Recruitment Challenges for Rare Disease Clinical Trials: A Systematic Review

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OBJECTIVE

To identify common challenges and successful recruitment strategies in rare disease clinical trials through a systematic review of the literature, with the goal of informing patient recruitment approaches in rare disease studies.

INTRODUCTION

- Enrolling patients with rare diseases like hereditary angioedema (HAE) into clinical trials is often hampered by low disease prevalence, geographic dispersion of eligible patients, and delayed, missed, or incorrect diagnoses.
- Traditional recruitment methods may not be sufficient in this context.
- Recent advances, such as digital tools, registries, and advocacy partnerships, offer alternative approaches but vary in effectiveness, and support in the literature is not well-consolidated.

METHODS

Protocol as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table 1**).

Table 1. Search Strategy

Database	PubMed (MEDLINE)
Search Period	January 1, 2000 – April 11, 2025
Search String (PubMed optimized):	("rare diseases"[MeSH Terms] OR "orphan diseases"[All Fields] OR "rare condition"[All Fields] OR "rare disorder"[All Fields]) AND ("patient recruitment"[MeSH Terms] OR "clinical trial enrollment"[All Fields] OR "recruitment strategies"[All Fields] OR "investigator recruitment strategies"[All Fields] OR "trial recruitment strategy"[All Fields] OR "patient identification"[All Fields] OR "recruitment intervention"[All Fields] OR "recruitment barriers"[All Fields] OR "enrollment facilitators"[All Fields])
Inclusion Criteria	• Original research articles (qualitative, quantitative, or mixed methods) • Focused on clinical trials in rare diseases or HAE • Describes how clinicians or site coordinators recruit patients • Published in English • Studies that describe how patients find clinical trial sites (included as secondary sources) • Full-text available
Exclusion Criteria	• Editorials, commentaries, case reports, consensus statements, abstracts without detail • General awareness campaigns not linked to recruitment • Non-English publications
Data Extraction	• Standardized form developed from an initial screen of the included articles • Discrepancies resolved by consensus or group review during an alignment meeting
Extracted Fields	• Study title, year, journal • Study design and setting • Description of recruitment strategies
Data Synthesis	• An initial alignment meeting agreed on terms for assessment in two categories based on preliminary screen of papers: challenges associated with recruitment for rare disease studies and strategies used to address recruitment challenges. • Individual assessment items were created based on qualitatively common themes in the articles. • A second alignment meeting resolved conflicting assessments; consensus was reached through discussion with majority agreement required for final classification. • Percentage cutoff for reporting the top findings were agreed upon for both the challenges and strategies data.

SUMMARY

1. **A SYSTEMATIC REVIEW OF 20 STUDIES WAS CONDUCTED FOLLOWING PRISMA GUIDELINES TO IDENTIFY COMMON CHALLENGES AND EFFECTIVE STRATEGIES FOR RECRUITING PATIENTS INTO RARE DISEASE CLINICAL TRIALS.**
2. **FOUR KEY CHALLENGES EMERGED: DIAGNOSTIC DELAYS, DISPERSED PATIENT POPULATIONS, LOW INTEREST, AND LACK OF AWARENESS AND TRUST IN RESEARCH.**
3. **FIVE COMMONLY RECOMMENDED STRATEGIES INCLUDED IMPROVING DIAGNOSTIC INFRASTRUCTURE, USING DIGITAL AND DIRECT-TO-PATIENT METHODS, TAILORING COMMUNICATION, ADDRESSING LOGISTICAL AND ETHICAL BARRIERS AND APPLYING PRESCREENING APPROACHES.**
4. **THESE FINDINGS MAY SUPPORT MORE EFFICIENT AND INCLUSIVE RECRUITMENT PLANNING IN FUTURE RARE DISEASE CLINICAL TRIALS.**

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RESULTS

IDENTIFICATION AND SCREENING OF ARTICLES

- Twenty-one articles were identified from PubMed and subsequently screened.
- The addition of the term "HAE" to the search string did not yield additional articles (**Figure 1**).
  After exclusion of one article for a lack of relevance, 20 articles were included in the systematic review (**Table 2**).

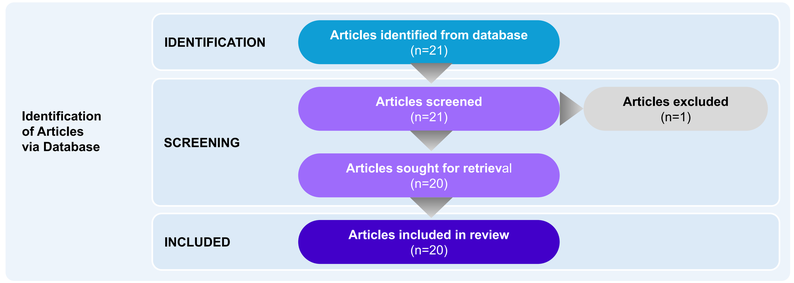


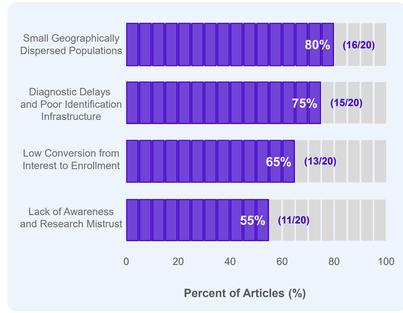
Figure 1. PRISMA Flow Diagram. Identification, retrieval, and selection of articles to determine the challenges and potential strategies to aid in the recruitment of patients to rare disease clinical trials.

Table 2: Summary of Included Studies

Reference	Location	Study Design	Disease State
Applequist J. et al. (2020) A novel approach to conducting clinical trials in the community setting: utilizing patient-driven platforms and social media to drive web-based patient recruitment. *BMC Med Res Methodol.* 20(58).	USA	Qualitative following COREQ	Granulomatosis with polyangiitis
Applequist J. et al. (2023) Direct-to-consumer recruitment methods via traditional and social media to aid in research accrual for clinical trials for rare diseases: comparative analysis study, *JMIR*. 25(339262).	USA, UK, Canada, Ireland, Germany	Various study designs	Various
Byrne N. et al. (2020) The role of primary care in management of rare diseases in Ireland. *Ir J Med Sci.* 189(3):771-776.	Ireland	Retrospective, cross-sectional survey	Various
Chen X,. et al. (2021) Identification of similar patients through medical concept embedding from electronic health records: a feasibility study for rare disease diagnosis . *Stud Health Technol Inform.* 281:600-604.	France	Model development and validation	Nephronophthisis-related diseases or syndromes
DeLozier S. et al. (2021) Real-time clinical note monitoring to detect conditions for rapid follow-up: A case study of clinical trial enrollment in drug-induced torsades de pointes and Stevens-Johnson syndrome. *J Am Med Inform Assoc.* 28(1):126-131.	USA	Automated recruitment model	Drug-induced torsades de pointes and Stevens-Johnson syndrome
Dwyer AA. et al. (2021) Validating online approaches for rare disease research using latent class mixture modeling. *Orphanet J Rare Dis.* 16(1):209.	Global	Secondary analysis of a cross-sectional needs assessment	Congenital hypogonadotropic hypogonadism
Goutaki M. et al. (2019) The Swiss Primary Ciliary Dyskinesia registry: objectives, methods and first results. *Swiss Med Wkly*. 149:w20004.	Switzerland	Prospective observational registry study	Primary ciliary dyskinesia
Gupta S. et al. (2011) Rare lung disease research strategies for improving identification and recruitment of research participants. *Chest*. 140(5):1123-1129.	Global	Descriptive report	Rare lung diseases
Hennocq Q. et al. (2024) Humanitarian facial recognition for rare craniofacial malformations. *Plast Reconstr Surg Glob Open*. 12(5):e5780.	Gaza, Ukraine	Primary research	Rare craniofacial malformations
Hwa YL. et al. (2019) Immunoglobulin light-chain amyloidosis: clinical presentations and diagnostic approach. *J Adv Pract Oncol* 10(5):470-481.	Global	Descriptive report	Immunoglobulin light-chain amyloidosis
Krischer J. et al. (2017) Experience with direct-to-patient recruitment for enrollment into a clinical trial in a rare disease: A web-based study. *J Med Internet Res*. 19(2):e50.	USA and Canada	Multi-center randomized controlled trial	Granulomatosis with polyangiitis (Wegener's)
Liu J. et al. (2022) Natural history and real-world data in rare diseases: applications, limitations, and future perspectives. *J Clin Pharmacol.* 62:S38-S55.	Global	Descriptive report	Various
Maaroufi M. et al. (2018) Federating patients identities: the case of rare diseases. *Orphanet J Rare Dis.* 31(1):199.	France	Registry development, pilot study	Various
Mak CM. et al. (2024) Computer-assisted patient identification tool in inborn errors of metabolism – potential for rare disease patient registry and big data analysis. *Clin Chim Acta*. 15:561-119811.	France	Feasibility trial	Various
McKinstry B. et al. (2007) Recruitment and retention in a multicentre randomised controlled trial in Bell's palsy: A case study. *BMC Med Res Methodol*. 7:15.	Europe	Multicenter randomized controlled trial	Bell's palsy
Okuma HS. et al. (2022) MASTER KEY Project: Powering Clinical Development for Rare Cancers Through a Platform Trial. *Clin Pharmacol Ther*. 108(3):596-605.	Japan	Platform trial	Rare cancers
Wilson A. et al. (2023) Development of a rare disease algorithm to identify persons at risk of Gaucher disease using electronic health records in the United States. *Orphanet J Rare Dis.* 18(1):208.	USA	Model development for the identification of patients from EHRs	Gaucher disease
Yu J. et al. (2020) Recruitment strategies and geographic representativeness for patient survey studies in rare diseases: Experience from the living with myeloproliferative neoplasms patient survey. *PLoS One*. 15(12):e0243562.	USA	Online survey	Myeloproliferative neoplasms
Zakrzewska JM. et al. (2018) Challenges recruiting to a proof-of-concept pharmaceutical trial for a rare disease: the trigeminal neuralgia experience. *Trials*. 19(1):704.	Global	Placebo-controlled, randomized withdrawal study	Trigeminal neuralgia
Zilber S. et al. (2023) Leigh syndrome global patient registry: uniting patients and researchers worldwide. *Orphanet J Rare Dis.* 18(1):264.	USA	Registry development	Leigh syndrome

COMMON RECRUITMENT CHALLENGES

- The top 4 recruitment challenges are shown in **Figure 2**.
- Other categories evaluated but not reported here because the number of papers was below the predetermined cutoff (55%) were ethical and logistical constraints in pediatrics, fragmented care and inconsistent data systems, and an overreliance on site-based referrals, and challenges in real-time identification of acute events.



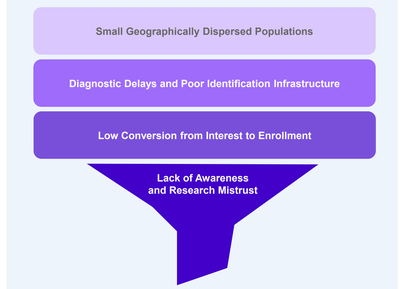


Figure 2. Common Recruitment Challenges. Left: The top 4 challenges for recruiting patients into rare disease clinical trials are presented as the percentage and the numbers of papers, out of a total of 20, citing these recruitment challenges. A cutoff of 55% was selected at the second alignment meeting. Right: schematic highlighting the major challenges with recruiting patients for rare disease clinical trials.

PROPOSED AND IMPLEMENTED STRATEGIES

- The top recruitment strategies are presented in (**Figure 3**).
- Other categories evaluated but not reported here because the number of papers was lower than the predetermined cutoff (45%) included partnership with advocacy groups.

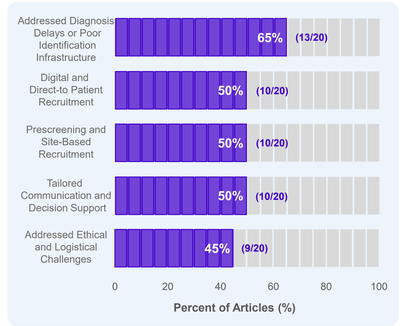


Figure 3. Proposed and Implemented Recruitment Strategies. Top recommended recruitment strategies either proposed or implemented to assist in the enrollment of patients into rare disease clinical trials. A cutoff of 45% was selected at the second alignment meeting. The percentage and the numbers of papers, out of a total of 20, citing this recruitment strategy are presented.

LIMITATIONS

- The papers spanned diverse study types, making direct comparisons of recruitment effectiveness across contexts challenging.
- Most papers focused on rare diseases or conditions broadly, not HAE specifically.
- Many studies described recruitment experiences or challenges qualitatively without rigorous data on enrollment rates, cost-effectiveness, or time to recruit, making it difficult to benchmark success.
- Positive or innovative recruitment strategies may have been favored for publication.
- The majority of the studies originated from high-income countries (e.g., US, UK, France), and these strategies may not translate well to other regulatory or healthcare environments.

CONCLUSIONS

- Recruitment for rare disease clinical trials presents persistent challenges that stem from diagnostic complexities, patient dispersion, and low conversion from interest to enrollment.
- Addressing structural barriers, such as delayed diagnoses and inadequate identification tools, combined with digital outreach, tailored communication, and ethical preparedness, may enable more timely and representative enrollment.
- These findings offer actionable guidance for trial sponsors and investigators seeking to improve recruitment outcomes in rare disease settings and shows a need to investigate these topics more thoroughly.