

EB Trial Failure

Results expert survey

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with support from ERN-Skin



Methods

- Cross-sectional online survey
- Healthcare professionals and researchers with expertise in EB (worldwide)
- About 300 invitations sent
- **85 answers**

Demographics

Professional Background

(Multiple answers were possible)

1. **73%** Dermatologists
2. **23%** Other EB specialists (Researcher, dentist, etc.)

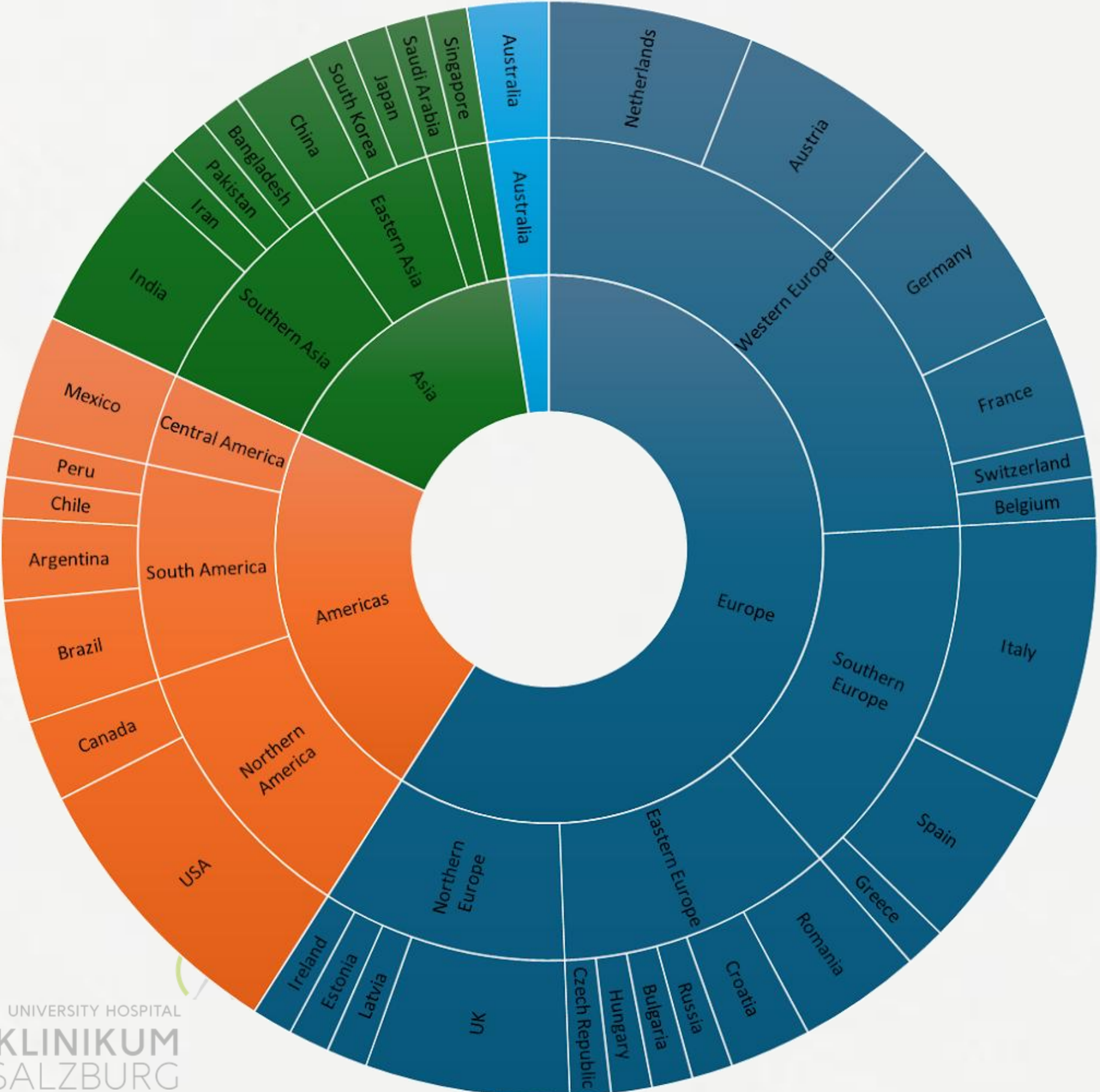
Experience

- **76.5%** ≥ 11 years EB experience
- **53%** served as Principal Investigator
- **Ø 3–4** clinical trials in past 10 years

Clinical Exposure

- Seeing on average **~ 8 EB patients/month**

Country of employment



Europe	59%
Americas	22.9%
Asia	15.7%
Oceania	2.4%

Descriptives

Trial Procedures

Per section

21. Please rate the following challenge in the context of EB clinical trials, according to your experience
Rate from 1 = no challenge at all to 5 = impeding challenge

C001

no challenge at all	minor challenge	moderate challenge	significant challenge	impeding challenge	Not applicable / No experience
<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Complex trial procedures for trial site / staff

1-2 questions selected as central question
→ facilitating comparison of sections

Comments: optional additional information, explanations

C013

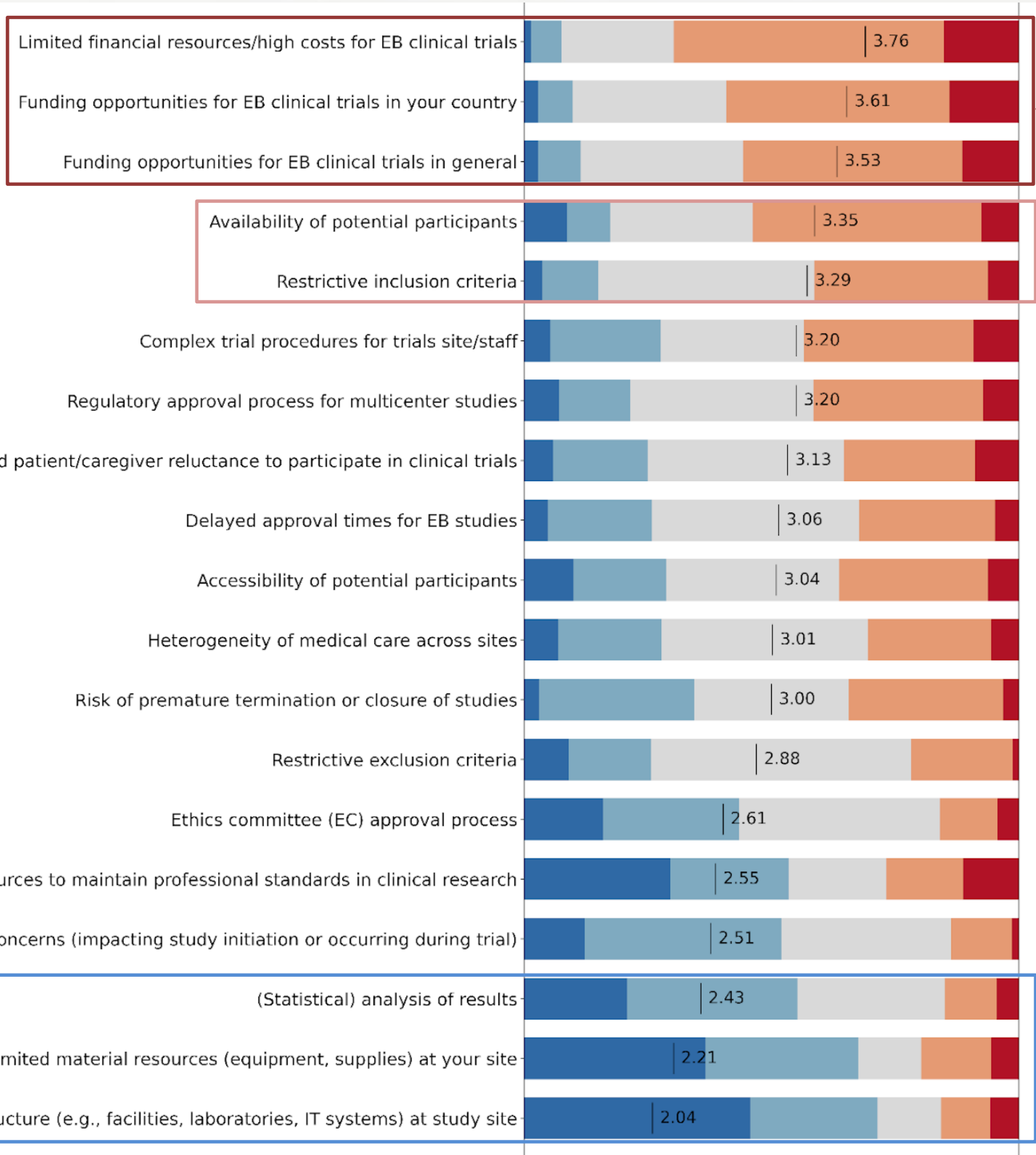
22. Please specify the main challenge(s) that you or your staff encounter in relation to the previous question.

C002

	no challenge at all	minor challenge	moderate challenge	significant challenge	impeding challenge	Not applicable / No experience
Unclear or ambiguous protocol instructions leading to inconsistent application	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Insufficient training on protocol requirements for trial staff	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Inflexible rules regarding protocol deviations or unexpected clinical situations	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
High number and/or complexity of tests or assessments	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Invasiveness of tests (biopsy, blood takes) per protocol	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Tight timeframes between visits, tests or assessments	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Multiple study arms	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Need for blinded assessment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Administrative workload at site (e.g. regulatory correspondence and documentation of evidence)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Coordination challenges across sites (e.g. heterogeneity of regulatory and legal requirements, multiple requirements)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Descriptives - Main challenges (ranked by mean score)

- 1 No challenge at all
- 2 Minor challenge
- 3 Moderate challenge
- 4 Significant challenge
- 5 Impeding challenge



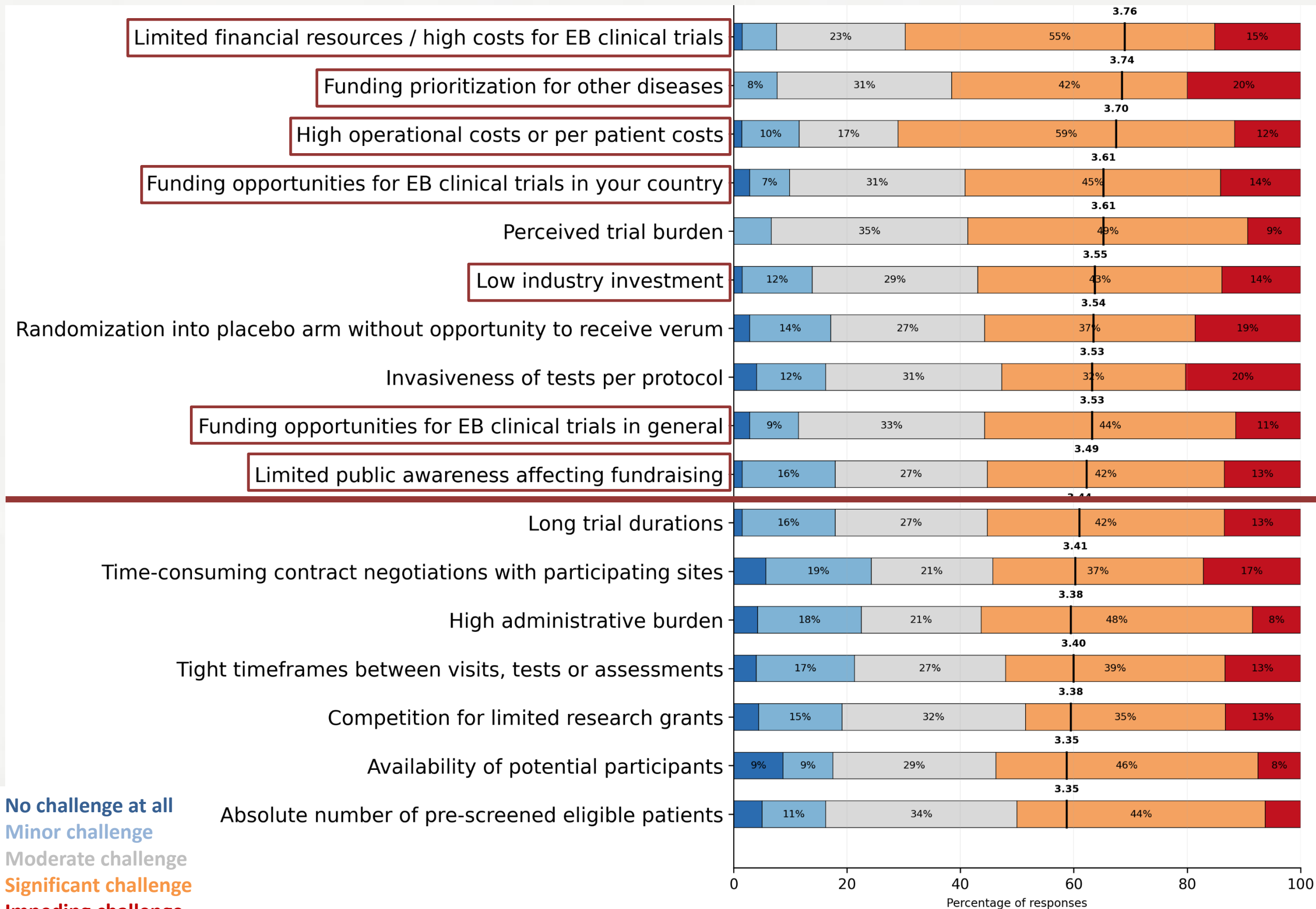
Top 3 highest: **Financial resources/Funding**

Recruitment

Top 3 lowest: **Statistical analysis, limited material resources, limited infrastructure**

Descriptives – Challenges with the highest mean scores across all survey items

(excluding items related to “barriers for patients”; ranked by mean score)



Financial barriers:

10 of the 131 main survey items (7.6%) addressed funding or cost-related aspects.

7 of these items (70%) are among the 10 highest-scoring challenges in terms of mean value.

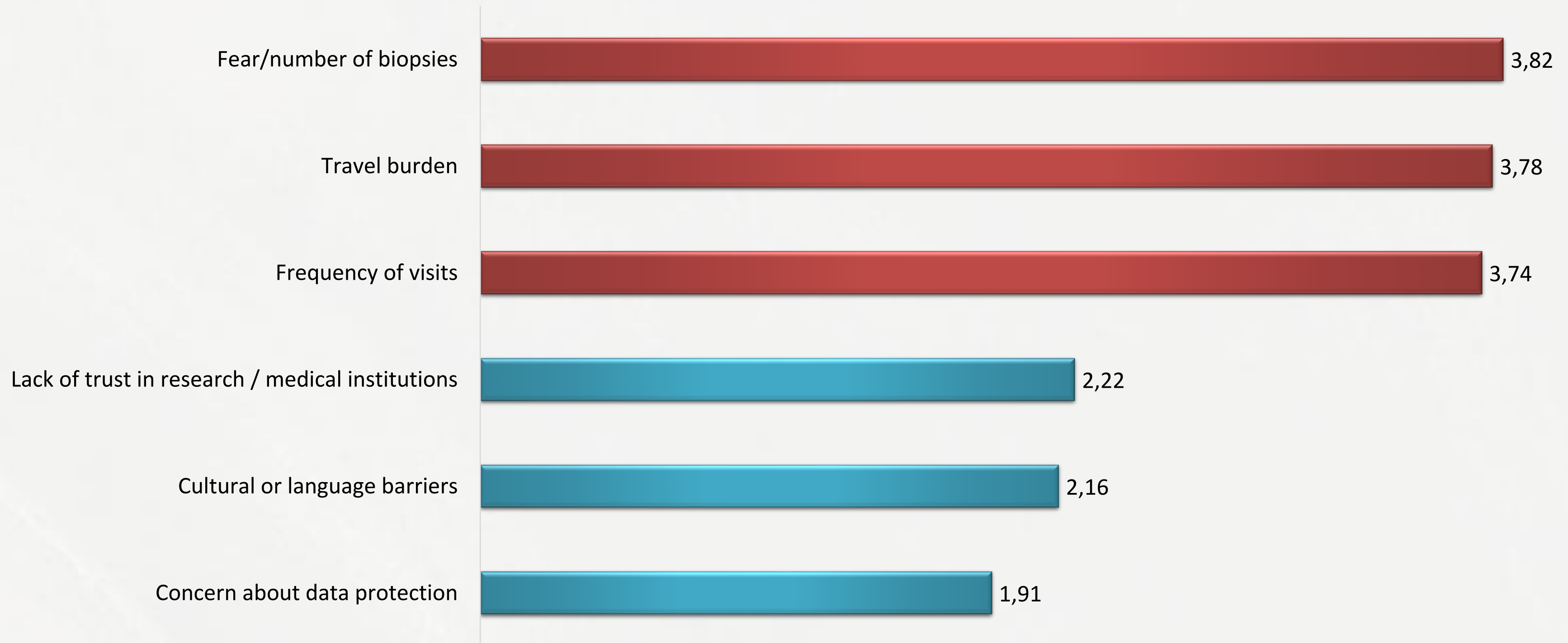
Contrast free-text answers

Focus points:

- Infrastructure/equipment (f.ex. capacity issues)
- Staffing limitations (lack of qualified staff)

- 1 No challenge at all
- 2 Minor challenge
- 3 Moderate challenge
- 4 Significant challenge
- 5 Impeding challenge

Descriptives - Barriers to trial participation for patients



Support free-text answers

- Trial burden → Travel distance, visit frequency
- Invasiveness of treatment (esp. biopsies should be reduced to minimum)

Descriptives

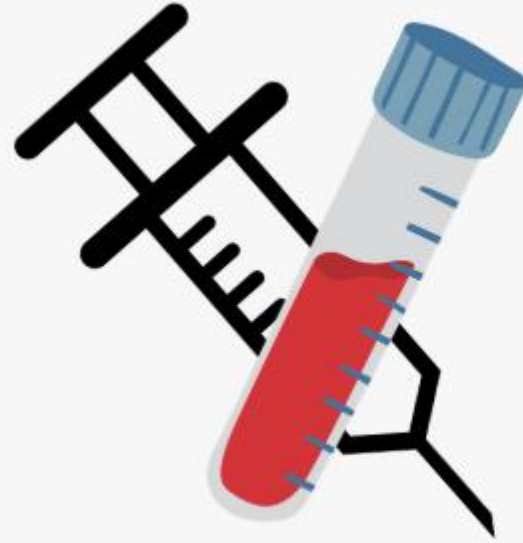
Acceptable trial burden

Visit frequency



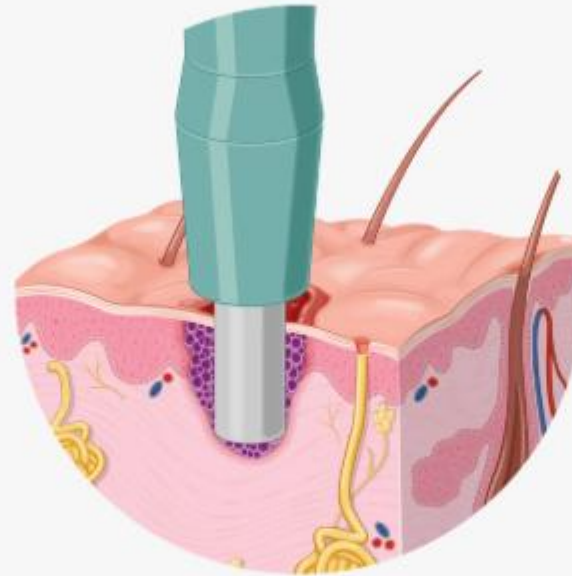
✓ Once monthly /
Every 2 weeks

Blood draws



✓ Max. every 3 months

Skin biopsies



✓ Max. every 3 months

Inpatient admission



✓ Short stay (1-3 days)

I.v. infusion



✓ Once per month /
max. every 3 months

Patients:
Max. every 4 weeks

Patients:
Max. 1 every 6 weeks

Patients:
Rather no admission at all

Subgroup analysis

Background Scoping review:

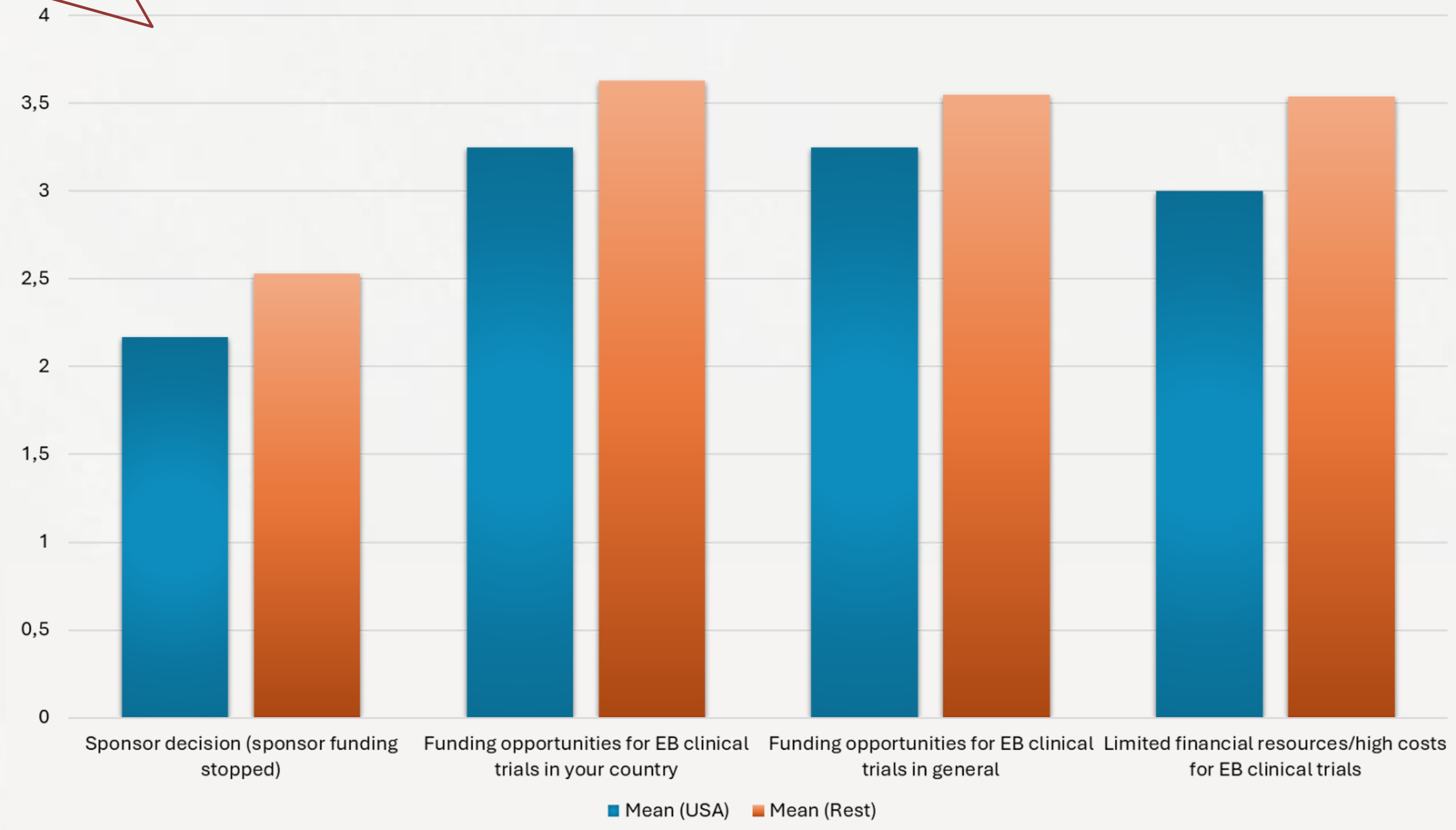
Successful trials were **mainly** performed in the **United States**.

Assumption Challenges related to trial organization that are frequently reported by other centers (e.g., funding or recruitment issues) are less prominent in the United States.

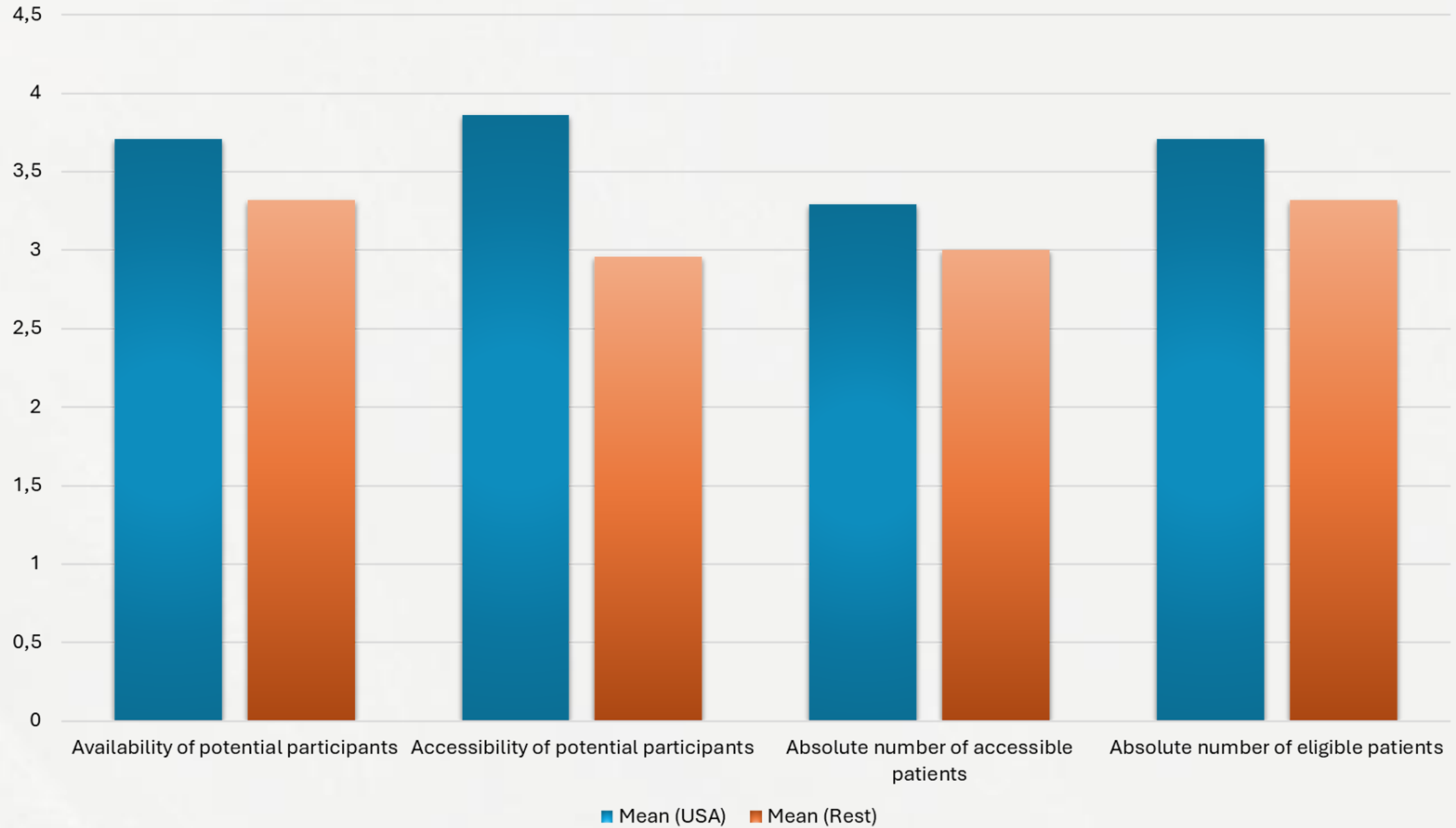
- Do US trials have less funding issues than the rest of the world?
- Do US trials have less recruitment issues than the rest of the world?

N (USA) = 4-6
N (Rest) = 49-67
→ Limited to **descriptive comparison**

Does the US have less funding issues than the rest of the world?



Does the US have less recruitment issues than the rest of the world?



Subgroup analysis

Does the ranking of main challenges differ between experts with extensive trial experience (defined as ≥ 4 trials) and those with less experience?

Main challenges - Much experience



Main challenges - Less experience




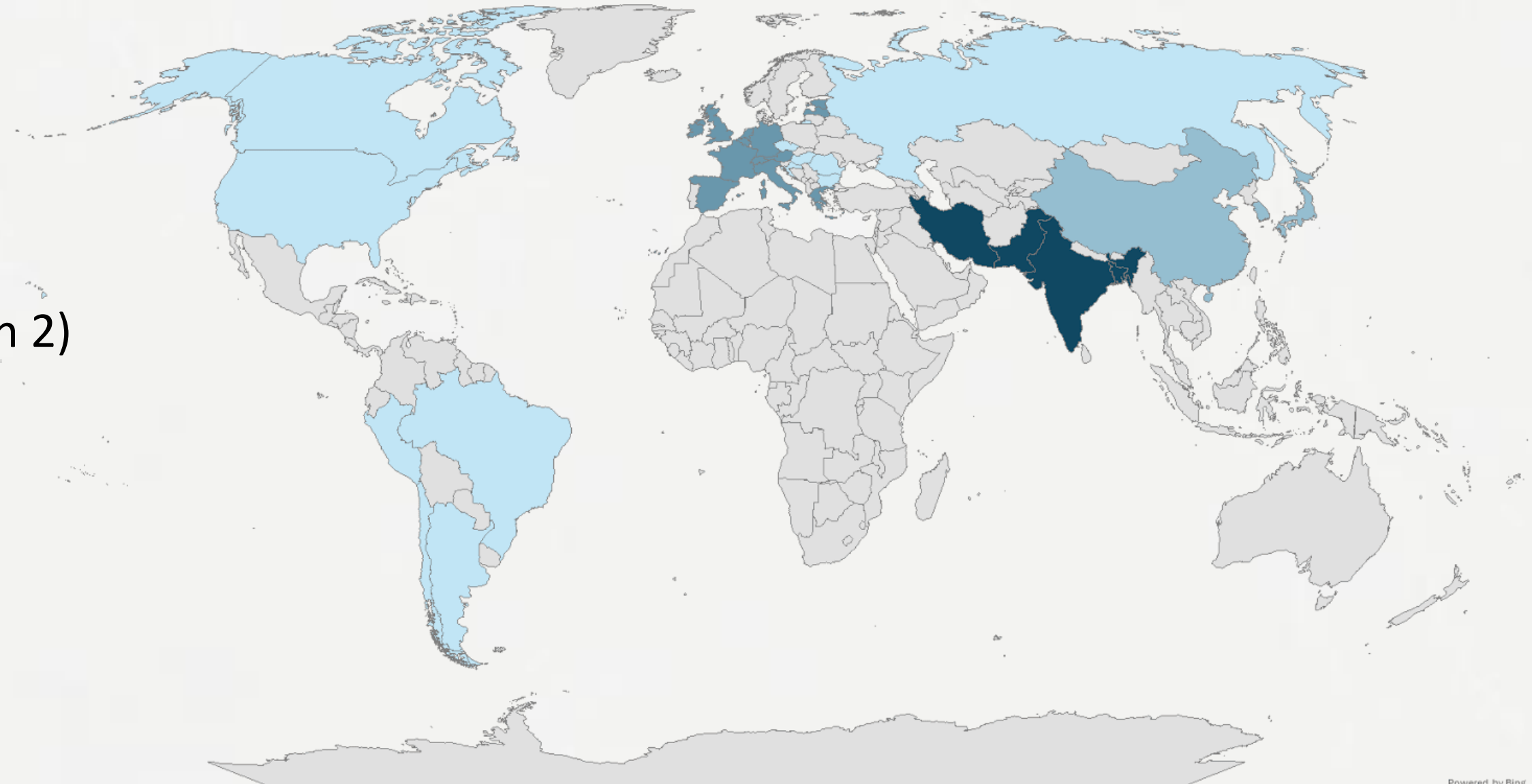
→ Experts with less experience perceive ethical regulatory processes as more challenging
 → Limited familiarity

Subgroup analysis

Regional Differences in Regulatory Approval Barriers

Ethics committee approval process

Median 
2 4



Ethics committee approval

Highest ratings in **Southern Asia** (Median 4)

Lowest in **Eastern Europe & Americas** (Median 2)

Trend (p=0.056) toward regional variation



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 SALZBURG

eb Haus
 Austria.



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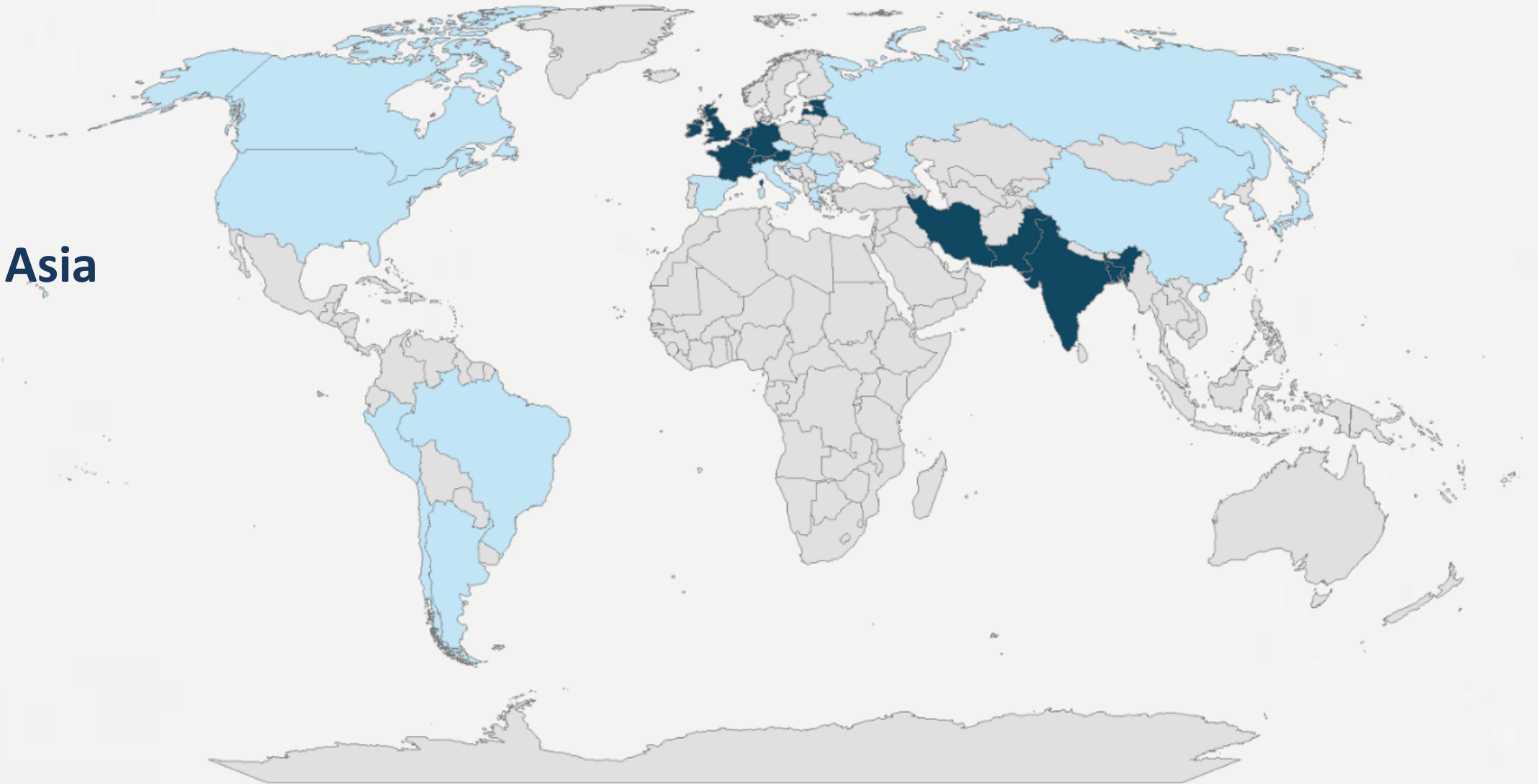
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Subgroup analysis

Regional Differences in Regulatory Approval Barriers

Regulatory approval process for multicenter studies

Median 
3 4



Multicenter Regulatory Approval

Highest in **Western/Northern Europe & Southern Asia**
(Median 4)

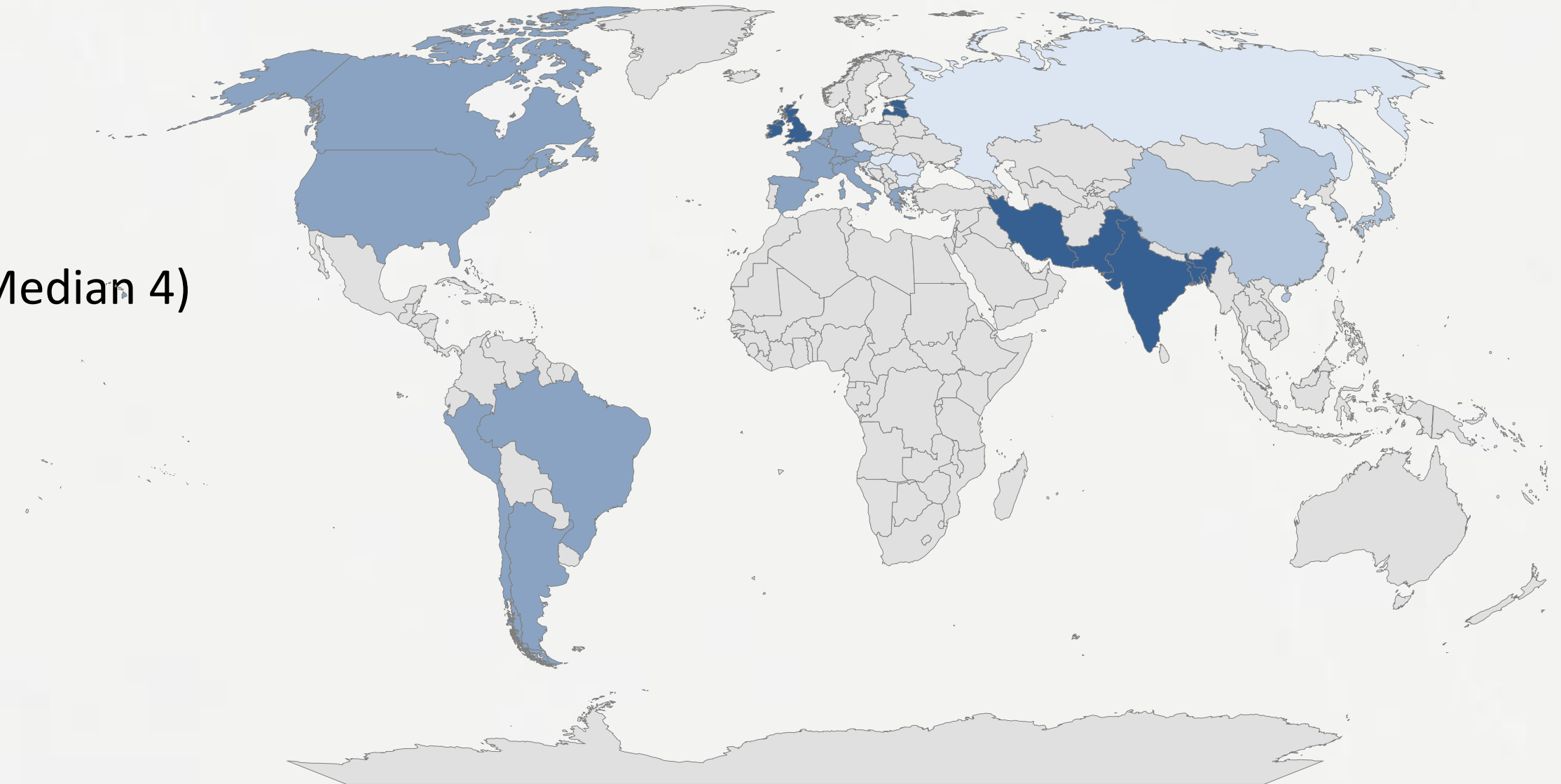
No statistically significant differences

Subgroup analysis

Regional Differences in Regulatory Approval Barriers

Delayed approval times for EB studies

Median 
2 4



Delayed Approval Times

Highest in **Southern Asia & Northern Europe** (Median 4)

Lowest in **Eastern Europe** (Median 2)

No significant regional differences



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Subgroup analysis

Regional Differences in Regulatory Approval Barriers

→ Findings exploratory due to small and varying subgroup sizes (4-15 countries/region)

- Regulatory approval barriers **seem higher in Southern Asia and Northern Europe**, and **lower in Eastern Europe**
- **Ethics committee approval** processes showed the strongest regional variation (trend level)
- Most regional differences were **not statistically significant**

Conclusions – Expert survey

Funding

- Financial constraints were among the top challenges
- EB trials rely heavily on industry and patient organizations
 - *Strong dependence on industry funding (mean 4.24)*
- Academic investigator-initiated trials struggle – EB trials are expensive and long

Recruitment and Patient Burden

- *Limited participant availability* is a fundamental obstacle (*mean 3.35*): *Cross-border participation barriers (mean 3.39)* , *competing trials (mean 2.61)*
- Patient burden is a major barrier to participation and retention according to experts
 - Invasive procedures (e.g., biopsies, blood draws), Travel burden, High visit frequency
 - Patient awareness and motivation are moderate challenges

Conclusions – Expert survey

Administrative and regulatory complexity

- Substantial administrative and regulatory friction, particularly for multicenter trials
 - *Contract negotiations between sites (mean 3.41)*
 - *Administrative workload (3.38)*
 - *Regulatory approval processes (3.20)*
 - *Varying regulatory standards between countries (3.19)*

Clinical heterogeneity and methodological challenges

- EB disease characteristics complicate trial design and analysis
 - *Variability in natural disease course (3.32), disease heterogeneity (3.26), small sample size (3.25), defining clinically meaningful endpoints (3.24), challenges measuring endpoints (3.18)*
- Only 8/70 experts believed a universal endpoint exists

Conclusions – Expert survey

Trial design challenges

- Eligibility criteria often exclude otherwise willing participants:
 - *Restrictive inclusion criteria (mean 3.29)*
 - *Requirement to pause established standard-of-care treatments (mean 3.22)*

Ethics

- Several ethical issues were perceived as **moderate challenges**, particularly those related to vulnerable patient populations and placebo use.

Less problematic factors

- Most EB trial centers have adequate technical infrastructure
- Human resource limitations were not the main challenges
- Access to statistical and analytical expertise