Healthcare Resource Use in Rare Disease Trials: A Systematic Review

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Introduction

- Healthcare resource utilization (HCRU) plays a critical role in clinical research as payers and health systems seek evidence of both clinical benefit and economic value.
- In rare diseases, the burden of resource utilization can be substantial due to complex treatment regimens and ongoing care needs.
- However, HCRU outcomes are not consistently captured in clinical trials, even though such data can strengthen value demonstration and inform cost-effectiveness and market access strategies.
- This challenge may be particularly relevant in rare disease settings, where small patient populations, heterogeneous disease presentations, and variable study designs can complicate the use of standardized measures.
- A more systematic collection of HCRU data in clinical trials could provide critical data on the economic impact of therapies.
- Beyond economic value, integrating HCRU data with trial data can help illustrate the patient journey and the broader impact of treatment on the healthcare system.

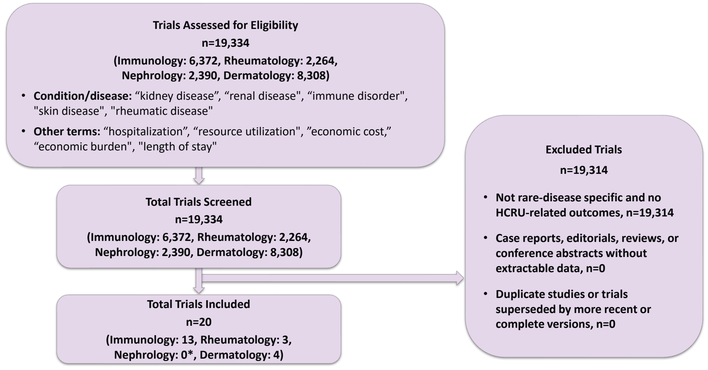
Objective

- To examine HCRU metrics reported from rare disease clinical trials across immunology, rheumatology, dermatology, and nephrology, to identify current practices, gaps, and potential opportunities.

Methods

- A systematic review of clinical trial registries, bibliographic databases, grey literature, and health technology assessment (HTA) reports was conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance.
- Eligible interventional or observational studies enrolled rare-disease populations across the four therapeutic areas and reported at least one quantifiable HCRU metric.
- Standardized extraction captured trial characteristics, HCRU endpoints, data sources and collection method, timing, analytic methods, reporting practices, and findings were summarized descriptively by therapeutic area and metric type.

Figure 1. Flow Diagram of Search Results



*One chronic kidney disease trial (EMPA-KIDNEY) contributed contextual data on hospitalization outcomes.

Table 1. Summary Table for Data Extraction

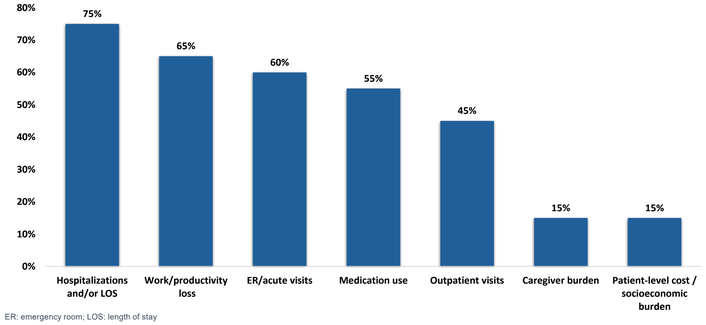
Variable Category	Variable Name	Description/Details
Publication Details	Authors	Names of primary and contributing authors
	Year of Publication	Year the study was published
	Journal Name	Full name of the journal
	Title of the Study	Official published title
	Volume, Issue, Page Numbers	Journal volume, issue, and page range
	DOI	Digital Object Identifier
	Trial Registration Number	Identifier linking to registered protocol
	Corresponding Author/Contact	Lead author's contact details
Study Characteristics	Trial Identifier	Registration number (e.g., ClinicalTrials.gov ID)
	Therapeutic Area	Nephrology, immunology, rheumatology, dermatology
	Specific Condition	Rare disease focus (e.g., Sjögren's syndrome)
	Study Phase	Phase II, III, etc.
	Geographic Location	Country or region of study
HCRU Measurement	HCRU Endpoints Reported	Types of resource utilization measured (e.g., hospitalizations)
	Definitions Used	How each HCRU endpoint was defined
	Data Sources	Methods for collecting HCRU data (e.g., EHR, self-report)
	Frequency/Timing of Measurement	When/how often HCRU data are collected
	Duration of Follow-up	Time period over which HCRU was assessed
Methodological Details	Data Collection Tools	Instruments/systems used (e.g., questionnaires, electronic Case Report Forms [eCRFs])
	Blinding of HCRU Assessment	Whether assessors were blinded
	Handling of Missing Data	Approaches to incomplete HCRU data
	Statistical Methods	Analytical approaches for HCRU outcomes
Reporting Practices	Level of Detail	Granularity (aggregate vs itemized reporting)
	Reporting of Costs	Whether resource use is translated into economic costs
	Adherence to Guidelines	Use of reporting standards (e.g., Consolidated Standards of Reporting Trials [CONSORT], Consolidated Health Economic Evaluation Reporting Standards [CHEERS])
Study Outcomes	HCRU in Hierarchy	HCRU as primary, secondary, or exploratory outcome
	Findings Related to HCRU	Key results or trends in resource utilization

HCRU: healthcare resource utilization

Results

- Twenty rare disease trials reported HCRU: Explicit HCRU for immunology = 12, dermatology = 4, rheumatology = 3, nephrology = 0; one chronic kidney disease (CKD) trial (EMPA-KIDNEY) contributed contextual hospitalization outcomes (**Figure 1**).
- All 20 trials (100%) reported ≥1 direct HCRU metrics. The most frequent direct endpoints were hospitalizations and length of stay (75%), emergency or acute visits (60%), medication or treatment utilization (55%), and outpatient visits (45%) (**Table 1**).
- Indirect HCRU was less frequent, including work/productivity loss (65%), caregiver burden (15%), and patient-level cost or socioeconomic burden (15%) (**Figure 2**).
- In immunology trials, hospitalization, ER visits, and work productivity remain the most consistently reported HCRU outcomes.
- In rheumatology trials, medication and treatment utilization, hospitalization, and diagnostic tests were the most frequently reported HCRU metrics.
- In dermatology trials, aggregated patient-reported HCRU, productivity loss, and socioeconomic burden are reported equally frequently.
- The eCRF was an important data collection tool across all trials, with data from patient diaries, medical charts, and patient-reported outcomes often transferred to it.
- Across disease areas, HCRU endpoints were usually secondary, captured via eCRFs, self-reported questionnaires, or claims data, with substantial heterogeneity in definitions, measurement windows, and units, and relatively few studies translating resource use into standardized cost outcomes.

Figure 2. Distribution of HCRU Metrics Across Included Trials in Immunology, Rheumatology, Dermatology, and Nephrology



ER: emergency room; LOS: length of stay

Table 2. Key HCRU Metrics Reported Across Included Trials (N=20)

HCRU Category	Metric	Trials Reporting, n (%)
Direct HCRU	≥1 direct HCRU metric	20 (100%)
	Hospitalizations and/or length of stay	15 (75%)
	Emergency room / acute visits	12 (60%)
	Medication / treatment utilization	11 (55%)
	Outpatient visits	9 (45%)
Indirect HCRU	Work / productivity loss	13 (65%)
	Caregiver burden	3 (15%)
	Patient-level cost / socioeconomic burden	3 (15%)

HCRU: healthcare resource utilization

Limitations

- Publicly available protocols, SAPs, and full-text documentation were not available for all trials
- Nephrology rare disease evidence was sparse
- Heterogeneous reporting limited direct cross-trial quantitative comparison

Conclusions

- HCRU metrics are rarely incorporated into trials for rare diseases in immunology, rheumatology, and dermatology. When incorporated, they are largely secondary, variably defined, and infrequently linked to cost.
- Measurement focused primarily on direct HCRU metrics, while indirect burden and cost-related outcomes were less commonly assessed.
- Prospective adoption of a core HCRU assessment with standardized definitions, data-collection tools, and costing approaches could improve comparability and support the generation of payer-relevant evidence in rare disease clinical trials.

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Disclosures

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