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Heterogeneity of reported outcomes in epidermolysis bullosa clinical research: a scoping review as a first step towards outcome harmonization

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Abstract

Background Epidermolysis bullosa (EB) is a rare, genetically and clinically heterogeneous group of skin fragility disorders. No cure is currently available, but many novel and repurposed treatments are upcoming. For adequate evaluation and comparison of clinical studies in EB, well-defined and consistent consensus-endorsed outcomes and outcome measurement instruments are necessary.

Objectives To identify previously reported outcomes in EB clinical research, group these outcomes by outcome domains and areas and summarize respective outcome measurement instruments.

Methods A systematic literature search was performed in the databases MEDLINE, Embase, Scopus, Cochrane CENTRAL, CINAHL, PsycINFO and trial registries covering the period between January 1991 and September 2021. Studies were included if they evaluated a treatment in a minimum of three patients with EB. Two reviewers independently performed the study selection and data extraction. All identified outcomes and their respective instruments were mapped onto overarching outcome domains. The outcome domains were stratified according to subgroups of EB type, age group, intervention, decade and phase of clinical trial.

Results The included studies ($n=207$) covered a range of study designs and geographical settings. A total of 1280 outcomes were extracted verbatim and inductively mapped onto 80 outcome domains and 14 outcome areas. We found a steady increase in the number of published clinical trials and outcomes reported over the past 30 years. The included studies mainly focused on recessive dystrophic EB (43%). Wound healing was reported most frequently across all studies and referred to as a primary outcome in 31% of trials. Great heterogeneity of reported outcomes was observed within all stratified subgroups. Moreover, a diverse range of outcome measurement instruments ($n=200$) was identified.

Conclusions We show substantial heterogeneity in reported outcomes and outcome measurement instruments in EB clinical research over the past 30 years. This review is the first step towards harmonization of outcomes in EB, which is necessary to expedite the clinical translation of novel treatments for patients with EB.

What is already known about this topic?

- An increasing number of clinical trials are being conducted to evaluate novel treatment strategies that offer the potential to change the disease course and alleviate symptoms of epidermolysis bullosa (EB).
- The lack of comparability of outcomes complicates interpretation and is a major challenge in the field of evidence-based research and drug development in EB.

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What does this study add?

- This review is the first to scope, map and collate the reporting of outcomes and outcome measurement instruments in EB research over the past 30 years.
- We identified 1280 outcomes that were grouped into 80 different outcome domains and 14 overarching outcome areas.
- We reveal heterogeneously reported outcomes and outcome measurement instruments throughout the research landscape of EB and imply the benefit of a harmonized and consensus-based EB outcome assessment.

What are the clinical implications of this work?

- The findings of this scoping review will improve the quality of evidence and generation of meaningful and useful research data, as more uniformity in outcome assessment in the field of EB is warranted.
- The decision about which outcomes to measure and which outcome measurement instruments to use should take the characteristics of the respective EB subtype into consideration.
- Future studies should objectively and transparently evaluate whether the available outcome measurement instruments for EB are fit for purpose and whether additional instrument development is needed.

Epidermolysis bullosa (EB) comprises a group of rare genetic skin disorders characterized by skin fragility, resulting in blistering and wounds upon minimal trauma. EB is subdivided into the following four main types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB.¹ Depending on the type of EB and the gene affected, EB may be complicated by wound healing problems, pseudosyndactyly, aggressive squamous cell carcinomas, extracutaneous involvement and early mortality.^{1–3}

Although EB is a rare disease, with a prevalence of 1–25 per million population and an incidence of 2–54 per million live births,^{4–6} it has a considerable impact on the lives of affected individuals, their families and caregivers.^{7,8} As no curative therapies are available, treatment of EB is limited to skin and wound care, providing relief of symptoms such as itching and pain, in addition to treatment of extracutaneous manifestations.^{9–11}

In the last few decades, significant progress has been achieved in the understanding of the underlying pathomechanisms of EB. This has led to research into the repurposing of drugs and the development of novel targeted therapies, particularly disease-modifying therapies that aim at sustainable or even permanent restoration of the affected protein.^{12–15}

These putative therapies are being evaluated in a growing number of clinical trials to explore their efficacy and safety. However, clinical trials in EB face many challenges, including the rarity of the disease, the genotypic and phenotypic heterogeneity, the individual needs of patients with EB, the timely and adequate recruitment of eligible patients, and the knowledge gaps in understanding the natural disease course of EB.^{16,17}

The many challenges of conducting EB trials, in conjunction with the heterogeneity in measuring and reporting outcomes, make it difficult to combine and compare results across studies.^{18,19} These factors hinder adequate secondary analyses of the available research data, which are mandatory for well-informed clinical and regulatory decision making.^{20,21}

There is an urgent need for harmonization of outcome selection in EB by providing a framework that suggests the minimum set of outcomes that should be measured and reported in clinical trials, also referred to as a core outcome set (COS).^{20,22} To devise a COS, it is imperative to gain insight into previously reported outcomes and outcome measurement instruments in EB.

Therefore, the aim of this review is to provide an overview of the outcomes and outcome measurement instruments reported in EB clinical studies, which could lead to a COS for EB.

Materials and methods

Our review was based on an unpublished protocol and was reported following the Joanna Briggs Institute methodology for Scoping Reviews^{23,24} and the PRISMA Extension for Scoping Reviews guidelines.²⁵

Definitions

An ‘outcome’ is a construct that refers to the ‘what’ to measure. In the context of a clinical trial it can be defined as ‘what is being measured on trial participants to examine the effect of exposure to a health intervention’.²⁶ Examples include *reduction of pain* or *increased expression of collagen VII in the skin*. Similar outcomes can be grouped into ‘outcome domains’, and similar outcome domains result in overarching ‘outcome areas’.²⁷ An ‘outcome measurement instrument’ refers to ‘how’ a particular outcome is being measured, for example by a single question, a questionnaire or a score based on physical examination.²⁶

Information sources

The following databases were searched to identify potentially relevant published articles: MEDLINE, EMBASE,

Table 1 Eligibility criteria

	Inclusion	Exclusion
Participants	A diagnosis of inherited epidermolysis bullosa (EB), regardless of EB type, age, sex, ethnicity or severity A minimum of three patients are included	Other skin fragility disorders, EB acquisita or very rare EB syndromes, e.g. Carmi syndrome Mixed study cohorts with other disorders Animal studies
Concept	A minimum of one treatment outcome is reported	Studies focusing only on diagnostic, maternity/pregnancy and anaesthesia-related outcomes
Context	Any country or study setting English full text available	Studies published before January 1991 Studies published in languages other than English
Types of sources	Interventional studies including (randomized) controlled clinical trials, before and after studies and interrupted time series studies Observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies Case series and case reports	Qualitative studies, reviews, commentaries and conference abstracts

CINAHL, PsycINFO, Cochrane CENTRAL and Web of Science. In addition, five clinical trial registries including ClinicalTrials.gov were searched to find protocols of unpublished clinical trials. The reference lists of relevant studies were screened for additional studies. Further details of these search strategies can be found in Appendix S1 (see Supporting Information).

Search

The search strategies were developed with the assistance of an experienced information specialist (S.W.). The structure of the search was based on two main concepts: (i) EB and (ii) outcome, study design or treatment (Appendix S1). The search strategies were peer reviewed using the Peer Review of Electronic Search Strategies checklist.²⁸ The search period covered from January 1991 to September 2021, as the first consensus classification paper for EB was published in 1991.²⁹ Duplicates were removed following a structured deduplication method.³⁰

Selection of sources of evidence

Studies were eligible for inclusion if they met the criteria provided in Table 1. After a pilot phase to ensure compliance with the eligibility criteria, the screening of titles, abstracts and full-text reports was performed by two independent reviewers (E.W.H.K., V.W.) using Rayyan (Doha, Qatar).³¹ Disagreements were resolved through discussion with a third reviewer (M.C.B.).

Data charting process

Two independent reviewers (E.W.H.K., T.W.) performed the data extraction, using a prepiloted data extraction tool in Microsoft Excel (2018) (Microsoft, Redmond, WA, USA). One reviewer (E.W.H.K.) collated and harmonized all extracted data, which was checked by another reviewer (T.W.). Consensus on extraction was reached through discussion or by consulting a third reviewer (M.C.B.). Data items included details of the study, patient characteristics, interventions, outcomes and outcome measurement instruments. All reported outcomes were extracted verbatim.

Synthesis of results

Based on an inductive approach, outcomes that were similar in wording or conceptualization were grouped into outcome domains and outcome areas by one reviewer (E.W.H.K.) and discussed with members of the review team (T.W., J.K., M.C.B.). Composite outcomes suiting multiple domains were classified within each of these eligible domains. For every outcome domain and area, the percentage of included studies measuring that particular domain or area was calculated. All analyses were stratified according to EB type, age group, type of intervention, decade and phase of clinical trial.

To classify the interventions into relevant treatment groups, a classification system considering the treatment objective of different interventions was developed (Table 2). This led to the following four groups: (i) disease-modifying

Table 2 Classification of therapies by potential of the intervention

Disease-modifying therapies	
(i) Interventions that restore or reduce the affected protein or its function, reflected by molecular outcomes in their corresponding clinical study	(ii) Interventions that modify the epidermolysis bullosa (EB) disease course without an effect on the affected protein, reflected by the reported outcomes in their corresponding clinical study
(a) Targeted: direct effect on the affected protein	(a) Influencing epithelial durability and integrity
(b) Nontargeted: indirect effect on the affected protein	(b) Changing the progression of damage caused by EB
	(c) Reducing general or local inflammation caused by EB
	(d) Altering the progression of squamous cell carcinoma
Symptomatic therapies and complication management	
(iii) Interventions with a primary symptomatic purpose only	
(iv) Interventions that reverse complications resulting from EB without targeting the restoration of affected proteins	

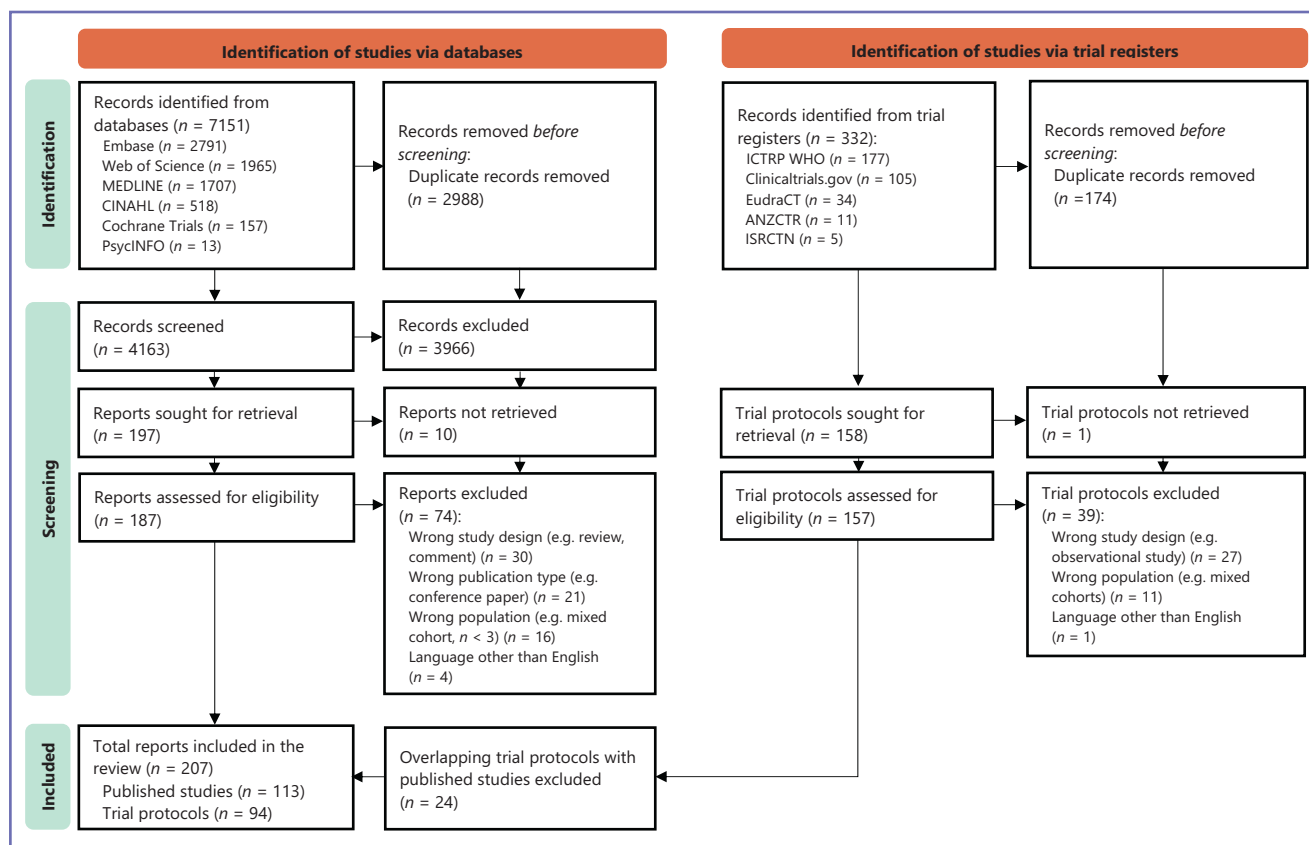


Figure 1 PRISMA flowchart showing the selection of sources of evidence in the review. ICRTP, International Clinical Trials Registry Platform; WHO, World Health Organization; ANZCTR, Australian New Zealand Clinical Trials Registry; ISRCTN, International Standard Randomized Controlled Trial Number.

interventions that have a (non)targeted effect on the affected protein; (ii) interventions that influence EB clinical outcomes without a(n) (in)direct effect; (iii) symptomatic interventions solely addressing pain or itching; and (iv) complication management, e.g. surgery.

Results

Study selection

After removing duplicates, 4163 published records and 158 clinical trial protocols records were identified. Based on title and abstract screening, 3966 (95.3%) publications were excluded. Full-text review was performed for 187 published reports and 157 clinical trial protocols, which resulted in 113 publications and 118 clinical trial protocols for data extraction (Figure 1). After data extraction, 24 clinical trial protocols were found to overlap with 25 published studies and were omitted from further analysis.

Finally, 207 studies were included in the review; 147 clinical trials (53 published clinical trials and 94 clinical trial protocols) and 60 cohort studies, case series and cross-sectional studies.

Study characteristics

The included studies ($n=207$) were mainly conducted in Europe (39.6%) and North America (29.5%). Recessive

Table 3 Characteristics of the included studies ($n=207$)

	N (%)
EB type	
EB simplex	21 (10.1)
Dystrophic EB ^a	32 (15.5)
Recessive dystrophic EB	89 (43.0)
Junctional EB	6 (2.9)
Kindler EB	–
Mixed cohort	59 (28.5)
Age group	
Adult	35 (16.9)
Paediatric	45 (21.7)
Any age	127 (61.4)
Geographical location	
Africa	3 (1.4)
Asia	28 (13.5)
Australia	6 (2.9)
Europe	82 (39.6)
Middle East	13 (6.3)
North America	61 (29.5)
South America	1 (0.5)
Multiple continents	8 (3.9)
Not specified	5 (2.4)

EB, epidermolysis bullosa. ^aNot further specified.

DEB (RDEB) was investigated in 43.0% of studies. Mixed cohorts of both children and adults were included in 61.4% of studies (Table 3).

We found an increase in published clinical trials ($n=53$), which corresponded with a vast increase in number of trial

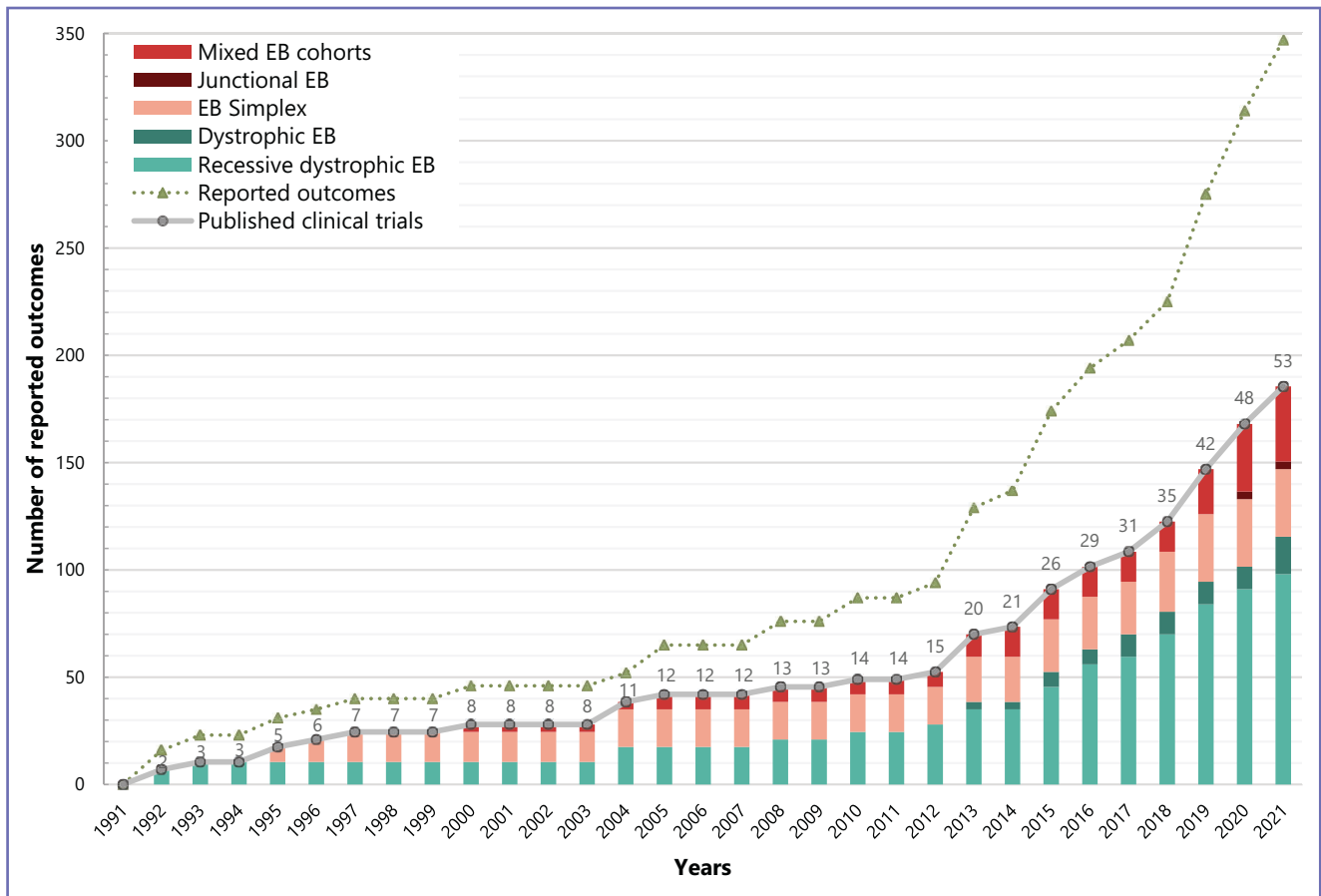


Figure 2 Reported outcomes in published clinical trials over time (1991–2021). EB, epidermolysis bullosa; JEB, junctional EB; EBS, EB simplex; DEB, dystrophic EB (not further defined); RDEB, recessive dystrophic EB.

outcomes reported over the past decade (Figure 2). Only 41.5% of the published trials defined a primary outcome. The registered trial protocol was referenced in 45.2% of the trials. Characteristics of the included trials can be found in Table S1 (see Supporting Information).

Treatment characteristics

Overall, 71% of all included studies ($n=207$) evaluated a locally administered intervention. A total of 143 studies focused on disease-modifying therapies and 17 studies focused on symptomatic therapy. Complication management by surgical intervention was performed in 35 studies. In the remaining 13 studies, miscellaneous interventions (e.g. iron supplementation or general dressings) were evaluated (Table S2; see Supporting Information).

Outcome domains

We extracted 1280 outcomes from all the included studies ($n=207$). These outcomes were grouped into 80 different outcome domains (Figure 3) based on overlapping outcome characteristics. We categorized similar outcome domains into 14 overarching outcome areas; cutaneous manifestations (69.6%) and safety (69.6%) were reported most frequently across all included studies (Table 4). Details of the remaining outcome areas and

their corresponding domains can be found in Table S3 (see Supporting Information).

The outcomes reported for distinct subtypes reflected their phenotypic appearance, e.g. wound healing in JEB (66.7%) and RDEB (41.6%), and reduction in blister formation in EBS (66.7%) (Table 4). The number of outcome domains investigated in the included studies was 21 for EBS, 45 for DEB, 71 for RDEB, 16 for JEB and 60 for mixed cohorts of patients (Table S4; see Supporting Information).

The outcome domains identified from paediatric-only studies ($n=45$) were mainly related to wound healing (33.3%), blister formation (24.4%), pain (26.7%), itching (15.6%) and developmental outcomes, e.g. weight and height status (20.0%). Adult-only studies ($n=35$) were comparatively more closely related to EB-specific quality of life (QoL) (25.7%) and molecular markers, e.g. protein expression (28.6%) and the presence of anchoring fibrils (20.0%) (Table S4; see Supporting Information).

Overall, 30.6% of all included clinical trials ($n=147$) reported primary outcomes related to wound healing. Secondary outcomes in clinical trials were more related to symptoms (pain 21.1%, itching 18.4%) and overall disease severity (15.6%) (Table S4). Later-phase clinical trials (\geq phase II) ($n=6$ studies) mostly reported wound healing (83.3%), and patient-reported outcomes such as pain and itching (both 50.0%). Nevertheless, heterogeneity was found in all clinical trial phases.

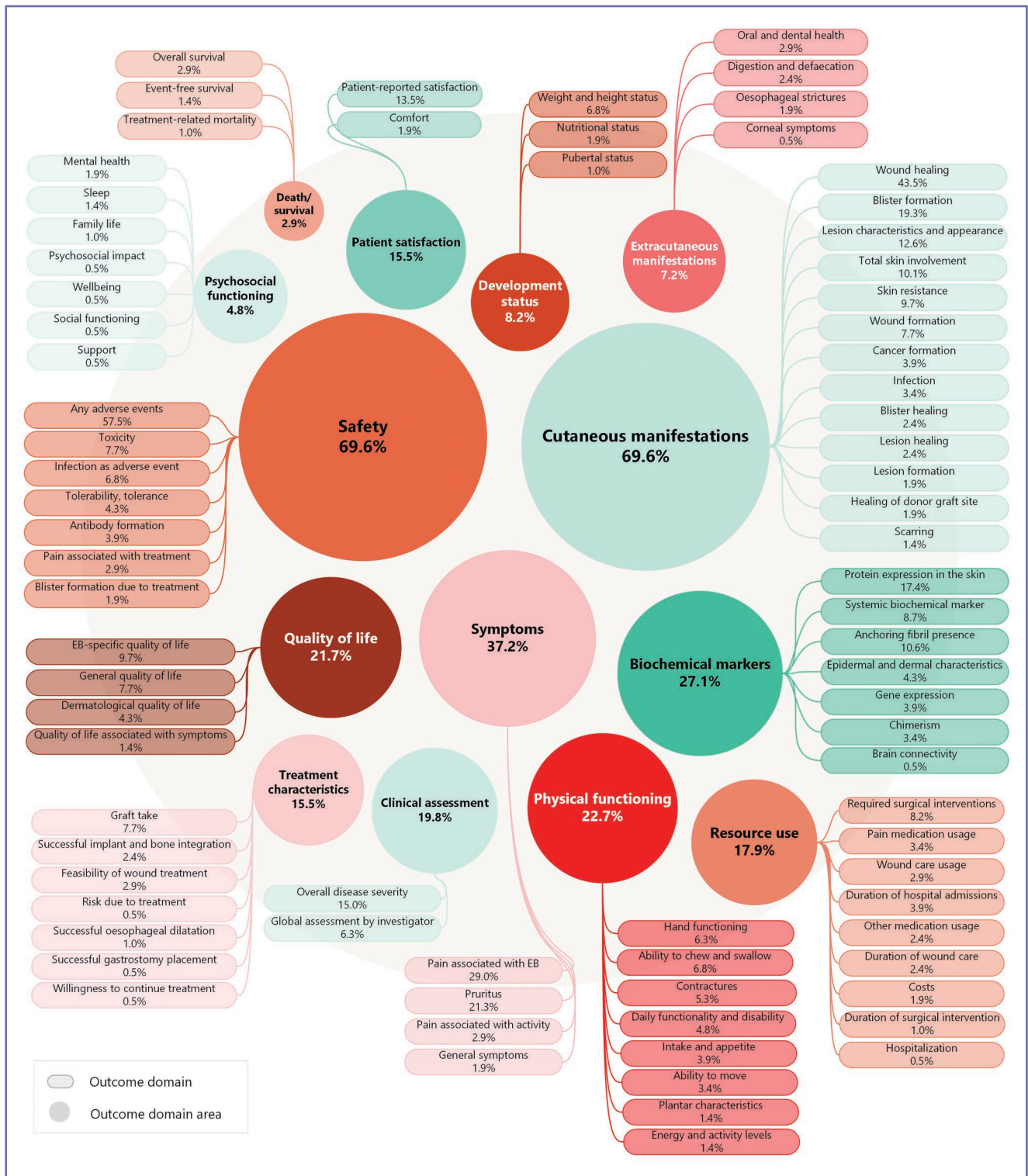


Figure 3 Outcome areas ($n=14$) and outcome domains ($n=80$) reported in the included studies ($n=207$) (percentage of studies measuring the area or domain). EB, epidermolysis bullosa.

Over time, the reported outcome domains of published studies ($n=113$) focused more on biochemical markers, such as protein expression (5.0% in 1991–2000 vs. 21.3% in 2011–2021), and patient-reported outcomes such as pain

(20.0% in 1991–2000 vs. 29.3% in 2011–2021) and itching (5.0% in 1991–2000 vs. 24.0% in 2011–2021) (Table S4).

Heterogeneity was also found among studies evaluating the same type of intervention. Targeted therapies were

Table 4 Outcome domains of cutaneous manifestations and safety in epidermolysis bullosa clinical research (1991–2021)

Outcome area	Outcome domain	Examples of outcomes	Total outcome reporting number	Number of studies reporting the domain					
				All studies (n = 207)	EBS (n = 21)	DEB (n = 32)	RDEB (n = 89)	JEB (n = 6)	Mixed/all (n = 59)
Cutaneous manifestations, N = 144 (69.6%)	Wound healing	Improvement in rate of wounds, complete healing of wounds, epithelialization rate	161	90 (43.5)	0 (0.0)	19 (59.4)	37 (41.6)	4 (66.7)	30 (50.8)
	Blister formation	Number of blisters, residual blistering, formation of bullae	50	40 (19.3)	14 (66.7)	5 (15.6)	14 (15.7)	0 (0.0)	7 (11.9)
	Lesion characteristics and appearance	Change in drainage, appearance of the wound, amount of exudate	31	26 (12.6)	0 (0.0)	4 (12.5)	16 (18.0)	0 (0.0)	6 (10.2)
	Total skin involvement	Body surface area involvement, percentage change from baseline in total area of blisters	24	21 (10.1)	1 (4.8)	3 (9.4)	10 (11.2)	0 (0.0)	7 (11.9)
	Skin resistance	Blister time for evaluation of skin fragility, suction blister time	24	20 (9.7)	2 (9.5)	1 (3.1)	13 (14.6)	1 (16.7)	3 (5.1)
	Wound formation	Erosion count, recurrence of wounds, time to erosion recurrence	19	16 (7.7)	0 (0.0)	3 (9.4)	9 (10.1)	1 (16.7)	3 (5.1)
	Contractures	Degree of recurrence, persistence of mild contractures, pseudosyndactyly progression	17	11 (5.3)	0 (0.0)	3 (9.4)	9 (10.1)	1 (16.7)	3 (5.1)
	Cancer formation	Squamous cell carcinoma formation, cancer growth, occurrence of neoplastic transformation	11	8 (3.9)	0 (0.0)	1 (3.1)	6 (6.7)	0 (0.0)	1 (1.7)
	Infection	Clinical improvement of skin infection, percentage of skin colonization, bacterial elimination in wounds	9	7 (3.4)	1 (4.8)	0 (0.0)	5 (5.6)	0 (0.0)	1 (1.7)
	Blister healing	Rate of healing of existing blisters, blister size	6	5 (2.4)	1 (4.8)	2 (6.3)	2 (2.2)	0 (0.0)	0 (0.0)
	Lesion healing	Healing time of lesions, clinical assessment of change in the treated area, lesion area	6	6 (2.9)	1 (4.8)	2 (6.3)	2 (2.2)	0 (0.0)	1 (1.7)
	Lesion formation	Recurrence of lesions, new ulceration	4	4 (1.9)	0 (0.0)	1 (3.1)	1 (1.1)	0 (0.0)	2 (3.4)
	Healing of donor graft site	Healing of blister graft donor sites	4	4 (1.9)	0 (0.0)	1 (3.1)	3 (3.4)	0 (0.0)	0 (0.0)
Scarring	Change in scar quality, evaluation and scoring of preoperative and postoperative hand scars	3	3 (1.4)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)	1 (1.7)	
Safety, N = 144 (69.6%)	Any adverse events	Clinical and laboratory parameters (haematology test, blood chemistry test, urinalysis), adverse events	146	119 (57.5)	10 (47.6)	17 (53.1)	58 (65.2)	6 (100.0)	28 (47.5)
	Toxicity	Peak plasma concentration, dose limiting toxicity, time to peak concentration	23	16 (7.7)	2 (9.5)	1 (3.1)	8 (9.0)	0 (0.0)	5 (8.5)
	Infection as adverse event	Number of infections, resistance to antibiotic treatment, infection of the fingers as complications	16	14 (6.8)	1 (4.8)	2 (6.3)	6 (6.7)	0 (0.0)	5 (8.5)
	Tolerability, tolerance	Patient-reported tolerability of treatment, global tolerance of treatment	11	9 (4.3)	3 (14.3)	1 (3.1)	3 (3.4)	0 (0.0)	2 (3.4)
	Antibody formation	Circulating collagen VII antibodies, T-cell responses to full-length type VII collagen	11	8 (3.9)	0 (0.0)	0 (0.0)	8 (9.0)	0 (0.0)	0 (0.0)
	Pain associated with treatment	Postoperative pain at donor site, burning and stinging upon application, pain during treatment	6	6 (2.9)	1 (4.8)	2 (6.3)	1 (1.1)	0 (0.0)	2 (3.4)
	Blister formation due to treatment	Intraoperative formation of bleeding bullae, oral mucosal ulcerations during treatment	4	4 (1.9)	0 (0.0)	0 (0.0)	4 (4.5)	0 (0.0)	0 (0.0)

EBS, epidermolysis bullosa simplex; DEB, dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa. The remaining outcome areas and domains, including examples of outcomes can be found in Table S3 (see Supporting Information). Data are presented as n (%).

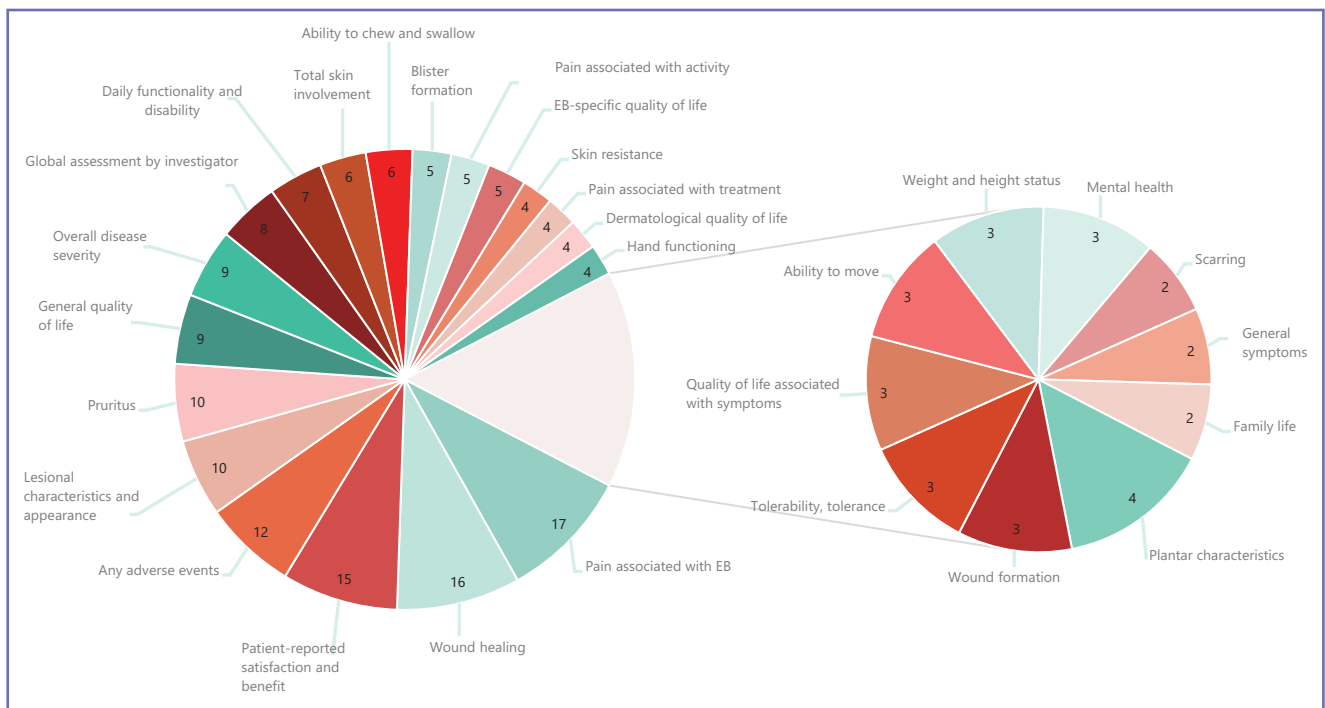


Figure 4 Number of different outcome measurement instruments applied per outcome domain in the included studies ($n=207$). Only outcome domains measured by more than one instrument are presented ($n=29$). Further details can be found in Table S5 (see [Supporting Information](#)). EB, epidermolysis bullosa.

mainly evaluated by molecular outcomes, e.g. expression and presence of proteins and anchoring fibrils (up to 47.4% for local interventions; 100% for systemic interventions). Complication management was mainly represented by outcomes that reflected the aim of surgery, e.g. hand functioning (69.2%) in hand surgery and developmental outcomes, e.g. growth status (100%) in gastrointestinal surgery (Table S4).

Outcome measurement instruments

A total of 200 different outcome measurement instruments, e.g. questionnaires, were used to measure the 80 outcome domains (Figure 4). Overall, 81% of the identified instruments were used only once in a single study. The visual analogue scale (VAS) was reported for the measurement of pain and itching in 31 and 19 studies, respectively (Table S5; see [Supporting Information](#)).

Overall, 21 different instruments were used to measure the outcome domains of the QoL area, of which the Quality of Life in EB (QOLEB) questionnaire was used in most studies ($n=16$). Disease severity was measured by nine different instruments, of which the EB Disease Activity and Scarring Index (EBDASI) was used most frequently ($n=16$), followed by the Instrument for Scoring Clinical Outcome of Research for EB (iscorEB) ($n=9$) and the Birmingham EB Severity Score (BEBSS) ($n=7$).

Discussion

In this review, we found striking heterogeneity in outcomes and outcome measurement instruments reported in EB

research over the past 30 years. From the 207 included studies, 1280 outcomes were extracted, inductively assigned to 80 outcome domains and summarized into 14 overarching outcome areas (Figure 3).

As EB encompasses a diverse group of skin fragility disorders with complex aetiologies and unique clinical phenotypes, a variety of outcomes was expected. Nevertheless, this review decisively shows that considerable heterogeneity exists even within studies of similar EB types, age groups, interventions and clinical trial phases. Furthermore, it is apparent that clinical trial development has progressed over the years and subsequently, the reporting of outcomes has evolved over time.

The lack of comparability of outcomes could lead to redundant research efforts by investigators and unnecessary burden for patients participating in clinical trials.³² Apart from the urgent need for evidence-based treatment options, this limited comparability is even more problematic for a rare disease such as EB, considering the sparse funding options and number of eligible trial participants.¹⁷ More homogeneous outcome assessment and reporting are essential to facilitate a better comparability of research data and allow for optimization of evidence-based medicine and therapy development.

The 80 different outcome domains identified in this review, represent the complexity of the disease course, phenotypic heterogeneity and clinical management of EB. When stratifying the outcome domains by EB type, a reporting pattern was noticeable regarding the respective prevailing symptomatology. Hence, wound healing was predominant in studies focusing on RDEB (41.6%) and JEB (66.7%), whereas blister formation was assessed mainly

within EBS (66.7%). Thus, the decision about which outcomes to measure should consider the characteristics of the respective EB type.

Although EBS represents the largest group within the EB population,⁵ the majority of included studies focused on RDEB. Given the disease severity of this subtype and the clear targets for treatment strategies such as gene therapy, there are good reasons why there is a focus on RDEB in current and upcoming clinical trials.^{12,33,34} However, the disease burden and medical need of patients with EBS might be overlooked.^{35,36} These patients may benefit from other types of studies investigating symptomatic and preventive interventions, with an appropriate choice of outcomes relevant for EBS.

Among the more severe EB types, wound healing is considered to be one of the most clinically meaningful outcomes from the perspective of patients and regulatory authorities.^{36–38} This was reflected by the frequent reporting of wound healing as an outcome domain and use as a primary outcome in the included studies. For an appropriate comparison of study results, similar and well-defined outcomes regarding wound healing are mandatory.

Based on regulatory guidance by the US Food and Drug Administration (FDA), wound healing can be defined as skin re-epithelialization without drainage or dressing requirements, confirmed at two consecutive trial visits at least 2 weeks apart.³⁸ However, unlike other chronic wound aetiologies, EB wounds have distinct healing characteristics and natural courses among EB subtypes, and even within individual patients.^{39,40} Such considerations mean that the FDA wound healing recommendations are not necessarily applicable to EB.⁴¹ These challenges in measuring wound healing, in combination with the importance of this outcome for patients, should impel the EB community to reach a consensus on how wound healing outcomes within clinical trials should be defined and measured.

The heterogeneity of reported outcomes is also reflected in the 200 different outcome measurement instruments reported, of which 81% were applied in only one study. When designing EB studies, it should be taken into consideration whether the instrument selected is appropriate for the specific study population. For instance, the use of an instrument to measure wound healing in patients with RDEB would not necessarily be appropriate for patients with EBS, as the underlying pathomechanisms and subsequent clinical presentations are different. When evaluating patients with EBS, the use of robust instruments for measuring blister formation is probably more relevant.

Of all the identified outcome measurement instruments, the VAS was the most frequently used to measure symptoms. Simple rating scales, such as the VAS, are extensively used and validated as unidimensional self-assessed scales.⁴² As pain in EB can be acute and chronic, and frequently involves multiple pain categories including nociceptive, nociplastic and neuropathic pain,⁴³ the pain treatment outcomes should be defined according to the suspected pathoaetiology. Hence, investigating the pain intensity using only a VAS may not adequately measure the reduction of EB-specific pain qualities and warrants the development and harmonized use of EB-specific validated pain instruments.

Several EB-specific measurement instruments (e.g. EBDASI, IscorEB, BEBSS) were frequently used to assess treatment efficacy. However, the frequent use of an

instrument in previous research does not necessarily mean that it is appropriate for the measurement of treatment efficacy in every study setting. It is important to take into consideration that these instruments attempt to combine symptoms and complications of EB, so that any change in the overall outcome is often not representative of the respective treatment intention. In addition to the measurement of treatment efficacy, EB-specific disease severity measurement instruments may serve as instruments to stratify patients according to severity prior to an intervention.

In order to choose appropriate instruments in the context of individual pathomechanistic treatment principles and goals, in addition to considering the linguistic and cultural differences in populations of patients with EB, further studies should objectively and transparently evaluate whether the currently available measurement instruments for EB are fit for purpose. The COSMIN checklist⁴⁴ can be used to evaluate the quality of the measurement properties of selected instruments, and to identify any gaps that could help to direct future instrument development.⁴⁵

The wide range of different interventions evaluated in the included studies reflect the multidimensional management of EB. Subsequently, many intervention-specific outcome domains were identified through this review, including clinical outcomes specific for local interventions (e.g. graft take), molecular outcomes for targeted interventions (e.g. collagen VII expression), and surgery-related outcomes in complication management (e.g. duration of intervention). As the consideration of study outcomes is largely dependent on the type of intervention, the stratified overview of previously reported outcome domains could serve as a resource for investigators designing future studies (Table S4).

Additionally, investigators should be aware that involvement of the regulatory authorities and patient advocacy groups is essential to ensure meaningful, relevant and appropriate outcome assessment, thereby increasing the chance of drug approval.⁴⁶ The consultation of these pivotal stakeholders can aid in addressing the needs of patients with EB, particularly with regard to clinical relevance and importance, minimally expected clinical effect, and implementation of patient-reported outcome measures according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.^{47,48}

The main strength of our review is its rigorous and systematic approach, which provides a comprehensive overview of the current state of outcome reporting in EB clinical research. All steps of the review process were carried out by two independent reviewers using piloted templates, thereby limiting selection bias and data extraction errors. In addition, the review incorporated a diverse range of perspectives on relevant outcomes by including sources with a variety of study designs and geographical settings.

However, this review has some limitations. Firstly, owing to feasibility reasons, our review only included reports from the past 30 years, which means that outcomes and outcome measurement instruments reported before that time were not included. In addition, reports written in languages other than English were excluded, but it is unlikely that including these reports would have changed the results. Moreover, as a result of our extensive search strategies that covered both major biomedical databases and trial registries, we have included a large number of studies and

are convinced that data saturation regarding outcomes has been reached. Secondly, the data extraction for this review was limited by a lack of precise and consistent reporting in both published studies and trial protocols. This emphasizes the importance of adhering to a more uniform and transparent reporting of outcomes in individual studies, which will improve future evidence synthesis.

In light of the findings of this review, the increasing number of clinical trials and upcoming novel targeted treatment strategies, a COS focusing on the 'what' and 'how' to measure, and collective identification of any gaps therein is warranted. To this end, EB researchers of the University Medical Centres of Groningen (the Netherlands), Salzburg (Austria) and Freiburg (Germany) have initiated a project to develop a COS for EB. This will involve harmonization of outcomes by defining core outcome domains and outcome measurement instruments as part of a consensus process with global engagement of stakeholders involved in EB research and management, including patients and their caregivers, medical experts, industry representatives and regulators.

In this review, we show the heterogeneity of outcomes in EB research over the past 30 years. Moreover, we demonstrate the urgency of continued development of appropriate outcome measurement instruments. To improve the quality of evidence and generation of meaningful and useful research data, harmonization of outcomes in a joint effort by all stakeholders in the field of EB is desperately needed. This review serves as the first big step towards greater uniformity in EB research.

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Conflicts of interest

E.W.H.K., T.W., S.W., P.C.v.d.A., B.H., A.M.G.P. and M.L. declare that they have no conflicts of interest regarding the scope of this work. J.K. is a member of the Board of Directors of the CHORD COUSIN Collaboration. D.K. has served as a consultant for Amryt Pharma, Fibrx Inc and Rheacell GmbH and is cofounder of Crowd Pharma. V.W. acts as consultant for Diaderm GmbH and TWi Biotechnology and holds shares of Diaderm GmbH, a company with an interest in drug development for EB. M.C.B. has served on the advisory boards of Amryt Pharma and Krystal Biotech Inc.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

Ethical approval was not required for this scoping review.

Supporting Information

Additional [Supporting Information](#) may be found in the online version of this article at the publisher's website.

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