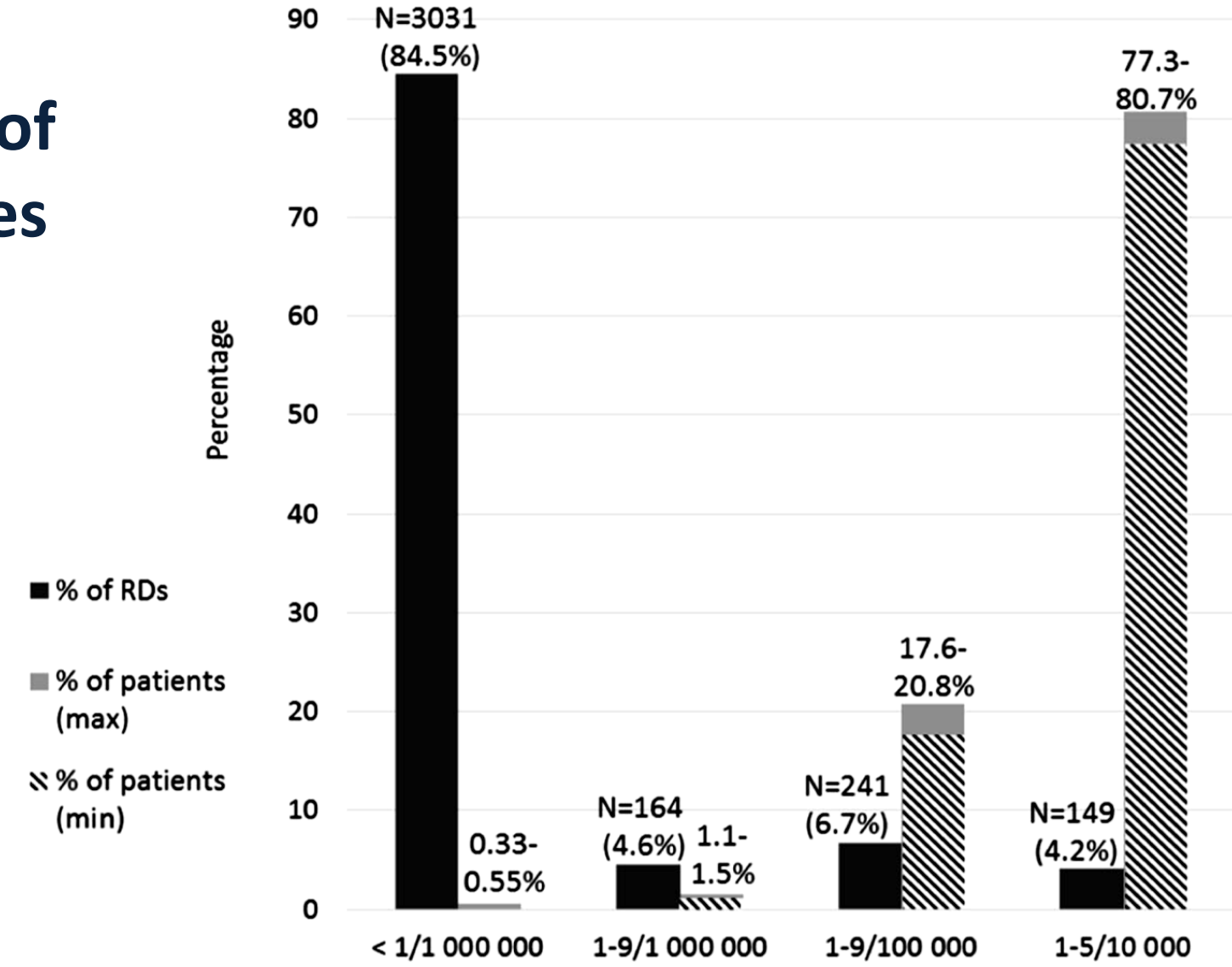
Ultra-rare & severe
Prevalence often below 1-10/ million inhabitant.

Highly heterogeneous
Significant clinical differences and evolution amongst patients

Little known
Extremely limited literature, including natural history.

Complex therapies
A technological shift to more complex therapies is often required.

The reality of rare diseases



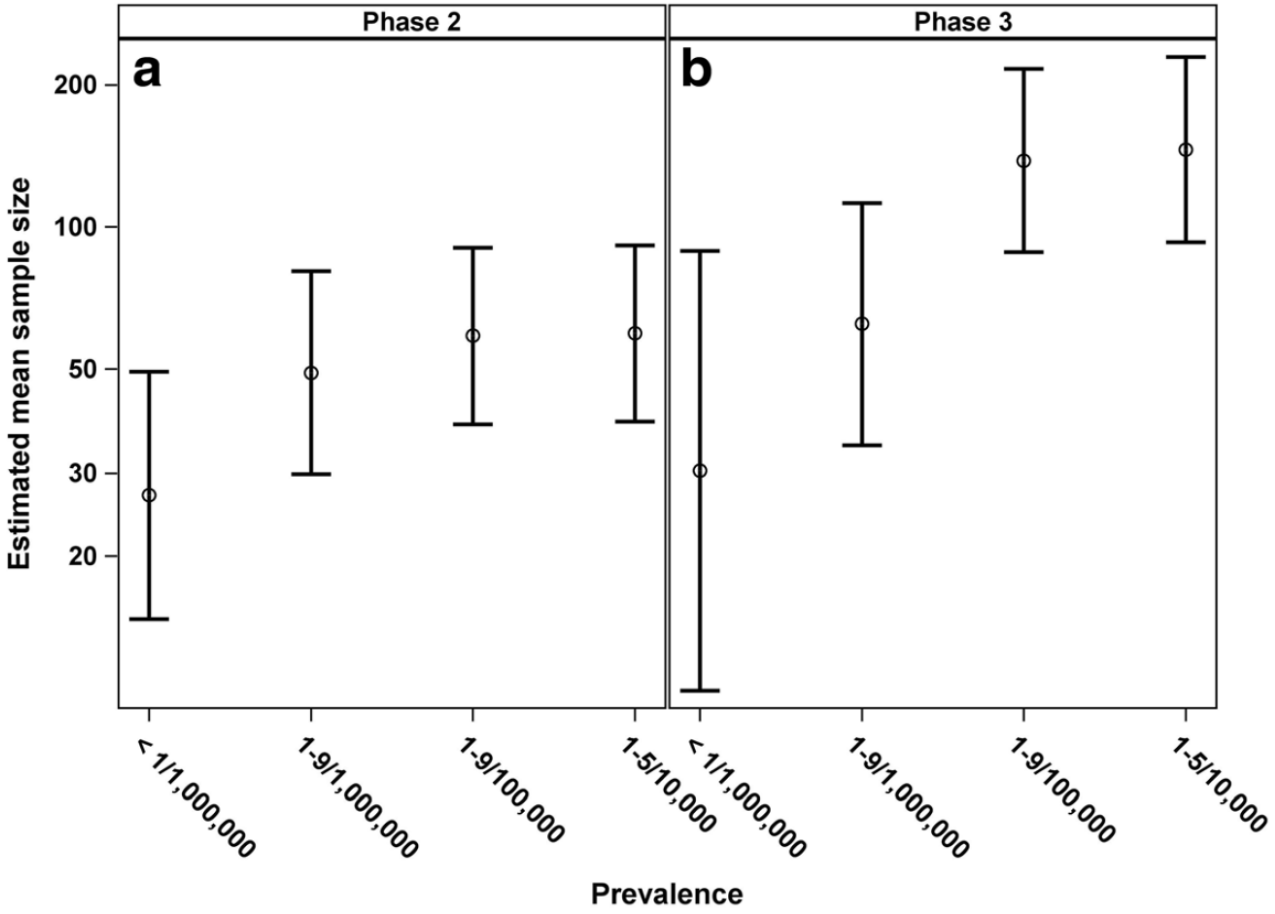
Orphanet database

SOURCE:
Eur J Hum Genet. 2020;28(2):165–73.

Effect of prevalence and phase of study on trial size

- Aggregated analysis of registered clinical trials for rare diseases
- Trials from ClinialTrials.gov; diseases from Orphadata
- 1567 trials (0.8% of total)
  - 1.2% - prev <1/1,000,000
  - 8.0% - prev 1–9/1,000,000
  - 50.5% - prev 1–9/100,000
  - 40.3% - prev 1–5/10,000

Effects of prevalence and phase of study adjusted by for prevalence, phase, gender, age, presence of a DMC, whether FDA regulated, intervention model, trial regions, number of countries, year of start, and number of arms



Hee et al. OJRD 2017

Clinical trial elements impacted by rarity

Trial elements

Design	Execution	Results
■ Sample size & power	■ Site identification	■ Representativeness
■ Study design	■ Patient identification & selection	■ Meaningfulness
■ Study population	■ Pt logistics	■ Confidence intervals
■ End-points	■ Test burden	■ Reproducibility
■ Concomitant medications		

Reasons for termination of clinical trials

(analysis of 3122 terminated trials in CT.gov)

Pack TR, bioRxiv (2015)

Enrollment: your valley of death. Or garden of heaven…

The reality …

- In many cases more than 1/3rd of **sites fail recruitment** targets
- 10% of zero-enrollment sites still resides in the high standard area
- **First month(s)** is/ are essential (and revealing)
- **Corrective actions** rarely work out

Reasons behind

- Patients do not exist *(eligibility criteria)*
- Patients are not seen at the site *(feasibility)*
- Patients are not identified *(protocol fluency / recruitment strategy)*
- Patients are not willing *(consent dialogue / study burden)*

The master root…

Protocol

Training

Procedures

Leading reasons for recruitment failure in clinical trials (academic and industrial alike)

From 49 interviews to investigators

- Overoptimistic recruitment estimates
- Too narrow eligibility criteria
- Lack of engagement of recruiters/trial team
- Lack of competence/training/ experience of recruiters
- Insufficient initial funding
- High burden for trial participants

Briel et al. Trials (2021)

What are industrial sponsors doing …

- Better investigator's training
- Better feasibility
- Assessment of patient's burden
- Lay language material / better consent forms
- Risk-based and remote monitoring
- Pt monitoring technologies
- Provide info and contact points for trials

The second consequence of poor quality: violations !!!

- Failure in consenting
  - Uninformed
  - Untimely
  - Unauthorized
- Failure to comply with protocol
- Failure to handle the IMP properly
- Failure to keep appropriate records
- Failure to communicate

  - Enrollment deviations
  - Data corrections
  - Protocol deviations

How to avoid violations…

- Master the protocol
  - Start from the unusual
  - Don't underestimate changes
- «Train hard, fight easy»
- Design a recruitment strategy
  (DB, pts, communication, competition)
- Forms, checklists, process flows
- Trace yourself
- Be active (IMs, monitoring visits)
- Think in terms of quality
  (analytics, KPIs, CAPAs)

SUMMARY – Clinical trials in rare diseases

Clinical trials are complex endeavors at high risk of failure

The most frequent failure concerns recruitment, followed by violations

The risk is even bigger in rare diseases

Lack of quality is the root cause of failure

Participating into industry-sponsored trials requires building quality practices (training, processes, data)