Barriers and facilitators to the implementation of guidelines in rare diseases: A systematic review

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Abstract

Background:

Rare diseases are individually rare but collectively common. They present a challenge to guideline implementation due to a low prevalence in the general population and the unfamiliarity of healthcare professionals. Existing literature in more common diseases references barriers and facilitators to guideline implementation. This systematic review aims to identify these barriers and facilitators in rare diseases.

We systematically identified barriers and facilitators to the implementation of guidelines in rare diseases from existing literature: A multi-stage strategy included searching MEDLINE PubMed, EMBASE Ovid, Cochrane library and Web of Science from the earliest date available to April 2021, Orphanet journal hand-search, a pearl-growing strategy from a primary source and reference/citation search.

We identified and trialled frameworks for the narrative synthesis of barriers and facilitators selecting the Integrated Checklist of Determinants of Practice which comprises of twelve checklists and taxonomies, 57 potential determinants. It was developed as a screening tool to identify determinants that warrant further in-depth investigation to inform design of future implementation strategies.

Results:

Thirty-nine studies were included, most of which were conducted in North America (56.4%). There were 154 barriers across 35 determinants (33 studies) and 52 facilitators across 24 determinants (22 studies). Fourteen diseases were included across seven WHO ICD-11 disease categories.

Individual health professional factors and guideline factors were the most commonly reported domains (56.5% of barriers and 65.4% of facilitators). Overall, the three most reported barriers were the awareness/familiarity with the recommendation, domain knowledge and availability of necessary resources. The three most reported facilitators were awareness/familiarity with the recommendation, agreement with the recommendation and ability to readily access the guidelines.

Particularly relevant to rare disease health technologies, the domain of incentives and resources included barriers to implementation in the form of technology costs, ancillary staff costs and more cost-effective alternatives. There was no mention in the included studies of influential people, patient advocacy groups or opinion leaders, or organisational factors influencing implementation.

Conclusion:

Key barriers and facilitators to the implementation of clinical practice guidelines in the setting of rare diseases were at the individual health professional and guideline level. Influential people and organisational factors were relatively under-reported and warrant exploration, as does increasing the ability to access the guidelines as a potential intervention.

Background And Objectives

Although rare diseases are individually rare, they are collectively common with an estimated global prevalence of 263–446 million people across 6000–7000 diseases(1, 2). While a proportion of rare diseases have no accepted medical technologies, others have expensive therapeutic options with varying levels of evidence due to participant factors including small sample sizes, geographical dispersion and disease heterogeneity(3, 4). Despite this, nearly six hundred orphan technologies to treat rare diseases have been approved by the Food and Drug Association in the US between 1983 and July 2020 with 552 on the market at the time of the NORD study(5). A third of National Institute for Health and Clinical Excellence (NICE) approved technologies are for rare diseases(6). These technologies have resulted in associated clinical practice guidelines, summarising up-to-date evidence and expert opinion leading to structured and practical recommendations to support decision making as prioritised by the World Health Organisation(4, 7).

The development and implementation of guidelines for rare diseases presents a greater challenge to patients, health professionals and guideline developers compared to more common diseases. This is related to limited health professional knowledge and experience in caring for those with specific rare diseases due to low disease prevalence(8). These factors may lead to guideline adherence worse than the 30–70% non-adherence to guidelines reported in non-rare disease areas(9–12). Frequently identified factors in existing systematic reviews include health professional level factors, a lack of knowledge(13), awareness of guidelines(13–15) and agreement with recommendations(13, 15). Influencing factors at the organisational level include the absence of leadership/senior support(13, 16, 17), difficulties with teamwork(13, 17), disagreements with colleagues(13, 14) and insufficient communication(13).

Although there is a growing number of guidelines being published to inform the use of medical technologies for rare diseases, there has been no published research to identify barriers and facilitators to the implementation of these recommendations in clinical practice. Such research is essential to ensure that people with rare diseases receive equitable high-quality healthcare. In this review, we aim to systematically identify and synthesise the factors influencing the implementation of CPGs in the rare diseases setting. This will enable more informed development, implementation and evaluation of guidelines as well as the development of targeted interventions to improve implementation.

Research Design And Methods

Study design

We conducted a systematic review according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. The study was registered on PROSPERO (CRD42021256061) then a protocol developed and published.

Studies were eligible for inclusion if they explored barriers and/or facilitators to the implementation of guidelines or consensus documents for rare diseases. We have used the definition of barriers and

facilitators as used by the Integrated Checklist of Determinants of Practice (ICDP) which consists of determinants of healthcare professional practice being factors that might prevent (barrier) or enable (facilitator) improvements in healthcare practice(18). The European Union definition of a rare disease affecting less than 1 person per 2000 was used with prevalence confirmed on the Orphanet website(19). Oncological rare diseases were excluded as they are predominantly managed by the oncology specialists rather than the related disease area. No restrictions were placed on the research design or publication date. Results were restricted to the English language due to limited resources for translation.

Search strategy

A comprehensive search strategy, including database and supplementary techniques, was developed to maximise recall and reduce publication bias. An additional file includes the complete search strategy [see Additional file 1].

Search strategy stages:

Stage 1: Rare diseases search

Stage 2: NICE specialised technology appraisal rare diseases search

Stage 3: Orphanet Journal hand-search 28/02/17–28/02/21

Stage 4: Pearl-growing subject search (20) from Denger et al (21)

Stage 5: Supplementary searches – grey literature, citations and references

Rare disease search

The SPIDER tool was used to formulate the initial research question and guide the overall search strategy(22). The SPIDER tool was chosen as the components are more relevant than alternatives, PICO and PICOS, to identify studies with the expected study design, qualitative and mixed-methods (Table 1). Databases searched include MEDLINE via PubMed, EMBASE via Ovid, Web of Science and Cochrane Library from inception to April 2021.

Table 1
SPIDER tool

Detailed SPIDER tool	Description	Search terms and synonyms
(S) Sample	Health professionals	*health professional* or doctor* or clinician* or consultant* or GP or general practitioner* or physician* or pharmacist**
(PI) Phenomenon of Interest	Clinical practice guidelines for rare diseases	*guideline* or guidance or prescrib* or clinical protocol* or prescription** *rare dis* or rare diagnos* or orphan dis**
(D) Design	Qualitative or mixed methodology	*Ovid Medline qualitative search filter(23)*: *((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. Or Interviews as topic/ or focus groups/ or narration/ or qualitative research/*
(E) Evaluation	Influencing factors	*barrier* or facilit* or help* or hinder* or compliance or comply or complies or accept* or conform* or approv* or adhere* or strateg**
(R) Research type	Qualitative	*Qualitative research/*

NICE specialised technology appraisal rare diseases search

NICE guidelines and technology appraisals effectively mandate the availability of technologies to people with rare diseases in England and Wales, making their adoption in clinical practice less equivocal. Published NICE technology appraisal guidance (TAG) and highly specialised technologies guidance documents were reviewed to identify non-oncological rare diseases with existing guidance on 27/02/2021(6). Twenty-nine current guidance documents were identified with twenty-four rare diseases as shown in Fig. 1 which were incorporated into the search strategy from the "Rare disease search". An additional file includes the rare diseases identified [see Additional file 2]. NICE recommendations were chosen as technologies have to be made available in the NHS within 3 months, so their use is unequivocal(24). As in the rare disease search, the database search included PubMed MEDLINE, Ovid EMBASE, Web of Science and Cochrane Library from inception to April 2021.

Orphanet Journal hand-search

Orphanet journal editions from 28/02/17 to 28/02/21 were hand-searched to identify any relevant studies. The Orphanet journal was chosen as it is peer-reviewed; focuses on research in rare diseases and publishes national/international guidelines as well as conference proceedings for rare diseases. Five years was selected as the timescale as 75.9% of NICE technology appraisal guidance documents, we identified in the previously mentioned rare disease search, for non-oncological rare diseases were

published between 2016 and 2020 [See Additional file 2]. Furthermore, the median time for the production of guidance for a NICE single technology appraisal is 48 weeks(25). Thus, the results from journal issues for the preceding five years when the search was undertaken in February 2021 should account for the time for NICE technology appraisal guidance publication, development and research into implementation in clinical practice.

Pearl-growing subject search

Through the “Rare disease search” we identified a primary manuscript published by Denger et al that explored the barriers and facilitators to guideline adherence for a specific rare disease, Duchenne’s Muscular Dystrophy(21). We developed a subject pearl-growing strategy using the Medical Subject Headings (MeSH) terms indexed for the study published by Denger et al. The MeSH term (guideline adherence*) was combined with the non-oncological rare diseases identified to have current NICE TA guidelines to search PubMed MEDLINE i.e. (*rare disease*) AND (guideline adherence*). The decision for the pragmatic search using PubMed Medline was suitable due to the comprehensiveness of the overall search strategy and the specificity of MeSH terms.

Supplementary searches

Grey literature was obtained through discussion with the NICE Health Technology Adoption team who support the uptake of new technologies recommended by NICE through system learning based on usage and clinical engagement data. Data sources were sought from this group given their experience in engaging with our stakeholders as well as the identification of obstacles and solutions to technology adoption in clinical practice. An additional file includes the grey literature provided [see Additional file 1].

References and citations of all included studies were hand-searched and assessed for suitability for inclusion with repeated cycles until no further studies were identified.

Study selection and data extraction

Following the elimination of duplicates, one reviewer (MG) reviewed the titles and abstracts according to the inclusion criteria. The full-text review was conducted by two independent reviewers (MG and JC) with any disagreements resolved by a third reviewer (JF). Reasons for exclusion were recorded on the data extraction template.

Data extraction was developed by reviewers then piloted and undertaken. Information included authors, publication year, database ID, location, ICD-11 disease category, study design, type of participant and number of responses.

Quality assessment

To ensure transparency, all included studies were appraised using best practice quality appraisal tools relevant to their specific research design. All appraisals were conducted by MG and verified by JF.

Data analysis and synthesis

Thematic analysis was performed using the Integrated Checklist of Determinants of Practice as this framework was specifically developed for healthcare improvement(18). The checklist was formed through the aggregation of the components from twelve existing checklists, frameworks and taxonomies for chronic diseases which were identified through a systematic review process. It consists of seven overarching domains and fifty-seven determinants of practice that could be interpreted as a barrier or facilitator. The determinants are sufficiently diverse and detailed to encompass factors identified in the included studies. Due to the heterogeneity of questions and study design, statistical aggregation was not appropriate.

Results

Search process

After eliminating duplicates 8094 titles were identified. 122 studies were selected for full-text review and 39 were included in the thematic synthesis (using the determinants of practice in the ICPD framework). The PRISMA flow chart summarising the review process is in Fig. 1. There was high inter-rater reliability for the inclusion of studies at the full-text review stage (kappa statistic 0.81). Additional files show the full multi-stage PRISMA flow chart [see Additional file 3] and the studies excluded at the full-text stage [see Additional file 4].

Study characteristics

Most included studies were conducted in the United States (51.3%) with the remaining studies being multi-national or from countries with a high Human Development Index. Publication dates ranged from 1995 to 2021 (median 2016, IQR 2013–2019) with an increasing trend in publication rate when studies from 2020 and 2021 were excluded (overall reduction in research due to COVID-19 pandemic). There were thirteen rare diseases across seven WHO ICD-11 categories in the included studies with diseases of the blood or blood-forming organs most prevalent (33.3%), see Table 2. An overview of the included studies is available as an additional file [see Additional file 5]

Table 2
WHO ICD-11 disease categories and rare diseases of the included studies

ICD-03: Diseases of the blood or blood-forming organs	**Orphanet prevalence***	**13 (33.3%)**
Atypical Haemolytic Uraemic Syndrome	1–9/100 000	1
Sickle Cell Disease	1–5/10 000	12
ICD-04: Diseases of the immune system		**4 (10.3%**
Rare Connective Tissues Disease (group)	-	1
Hereditary Angioedema	1–9/100 000	2
Primary Antibody Deficiency	1–9/100 000	1
ICD-05: Endocrine, nutritional or metabolic disease		**1 (2.6%)**
Urea Cycle Disorders (group of disorders)	-	1
ICD-08: Diseases of the nervous system		**7 (17.9%)**
Duchenne Muscular Dystrophy	1–9/100 000	5
Spinal Muscular Atrophy (group)	-	2
ICD-09: Diseases of the visual system		**2 (5.1%)**
Rare Non-Infectious Uveitis (group)	-	2
ICD-12: Diseases of the respiratory system		**10 (25.6%)**
Cystic Fibrosis	1–5/10 000	4
Idiopathic Bronchiectasis	-	1
Idiopathic Pulmonary Fibrosis	1–5/10 000	5
ICD-13: Diseases of the digestive system		**1 (2.6%)**
Primary Biliary Cholangitis	1–5/10 000	1
Not applicable		**1 (2.6%)**
Non-specific	NA	1
* Disease prevalence when Orphanet database searched on 22/02/2022(26)		

Questionnaire-based approaches were the most frequent data collection method, twenty studies (51.3%). Most studies reported the perceptions or experiences of respondents (n = 32, 82.1%) rather than observational results (n = 5, 12.8%) or expert opinion (n = 2, 5.1%). Health professionals not regularly working with rare disease patients were the most common respondent type (n = 19) compared to non-health professionals (n = 8) and rare disease health professionals (n = 7). An additional file has the full

description of the included studies [see Additional file 5]. Studies rated as having a higher risk of bias in their specific quality appraisal tool were only included where their identified determinants of practice were supported by other studies included in the review with a low risk of bias. An additional file includes further details of the quality assessment [see Additional file 6].

Determinants of practice – barriers and facilitators

In accordance with the definitions used by the Integrated Checklist Determinants of Practice (ICDP), determinants are considered barriers if their presence impedes the implementation of or adherence to rare disease guideline(s). In contrast, they are considered facilitators if their presence promotes the implementation of or adherence to the rare disease guideline(s)(16). We considered a determinant as neutral when it could be interpreted as having a positive or negative impact.

The data synthesis produced 154 examples of reported barriers across 33 studies corresponding to 35 determinants in the ICDP and 49 examples of reported facilitators across 22 studies corresponding to 24 determinants in the ICDP. Figures 3 and 4 summarise identified factors with a comprehensive analysis in additional files [see Additional files 7 and 8].

The individual health professional factors domain was the most prevalent domain. Awareness and familiarity with the recommendation (determinant 2.1.2) was the most reported individual determinant of practice (Table 2). An additional file includes the contribution of individual studies to the determinants of practice [see Additional file 9].

Table 3
Top 3 determinants identified in included studies

Top 3 barriers	Top 3 facilitators
Awareness and familiarity with the recommendation (n = 13)	Awareness and familiarity with the recommendation (n = 9)
Domain knowledge (n = 9)	Agreement with the recommendation (n = 8)
Availability of necessary resources (n = 9)	Accessibility of the recommendation (n = 5)

Guideline factors

The quality of evidence, clarity and feasibility of the recommendation were the highest reported determinants in this domain potentially limiting the implementation of guidelines in the included studies. This included a lack of sufficient evidence(21, 27–30) and dependence on expert opinion(31). Clarity of guideline recommendations was considered to facilitate implementation through avoidance of jargon, lengthy and text-heavy guidance(28, 32); and clear indications for initiation(29). The included studies reported difficulties retrieving guidelines(33–35), poor dissemination(36) and insufficient translation to other languages(33).

Feasibility of recommendations influences the likelihood of implementation through sufficient time in clinical practice to implement recommendations(36–39), perceived suitability of recommendations for healthcare in practice(21, 30, 32, 36) and adaptability of the recommendations to different healthcare systems(29, 36). The accessibility of recommended interventions also presents an obstacle to implementation requiring sufficient technology access/fluency(32), access to investigations(34, 40) or alternatives being more accessible/feasible(38, 41).

Supporting information technology was cited as a facilitator to implementation of guidance by three studies through the use of mobile apps(42), guidelines applications(32) and electronic medical records(43). Insufficient digital resources impair guideline dissemination leading to under-utilisation(44).

Individual health professional factors

Awareness and familiarity with the recommendations were reported to influence implementation in a large number of included studies(27, 29, 31, 32, 34–37, 40, 42–54). This was present in studies involving health professionals working in specialist rare disease centres (n = 7, 17.9%) as well as health professionals not routinely working with rare disease patients (n = 19, 48.7%). All health professional study participants not routinely working with rare disease patients were in the same disease area or could be expected to implement the recommendations for rare disease patients. Low frequency of encountering patients with the specific rare disease was reported as a potential reason for limited awareness/familiarity(21, 31). Some studies included suggestions to improve awareness including education(35, 47), inaccessibility(42), regional network and awareness campaign(34).

Health professionals' knowledge in the rare disease subject area (domain knowledge) limited the implementation of recommendations (21, 30, 35, 36, 39, 43, 46, 49, 55, 56). There was no further exploration of potential reasons although other related findings included a lack of specific training(21, 30, 39, 56) and insufficient skills(29, 55).

The perception of guidelines by health professionals may explain some variation in practice due to their agreement with using guidelines in clinical practice(29, 35) or agreement with the specific recommendations(29, 31, 35, 36, 38, 40, 44, 45, 48, 49, 55, 57, 58). Outcome expectancy impaired the implementation when it was perceived that the recommendation would not affect patient outcomes(31, 44) or that health professionals anticipated poor patient compliance(44, 49, 55), expected adverse outcomes(56) or that recommendations may cause anxiety to patients(38). Attitudes and emotions of health professionals were found to negatively affect adherence to recommendations in Sickle Cell Disease (SCD) care related to perceived opiate-seeking behaviour(27, 56, 59).

Health professional self-reported capability (efficacy) in managing patients with a rare disease limited implementation, non-rare disease specialists feel unable to provide care(42, 55), adhere to recommendations(35) or interpret outcomes of recommendations(44). This is potentially coupled with professionals' failure or delays in prescribing recommended therapies representing professionals' behaviour(49, 60).

Patient factors

Patient needs or demands of their healthcare providers were reported to potentially influence guideline implementation. These factors included the home-to-clinic distance for patients(37, 61), perceived additional costs to patients(31, 56, 61), inflexibility of clinic timing(61) and unrealistic patient expectations(30). Some studies suggested that implementation of recommendations could be supported through recognising patient needs and developing guidelines in a patient-centred method(21, 36, 43).

Patient knowledge and beliefs were recognised as a barrier through patients being unaware of the need to attend for recommended interventions(61, 62) and disagreement with the guideline recommendations(55). Patient and caregiver unawareness of the guidelines or disease knowledge was identified as a factor that may limit their engagement and potentially impeding guideline implementation(21, 32, 36, 37, 39).

Patient preferences for the location of their care(21), patient-focussed priorities(21, 30, 38) and avoidance of additional treatment burden(29) were reported to possibly limit the implementation of some recommendations. This could manifest in an adversarial manner through poor medication adherence(29, 56, 59) or low outpatient attendance(31, 55, 56). Authors suggest that engagement with patients and caregivers could increase adherence to guidelines(21, 32, 63). Denger et al suggest that patients adhering to recommendations may encourage other patients with the same disease to adhere to recommendations as a form of peer pressure. They also propose that recommendations that do not interfere with patients' everyday life are more likely to have better adherence(21). Interpersonal relationships between health professionals and patients/caregivers have been suggested to influence patients' motivation and willingness to participate in care(64). A patient's motivation could then impede implementation for example people with SCD have described being demotivated to attend hospital for fear of being perceived to be drug-seeking and facing potential discrimination(56, 59, 61).

Professional interactions

Some studies described poor communication and coordination between primary and secondary care potentially impeding the implementation of recommendations(37, 39, 42, 43, 64). These findings contrast those of Heutinck et al who reported that surveyed physicians were satisfied with the inter-professional communication about Duchenne Muscular Dystrophy patient care although reasons for this outlying study were not explored further(31). Referral processes were believed to be underlie some of these inter-professional communication difficulties including practical difficulties(43), lack of awareness of processes(46) or insufficient information on referrals(41). A notable absence in this domain was the role of influential people including opinion leaders and patient groups which have been recognised as potentially having a role in guideline implementation for more common diseases(65, 66).

Financial incentives and resources

Availability of resources and financial disincentives were found to impair guideline implementation. Specific reasons for the reduced availability of necessary resources and financial considerations included

unavailable/insufficient therapies(31, 34, 64), health technology costs for the recommended intervention(21, 38, 64), inappropriate clinical spaces/schedules(37, 44), ancillary staff costs(31, 37), general costs(21, 29) and inadequate time(32, 37, 43, 55). More cost-effective alternative preparations may also impede adherence to recommendations in guidelines(39). Utrankar et al suggest financial incentives or penalties can improve the completion of guideline-derived objectives(32). Insufficient support staff was believed to impair the ability of clinicians to comply with recommendations through poor coordination(31), resource management(35) and delayed interpretation of results(55).

Capacity for organisational change

The capacity for organisational change was not a feature of the included studies. This could be related to the predominantly patient or health professional focus of these studies which would not involve in-depth assessment of organisational factors.

Social, political and legal factors

The main hurdle described by the studies at the social, political and legal level were payer or funder policies. Proposed mechanisms included insufficient insurance coverage(56), difficulties obtaining reimbursement(29, 36, 44, 55) and a failure to recognise therapy services as essential(21). It is important to recognise that these findings were predominantly reported in studies performed in the United States (n = 5, 71.4%). Masese et al described respondents believing that their ability to good care was not influenced by insufficient insurance coverage. However, they did not specifically enquire about whether it influenced their ability to follow recommendations or patients' behaviours(43). Alternatively, an insurance-based healthcare system may promote greater guideline adherence as health professionals' decisions may not be influenced by a limited healthcare budget as described by Benson et al as medical care is partly compensated by insurance companies(45). Regulatory oversight was considered a barrier to analgesic management of SCD related pain by Fearon et al but the responses did not explore this further(56).

Discussion

This systematic review identified, quality appraised and synthesised thirty-nine studies assessing factors influencing clinical practice guideline implementation. There has been increased publication of studies assessing guideline implementation over the last twenty years prior to the COVID-19 pandemic. There is consistent evidence that individual health professional factors and guideline factors are some of the most frequent barriers as recognised by many rare disease organisation strategies including the UK Rare Diseases Framework(67), EURODIS: Recommendations from the Rare 2030 Foresight Study(68), Canada's Rare Disease Strategy(69) and Australian National Strategic Action Plan for Rare Diseases(70).

Frequently mentioned barriers were in the individual health professional factors domain with the most prevalent determinant of practice influencing guideline implementation being health professional awareness and familiarity with recommendations. This has also been reported in existing systematic reviews for more common diseases(13–15, 65). Fischer et al demonstrated similar findings in their

scoping review then proposed that opinion leaders and continuous education can improve health professionals' familiarity with recommendations and knowledge(65). Unexpectedly, there was an absence of influential people being reported as a facilitator to guideline implementation in the included studies. An opinion leader can be described as an individual who is perceived as credible, trustworthy and able to exert influence on others' decision-making(71). Local opinion leaders alone or combined with other interventions have been shown to be effective in promoting evidence-based practice(72). Key opinion leaders are already involved in the development stage of new technologies, policies and guidelines in the rare disease field(73).

Supporting information technology can help facilitate implementation through the use of mobile apps, websites and electronic records. Mobile devices and apps can increase clinical decision making, improve patient outcomes and prompt health professionals to perform clinical actions(65, 74).

Patient Advocacy Groups (PAGs) are influential in rare disease research with high participation and perceived benefit by the Rare Diseases Clinical Research Network (RDCRN). They have an additional role in information dissemination with 96% of PAGs working with the RDCRN communicating activities within the patient community(75). However, patient involvement was less prevalent in clinical guideline development, as reported by Armstrong & Bloom, with only 13% of 101 surveyed organisations developing guidelines involving patients/PAGs at least some of the time. Furthermore, only 20% develop associated patient-facing guideline summaries(76). This study was based on U.S. organisations which is relevant to our review given that over half of the included studies were from the U.S. There is no formal National Rare Disease Plan for the U.S. with policy varying between states(77). However, other national strategic action plans for rare diseases have recognised the importance of patient advocacy groups(68, 70).

Strengths & limitations

The strengths of this review include the aggregation of determinants of practice from different regions, healthcare settings and rare diseases supporting the generalisability of findings. Barriers and facilitators examined were to recommendations from the NICE organisation, based in England & Wales, and other international organisations publishing guidelines for use the care of people with rare diseases. Synthesis was supported by a range of existing systematically developed, validated and peer-reviewed tools. Weaknesses included the English language restriction and prevalence of studies from high-income countries.

Recommendations for clinical practice and future research

- An approach to improve guideline implementation from systematic reviews for common diseases and notable absence in this review would be further involvement of opinion leaders and patient advocacy groups in the rare disease communities.

- Familiarity, knowledge and information retrieval by health professionals could be improved through sign-posting via a mobile app or dedicated website.
- Future clinical practice guideline research should focus on all stages of the process including development, implementation and evaluation to optimise care for patients with rare disease. Researchers should endeavour to include patients at each stage from development to implementation and evaluation.
- Future research should assess the potential impact and methods of modifying specific determinants of practice. This may be best approached through a single disease model to give in-depth understanding of the factors leading to sustained change.

Conclusions

Current literature suggests key barriers and facilitators to the implementation of rare disease guidelines are in the individual health professional and guideline domains. There were issues regarding the difficulties accessing guidelines for rare diseases which could be approached through information technology approaches. Influential people and organisational factors were relatively under-reported so represent potential options for interventions to improve implementation.

Abbreviations

CPG – Clinical Practice Guideline

ICDP – Integrated Checklist of Determinants of Practice

NICE - National Institute for Health and Care Excellence

NORD - National Organization for Rare Diseases

PAGs – Patient Advocacy Groups

RDCRN – Rare Disease Care Research Network

SCD – Sickle Cell Disease

TA – Technology Appraisal

TA – Technology Appraisal Guidance

WHO - World Health Organisation

Declarations

Ethics approval and consent to participate:

No ethical approval or consent to participate required

Consent for publication:

Not applicable

Availability of data and materials:

All data generated or analysed during this stage are included in this published article [and its supplementary information files]

Competing interests:

MG declares that he has no competing interests.

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Authors' contributions:

Conceived the ideas of design of the study: JF and AO

Search strategy design: MG, AS and JF

Performed data collection: MG

Data analysis and interpretation: MG, JC and JF

Primary author: MG

Provided revisions to scientific content of manuscript: MG, JC, AS, AO and JF

Provided stylistic/grammatical revisions to manuscript: MG, JC, AS, AO and JF

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Figures

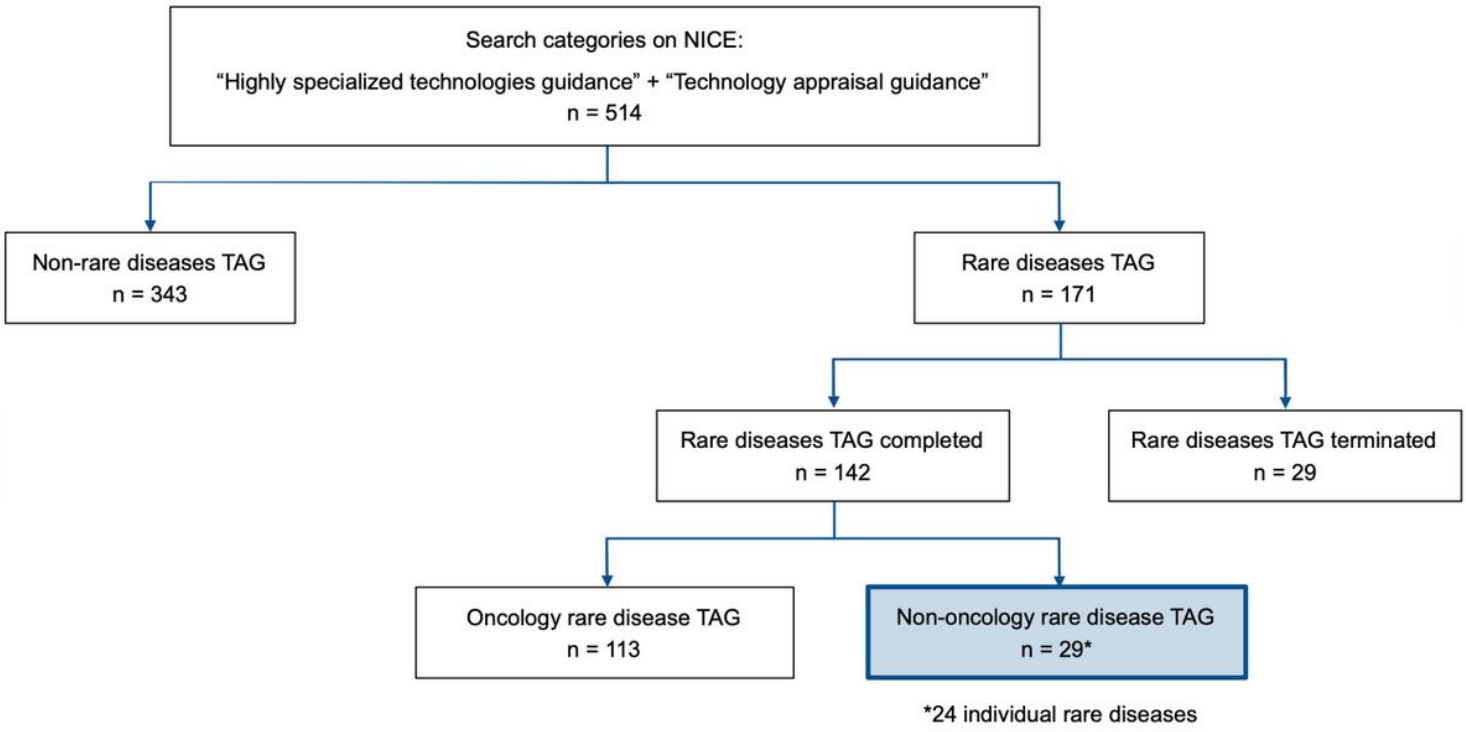

Figure 1

NICE technology appraisals to identify rare diseases with existing technology appraisal guidance

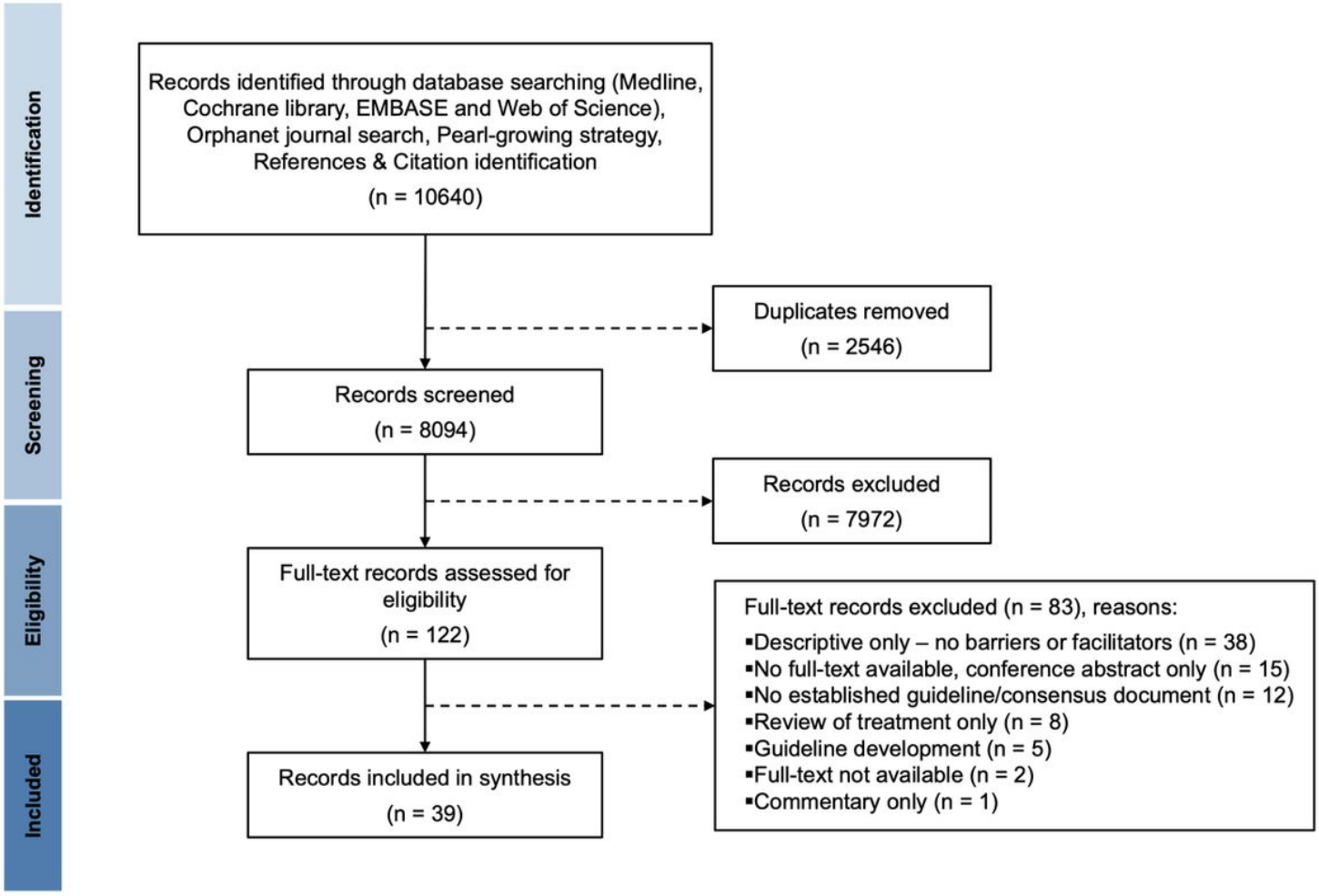

Figure 2

PRISMA flow chart

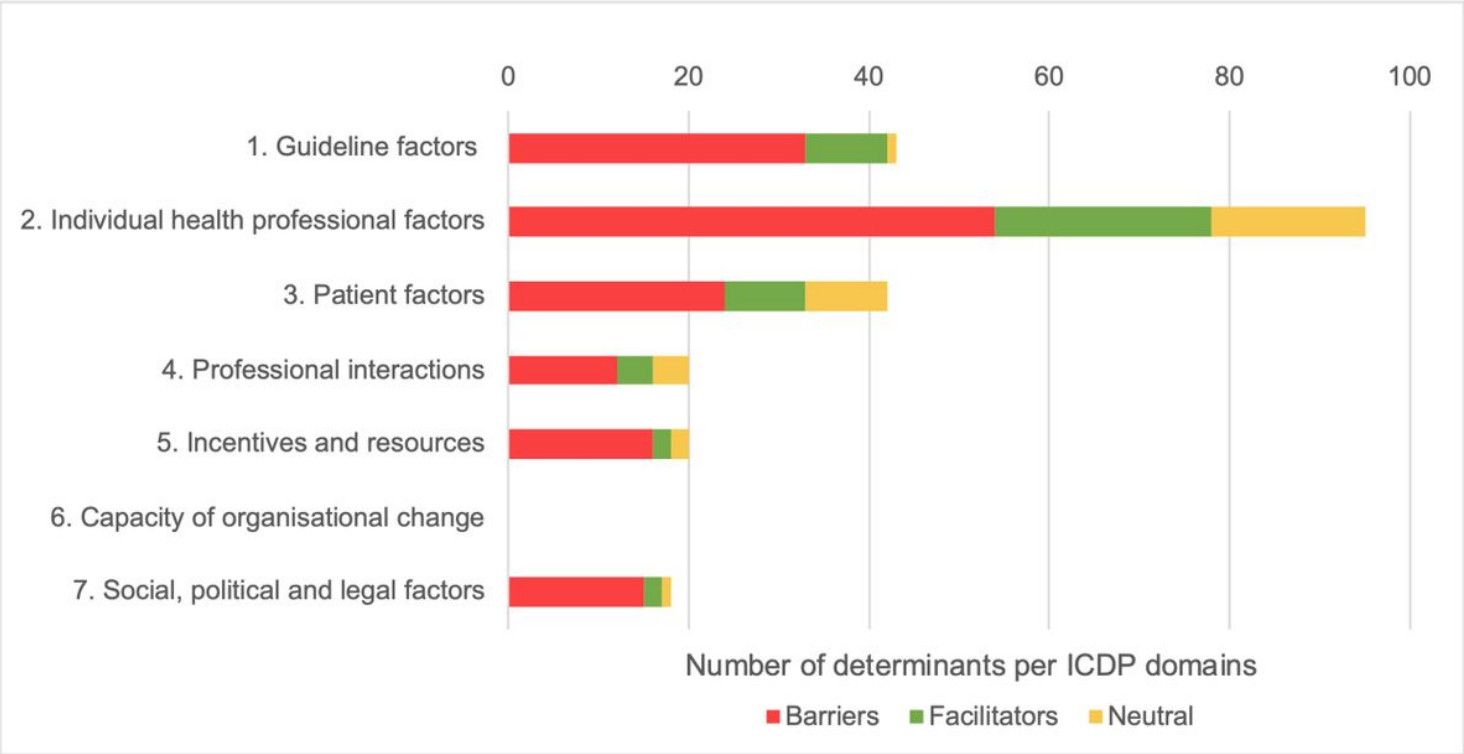

Figure 3

Stacked bar chart of barriers, facilitators and neutral determinants across the seven determinants of the ICDP

Determinants of practice	B	F	N
1 Guideline factors	**33**	**9**	**1**
1.1 1.1.1 Quality of evidence supporting the recommendation	5	1	
1.1.2 Strength of recommendation	1		
1.1.3 Clarity	4	1	
1.1.4 Cultural appropriateness	1		1
1.1.5 Accessibility of the recommendation	6	4	
1.1.6 Source of the recommendation	2	1	
1.1.7 Consistency with other guidelines	1	1	
1.2 1.2.1 Feasibility	8	1	
1.2.2 Accessibility of the intervention	4		
1.3 1.3.1 Compatibility	1		
2 Individual health professional factors	**54**	**24**	**18**
2.1 2.1.1 Domain knowledge	9	3	5
2.1.2 Awareness and familiarity with the recommendation	13	9	6
2.1.3 Knowledge about own practice		1	1
2.1.4 Skills needed to adherex	5		1
2.2 2.2.1 Agreement with the recommendation	6	8	4
2.2.2 Attitudes towards guidelines in general	2		
2.2.3 Expected outcome	7	1	
2.2.4 Intention and motivation	3	1	
2.2.5 Self-efficacy	5	1	1
2.2.7 Emotions	2		
2.3 2.3.1 Nature of the behaviour	2		

Determinants of practice	B	F	N
3 Patient factors	**24**	**9**	**10**
3.1 Patient needs	5	3	1
3.2 Patient beliefs and knowledge	6	2	2
3.3 Patient preferences	4	1	3
3.4 Patient motivation	3	2	1
3.5 Patient behaviour	6	1	3
4 Professional interactions	**12**	**4**	**4**
4.1 Communication and influence	6	2	1
4.2 Team processes	3		3
4.3 Referral processes	3	2	
5 Incentives and resources	**16**	**2**	**2**
5.1 Availability of necessary resources	9		1
5.2 Financial incentives and disincentives	1	1	1
5.7 Assistance for clinicians	6	1	
7 Social, political and legal factors	**15**	**2**	**1**
7.1 Economic constraints on the healthcare budget	5	1	
7.3 Legislation	2		
7.4 Payer or funder policies	7	1	1
7.5 Malpractice liability	1		

B *Barriers* **F** *Facilitators* **N** *Neutral*

Figure 4

Abbreviated overview of barriers, facilitators and neutral determinants influencing guideline implementation across the seven domains of the ICDP

Supplementary Files

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