

Orthodontic trial outcomes: plentiful, inconsistent and in need of uniformity? A scoping review

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Abstract

Introduction: The selection of appropriate outcomes that matter both to patients and operators is increasingly appreciated with core outcome sets in clinical trials gaining in popularity. The first step in core outcome set development is the generation of a list of possible important outcomes based on a scoping literature review. Moreover, outcome heterogeneity is known to detract from the findings of systematic reviews and meta-analyses. The aim of this study was to identify the range of outcome domains and specific outcome measures in contemporary orthodontic research.

Methods: Multiple electronic databases were searched from December 31st 2012 to December 31st 2016 to identify clinical trials of orthodontic interventions, with no language restrictions. Abstracts, eligible full-texts and reference lists were screened and all reported primary and non-primary outcomes and methods of measurement were recorded.

Results: The search identified 1267 abstracts, of which 189 full-text articles were retrieved and 164 studies were included in the analysis. A total of 54 outcomes were identified and categorised into 14 outcome domains. The most frequently measured outcomes were patient-reported pain; periodontal health; tooth angulation/inclination changes; treatment duration; followed by rate of tooth movement; and skeletal changes. Outcomes were assessed following the overall course of treatment in just 14 studies.

Conclusions: Patient perspectives are increasingly being accounted for in orthodontic trials; however, there is little consistency in outcome selection amongst them. The identified list of outcomes will be used to inform a ranking exercise with service users and providers to establish an agreed core outcome set for future orthodontic clinical trials.

No highlights included.

Highlights

We aimed to identify the range of outcome domains and measures in orthodontic research

We identified 54 outcomes and categorized them into 14 domains

Pain, periodontal health, tooth angulation/inclination, treatment duration were most common

Outcomes were assessed after the overall course of treatment in just 14 studies.

Identified outcomes will help establish core outcome set for future clinical trials

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Introduction

Outcomes from clinical trials may be used to assess the relative merits and demerits of an intervention¹. These outcomes are measured by utilising tools to determine changes in the health state of a patient resulting from a healthcare intervention. These may be applied to a variety of contexts from measuring outcomes relating to physiological change, disease status and delivery of care, to symptoms or self-perceptions. Outcomes and outcome measures should be clearly defined and relevant to key stakeholders, including consumers and providers of care alike, if they are to have meaning and relevance²⁻⁵. When one or more outcomes are used to reflect changes within a broader concept, which may not be directly measurable itself, the latter is known as an outcome domain⁶. A variety of different outcomes can thus be grouped together under the same umbrella outcome domain. For instance, in an orthodontic study evaluating the duration of treatment or the number of different archwires used to reach a desired state, both these outcomes might be

categorized to the same overall outcome domain of cost-effectiveness or healthcare utilisation.

There is a wealth of evidence that outcome heterogeneity is pervasive across the fields of healthcare research⁷⁻⁹. In orthodontic research, a frequent conclusion of systematic reviews is lack of quality evidence; inability to synthesise disparate studies; and need for further research. This inability to perform meaningful syntheses is one of a number of issues relating to the use of inconsistent outcomes (termed 'outcome heterogeneity') within clinical research studies. This outcome heterogeneity was, for example, exemplified in a Cochrane review evaluating orthodontic interventions to distalize maxillary first molars, where differences in outcomes and incomplete reporting of data precluded meta-analysis of the four included studies assessing the effectiveness of a distalizing appliance compared to an untreated control¹⁰.

Similar problems may be encountered in studies evaluating orthodontic treatment outcomes and occlusal stability. Numerous indices exist, each measuring slightly different outcomes thus making comparisons between trials difficult. For example, the Index of Complexity Outcome and Need¹¹ may be used to assess final occlusion, while the Peer Assessment Rating¹², American Board of Orthodontics system¹³ or even a simple irregularity index¹⁴, which assesses alignment of the anterior mandibular segment may be applied in the evaluation of treatment outcome and stability. The correlation between such indices is varied^{15,16} and the heterogeneity in measured outcomes renders comparisons problematic. This inconsistency amongst orthodontic studies considering effectiveness of interventions may render evidence synthesis and meta-analysis impossible and, consequently, hinders interpretation of their results. This was evident in an analysis of 157 orthodontic systematic reviews in five leading orthodontic journals and the Cochrane Database, with meta-analysis present in only 43 of the reviews (27.4%) and a median of only four trials per meta-analysis¹⁷. Similarly, in a recently published systematic review assessing oral health related quality of life (OHRQoL) following orthodontic treatment, only 3 studies out of a potential 13 were included in their meta-analysis, as the OHRQoL outcome measure used in these studies was the Child Perception Questionnaire 11-14, while the remaining studies used

alternatives including the Oral Health Impact Profile-14 or the Oral Impacts on Daily Performance instrument¹⁸.

In order therefore to improve data synthesis and reduce outcome heterogeneity and reporting bias, agreement is needed concerning the outcomes to collect and how to measure them. This will be achieved through the establishment of a core outcome set (COS) that will need to be measured as a minimum in all clinical trials for a specific condition⁴. COS development is now established and supported through the Core Outcome Measures in Effectiveness Trials (COMET) initiative¹⁹ with successful development of outcomes sets within childhood asthma and otitis media, for example^{20,21}.

An initial stage of COS development is to perform a scoping systematic review to ascertain the nature of outcomes within a specific research area^{9,22,23}. This list is typically complemented by data obtained from patients and other stakeholders before being refined in a subsequent consensus process, leading to the development of an orthodontic core outcome set. The aim of this scoping review is therefore to update a previous scoping review in relation to orthodontic outcome domains²⁴ but also to identify both outcome domains and specific measures employed in contemporary orthodontic research.

Materials and Methods

The protocol for the overall study of COS development has been registered on the COMET website and has been published²⁵. A scoping review of recently published orthodontic clinical trials was carried out and a previous review²⁴ was updated.

Eligibility criteria

The following inclusion criteria were used in this scoping review:

Study design: Randomized Controlled Trials (RCTs) and Controlled Clinical Trials (CCTs). All parallel-group trials, including those of cross-over or cluster design, were considered eligible for inclusion.

Participants (P): Children and young people undergoing orthodontic treatment, with no age restrictions.

Interventions (I): Any orthodontic treatment intervention was to be included.

Control (C): Any comparison group was to be included with no restrictions placed on control groups.

Outcomes (O): All reported outcomes (primary and secondary) were identified with separate demarcation of primary and secondary outcomes and related measurement tools.

Exclusion: Retrospective studies and laboratory-only studies were excluded. Studies involving solely adult patients or patients undergoing orthognathic surgery; patients with cleft lip and/or palate; obstructive sleep apnoea; syndromic conditions or medical history complications were excluded.

Search strategy for identification of studies

The following electronic databases were searched: MEDLINE via Ovid, EMBASE via Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO, psycINFO via EBSCO and the Cochrane Central Register of Controlled Trials (CENTRAL), via the Cochrane Library (Appendix 1) to identify relevant studies from December 31st 2012 to December 31st 2016. No language restrictions were applied and attempts were made to translate any non-English studies identified. In addition, the reference lists and trials identified in recently published Cochrane systematic reviews were cross-checked to ensure that no relevant studies were omitted.

Data extraction

The abstracts of all studies identified were assessed by one reviewer (XX) with a range of expertise including orthodontics, patient-reported outcome measures and trial design. Full-text reports of studies which met the inclusion criteria and for which there was insufficient information in the title and/or abstract to make a clear decision were obtained. A second reviewer (XXX) helped to resolve any uncertainty regarding final inclusion until a consensus was reached.

All primary and any secondary outcomes were identified and recorded together with the specific outcome measures or tools used to measure each outcome based on the data

presented. Where delineation of primary or secondary outcomes was unclear, the primary outcome was inferred from the aim of the study, the sample size calculation, or from the first reported outcome in the results section. Any subsequent outcomes reported in the results were also identified and recorded as secondary outcomes. Where uncertainty persisted in relation to delineation of primary or secondary outcomes, all were recorded as primary outcomes and a note was made in the pre-piloted data extraction sheet.

The specific stage of treatment during which the trial was conducted was also recorded. Finally, all identified outcomes were grouped under broader outcome domains. The outcome domains were developed iteratively following inspection of the results and refined by two reviewers (AT and PSF) until consensus was reached.

Results

Study selection and characteristics

One thousand, two hundred and sixty-seven papers were identified through electronic searching and cross-referencing of sources. Following removal of duplicate records, 675 abstracts were screened, of which 189 full texts were assessed for eligibility. Of those, 164 met the inclusion criteria and were included in the review (Figure 1). Publications derived from the same trial but involving different outcomes or follow-up periods were considered as separate studies. The characteristics of all included trials and the outcomes they measured are shown in Appendix 2.

A significant proportion (n=59, 36%) of trials related to the initial stages of treatment e.g. investigating the rate of initial orthodontic alignment or pain experience following separator or fixed appliance placement. Twenty-four studies (n=15%) investigated the effects of different brackets or archwires during initial and mid-stages of treatment (i.e. typically alignment and levelling occurring in the first 6-9 months of treatment or until passive engagement of working archwires), with just 14 (8.5%) studies encompassing active treatment in its entirety (Table 1). Treatment stage was unclear in nine (5%) studies.

Results from analysis of individual studies

Overall, 54 outcomes were identified from the 164 included trials. These were subsequently grouped into relevant outcome domains (Table 2) with the frequency of their use as primary and/or secondary outcomes also calculated (Table 3). The most frequently reported primary outcome was pain (n=26, 16%), followed by rate of tooth movement (n=19, 12%) and skeletal relationship (n=17, 10%). Treatment duration was the most frequently reported secondary outcome (n=18, 11%), followed by tooth angulation and inclination changes (n=12, 7%), and periodontal condition (n=9, 5%). When both primary and secondary outcomes were combined, pain was still the most frequently reported outcome (n=30, 18%), followed by periodontal health (n=25, 15%) and tooth angulation/inclination (n=23, 14%; Figure 2).

The specific outcome measures and tools used to assess the outcomes are shown in Table 4. Twenty-six (48%) of the 54 identified outcomes were assessed using two or more different measurement tools. The heterogeneity in measuring outcomes is exemplified in the measures of eruptive changes, where some studies used cone beam computed tomography (CBCT) radiographs, while others used dental panoramic (DPT) or DPT and upper standard occlusal (USO) radiographs and others used study casts or clinical findings. The same is true for the outcomes of enamel demineralisation, speech assessment, tooth movement, pain, appliance usage/compliance, periodontal health, archform changes, tooth angulation /inclination and treatment duration with numerous outcome measurement tools applied for each of these.

Discussion

Summary of evidence

A large number of outcomes were assessed within these clinical trials with little consistency being observed. This outcome heterogeneity was compounded by the use of an array of disparate measurement tools. In addition, in keeping with a previous review over a 5-year period, outcomes appear to remain centered on the assessment of morphological changes with patient-centered outcomes remaining under-represented²⁴. **It is disappointing that quality of life and the impact of malocclusion or treatment are not assessed more often in studies, although this mirrors previous research^{22,24,26}. Patients perceive health outcomes and health states in terms of their overall impact on their lives and experiences and often**

have different perspectives about a condition to clinicians, who may not realise that certain outcomes are important to patients²⁷⁻²⁹.

The continued emphasis on clinician-centered outcomes mirrors the findings within dental research more widely⁵. The latter scoping review of 220 dental RCTs revealed that 34% of the 409 identified outcomes were patient-centered, 44% were clinician-derived and the remaining 22% had a combined patient and clinician focus⁵. However, patient-centered outcomes were more frequently employed in the trials in the present review than determined previously; much of this related to pain experience. It is perhaps surprising that pain was the most frequently measured outcome in the included trials, although this is important to measure particularly when comparing new or more invasive procedures. It is arguably, however, a relatively straightforward outcome to measure, usually involving a simple visual analogue scale, allowing ample comparative data to be collected over a short period of time, **without the need for numerous, expensive resources**. ~~Clinical trials measuring pain as an outcome can therefore be conducted without the need for numerous, expensive resources and similarly they can be completed within a short timeframe.~~ This could also explain why most studies in the review chose pain perception as the sole primary outcome. Nevertheless, there was disparity in the selection of measurement tools to assess pain among the included studies (Table 4). It is, however, not possible to predict whether this outcome will ultimately be part of the COS. Previous research on COS development of key health outcomes for children and young people with neurodisability suggested that the latter tend to view outcomes as complex, inter-related constructs that are not independent of each other³⁰. Pain and other similar low-level outcomes, are therefore seen as facilitators (or inhibitors) that contribute to the achievement of higher level outcomes, such as emotional well-being, although achievement of such health states is not dependent on fulfilment of all lower-level outcomes³⁰. As such, it would be intuitive to expect that pain experience may be viewed as a transient feature of treatment itself and that other features are given greater gravitas in respect of orthodontic treatment outcomes.

The inconsistency in relation to outcome domains and measures brings the need for an orthodontic core outcome set into sharp focus. Moreover, it appears that considerable work will be required following COS development to refine the identified outcomes, to ensure

that unified measures can be used in clinical trials in the future²⁴. Such work can be facilitated through the use of the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist, which provides standards for evaluating the methodological quality of studies on the measurement properties of health measurement instruments³¹. In an initiative analogous to the development of CONSORT and PRISMA to overcome issues pertaining to reporting, COSMIN was developed to improve the selection of health measurement instruments. A recent study by Gilchrist et al³² evaluated commonly used OHRQoL outcome measures and provided recommendations for refinements, with, ~~for~~ ~~example,~~ better responsiveness of instruments to longitudinal change being recommended, and advice for researchers in order to select the most appropriate measure in future projects.

While the breadth of outcomes identified in the present review reflects unwanted inconsistency among orthodontic clinical trials, it is actually helpful in terms of COS development. ~~The aim of the initial stages of development is to undertake a wide and sensitive search of orthodontic research to identify all possible outcomes.~~ Ultimately, the **outcomes identified** will be complemented by patient data and will then be refined within the final outcome set. This process will be facilitated by the conversion of these outcomes into patient-friendly language. Moreover, the number of outcomes identified within this scoping review is not prohibitive. In a previous COS development project concerning otitis media with effusion in children with cleft lip/palate, the number of outcomes taken to each of the three Delphi rounds for ranking were 45, 47 and 49, respectively³³.

Limitations

Although scoping reviews aim to be as holistic as possible, it was decided not to include observational-type studies in this review and not to perform a search of unpublished or grey literature. Arguably, inclusion of such studies may have been beneficial, as patient reported outcomes are often incorporated in cohort studies, for example. However, it was felt that any patient-important outcome would also emerge from the qualitative research involving patients as part of COS development. Additionally, as the COS is directed at standardizing outcome measures in clinical trials, it was felt that including clinical trials only would be the most suitable approach. Moreover, in the present review the eligibility criteria were

broadened to include controlled clinical trials rather than randomized trials, in isolation. This may explain why the number of studies included were greater in this review (n=164) conducted over a four-year period, than in a related previous study covering a 5-year period in which 133 RCTs were included²⁴.

Conclusions

Outcome heterogeneity in contemporaneous orthodontic trials is problematic, likely complicating attempts to combine their results due to the diversity in the selection of outcomes and outcome measurement tools. Development and subsequent adoption of a core outcome set in future trials will help overcome these issues, while ensuring that future research is patient-centered.

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FIGURE LEGENDS

Figure 1. PRISMA flowchart

Figure 2. Most frequently reported primary (blue) and secondary (orange) outcomes in orthodontic clinical trials over a 4-year period (n=164)

TABLE CAPTIONS

Table 1. Number of trials according to treatment stage

Table 2. Outcome measures (n=54) grouped in outcome domains (n=14) with numbers of unique studies assessing domain

Table 3. Number of studies reporting outcome as primary or secondary with most frequently reported outcomes highlighted

Table 4. Tools used to measure outcomes within the clinical trials (n=164)

Table 1. Number of trials (n=164) according to treatment stage

Treatment Stage	Number of Studies (n=164)
Initial (initial days or weeks of treatment)	59
Initial-mid / Mid (alignment and levelling up to placement of working archwires)	24
Interceptive	21
Post-debond / Retention	20
Final (space closure and finishing)	17
Whole treatment	14
Unknown	9

Table 2. Outcome measures (n=54) grouped in outcome domains (n=14) with numbers of unique studies assessing domain

Harms (n=60)	Function (n=2)	Hard tissues/skeletal (n=25)	Soft tissues (n=14)	Occlusal / alignment change (n=38)	Dental development and morphology (n=5)	Periodontal (n=25)	Microbiological /Physiological (n=18)	Knowledge and satisfaction (n=5)	QoL (n=4)	Compliance (n=13)	Appliance Integrity (n=18)	Efficiency/Cost-effectiveness (n=39)	Other (n=5)
Pain (n=30)	Speech (n=1)	Skeletal relationship (n=20)	Soft tissue profile changes (n=13)	Tooth angulation / inclination (n=23)	Eruptive changes (n=6): Eruption/non-eruption (n=3); Improvement in position (n=3)	Periodontal health (n=25)	Microbial composition / count (n=13)	Satisfaction (n=2)	Anxiety (n=3)	Appliance breakages (n=2)	Fixed appliance attachment and bond failure / strength (n=9)	Treatment duration (n=22): overall treatment time (n=4); functional/ interceptive (n=8); chairside duration (n=4); initial alignment (n=3); space closure (n=1)	Personality traits (n=3)
Enamel demineralisation (n=13)	Mandibular excursions (n=1)	Bone levels (n=2)	Gingival margin aesthetics (n=1)	Arch dimensions / changes (n=13)	Enamel reduction (n=1)		Inflammatory markers / response (n=4)	Information comprehension / recall (n=2)	Self-esteem (n=1)	Oral hygiene incl. toothbrushing duration and fluoride consumption (n=6)	Fracture of functional appliance (n=2)	Rate of tooth movement (n=20): space closure (n=13); initial alignment (n=6); overall treatment (n=1)	Orthognathic treatment need (n=1)
Patient reported adverse effects (n=5)		Bone density (n=1)		Alignment relapse (n=2)			Plaque and/or salivary pH (n=3)	Acceptability (of appliance) (n=1)	Malocclusion impact (n=1)	Duration of removable appliance wear/day (n=5)	Miniscrew force / stability (n=2)	Treatment success (n=3)	Airway volume (n=1)

Table 3. Number of studies reporting outcome as primary or secondary with most frequently reported outcomes highlighted

	Primary Outcome (number of studies)	Secondary Outcome (number of studies)
Adhesive retention	0	4
Airway volume	0	1
Alignment relapse	2	0
Anxiety	1	2
Appliance (miniscrew) stability	2	0
Appliance breakages	0	4
Appliance usage / compliance	1	4
Archform changes	12	1
Archwire Coating	1	0
Archwire Strength	0	1
Attendance	0	1
Bond failure	8	2
Bone density	0	1
Bone levels	0	2
Caries	0	3
Condylar changes	1	0
Direct (appliance/material) and indirect (societal) costs	1	1
Enamel demineralisation	9	4
Enamel reduction	0	1
Enamel roughness	1	0
Eruptive changes	5	2
Gingival irritation	0	1
Gingival margin aesthetics	1	0
Halitosis	1	1
Inflammatory response	2	2
Information comprehension	2	1
Malocclusion impact	0	1
Mandibular excursion	1	0
Microbial composition / count	6	7
Mobility/failure (of TAD)	0	1
Mucosal ulceration	1	0
Occlusal outcome	1	2
Oral hygiene compliance	4	2
Orthognathic treatment need	0	1

Other periodontal adverse effects	0	1
Pain	26	4
Patient acceptability	1	0
Patient reported adverse effects	1	4
Patient satisfaction	0	2
Periodontal health/ condition	16	9
Personality traits	1	2
pH - plaque/ saliva	2	1
Root contact	0	1
Root resorption	2	3
Salivary metal ions	2	0
Self-esteem	0	1
Skeletal relationship	17	3
Soft tissue Changes	10	3
Speech assessment	1	0
Suture anatomy	1	0
Tooth angulation / inclination	11	12
Tooth movement rate	19	1
Treatment (stage) duration	4	18
Treatment success	0	1

Table 4. Tools used to measure outcomes within the clinical trials (n=164)

	Outcome measurement tool	Number of studies using tool
Adhesive retention	Clinical examination (adhesive remnant index)	3
	Electron microscopy (adhesive remnant index)	1
Airway volume	Acoustic rhinometry	1
Alignment relapse	Study casts (Little's index)	2
Anxiety	Spielberger State-Trait Anxiety Inventory for Children (STAIC)	2
	Visual analogue scale	1
Appliance (miniscrew) fracture	Clinical findings	1
Appliance (miniscrew) stability	Insertion and removal torque via torque tester	1
	Insertion torque and periotest for mobility	1
Appliance breakages / fractures	Clinical findings	4
Appliance usage / compliance	Chart / logbook of wear	2
	Timers and patient charts	1
	Timers	1
	Questionnaire	1
Archform changes	Study casts	10
	CBCT scans	2
	Clinical findings	1
Archwire Coating	Differential scanning calorimetry	1
Archwire Strength	3 point bend test	1
Attendance	Notes review	1
Bond failure	Clinical findings	9
	Laboratory testing	1
Bone density	CBCT scans	1
Bone levels	Periapical radiographs	2
Caries	DMFS scores	2
	ICDAS scores and DMFS scores	1
Condylar changes	CBCT scans	1
Direct (appliance / material) and indirect (societal) costs	Cost minimisation analysis	2
Enamel demineralisation	Clinical findings	4
	Laser fluorescence	3

	Quantitative light-induced fluorescence	3
	Intraoral photographs	3
Enamel reduction	Study casts	1
Enamel roughness	Scanning electron microscopy of study casts	1
Eruptive changes	Clinical examination	2
	DPT radiographs	1
	DPT + USO radiographs	1
	CBCT scans	1
	Study casts	1
	Unknown	1
Gingival irritation	Clinical findings	1
Gingival margin aesthetics	Questionnaire with VAS	1
Halitosis	Halimeter	1
	Halimeter and tongue coating index	1
Inflammatory response	GCF samples	4
Information comprehension	Questionnaire	2
	Face to face interviews	1
Malocclusion impact	Oral Aesthetic Subjective Impact Score (OASIS)	1
Mandibular excursion	3D Kinesiograph computer system	1
Microbial composition / count	Plaque samples	6
	Salivary samples	5
	Plaque and salivary samples	1
	Elastomeric modules testing	1
Mucosal ulceration	Clinical findings and photographs	1
Occlusal outcome	PAR scores	3
Oral hygiene compliance	Plaque index and gingival index	3
	Diary / logbook inspection	2
	Plaque index and wear on toothbrush	1
Orthognathic treatment need	Expert panel consensus using records	1
Other periodontal adverse effects	Periapical radiographs	1
Pain	Visual analogue scale	25
	Numeric / categorical scale	2
	Multichannel continuous electron-cephalogram signals	1
	Patient reported questionnaire	1
	Unknown	1
Patient acceptability	Questionnaire	1
Patient reported adverse effects	Verbal reports	3
	Questionnaire	2

Patient satisfaction	Patient reported questionnaire	1
	Unknown	1
Periodontal health/ condition	Plaque index	19
	Gingival index	15
	Bleeding on probing	15
	Pocket depth	8
	Clinical attachment level	3
	Periapical radiographs	1
Personality traits	Spielberger State-Trait Anxiety Inventory for Children (STAIC)	2
	Eysenck personality questionnaire	1
pH - plaque/ saliva	Plaque and salivary samples	1
	Plaque samples	1
	Salivary samples	1
Root contact	CBCT scans	1
Root resorption	CBCT scans	3
	Periapical radiographs	2
Salivary metal ions	Salivary samples	2
Self-esteem	Piers Harris questionnaire	1
Skeletal relationship	Lateral cephalograms	19
	CBCT scans	1
Soft tissue Changes	Lateral cephalograms	12
	Optical laser scans	1
Speech assessment	Speech therapists panel	1
	Software spectrographic evaluation	1
	Laypersons panel	1
Suture anatomy	CBCT scans and radiologists level classification	1
Tooth angulation / inclination	Lateral cephalograms	21
	Study casts	1
	CBCT scans	1
Tooth movement rate	Study casts	15
	Lateral cephalograms	2
	Clinical findings using digital calipers	2
	CBCT scans	1
Treatment (stage) duration	Notes review	8
	Clinical findings	7
	Chronometer / timer	4
	Study casts	3
Treatment success	Clinical findings	1

Figure 1
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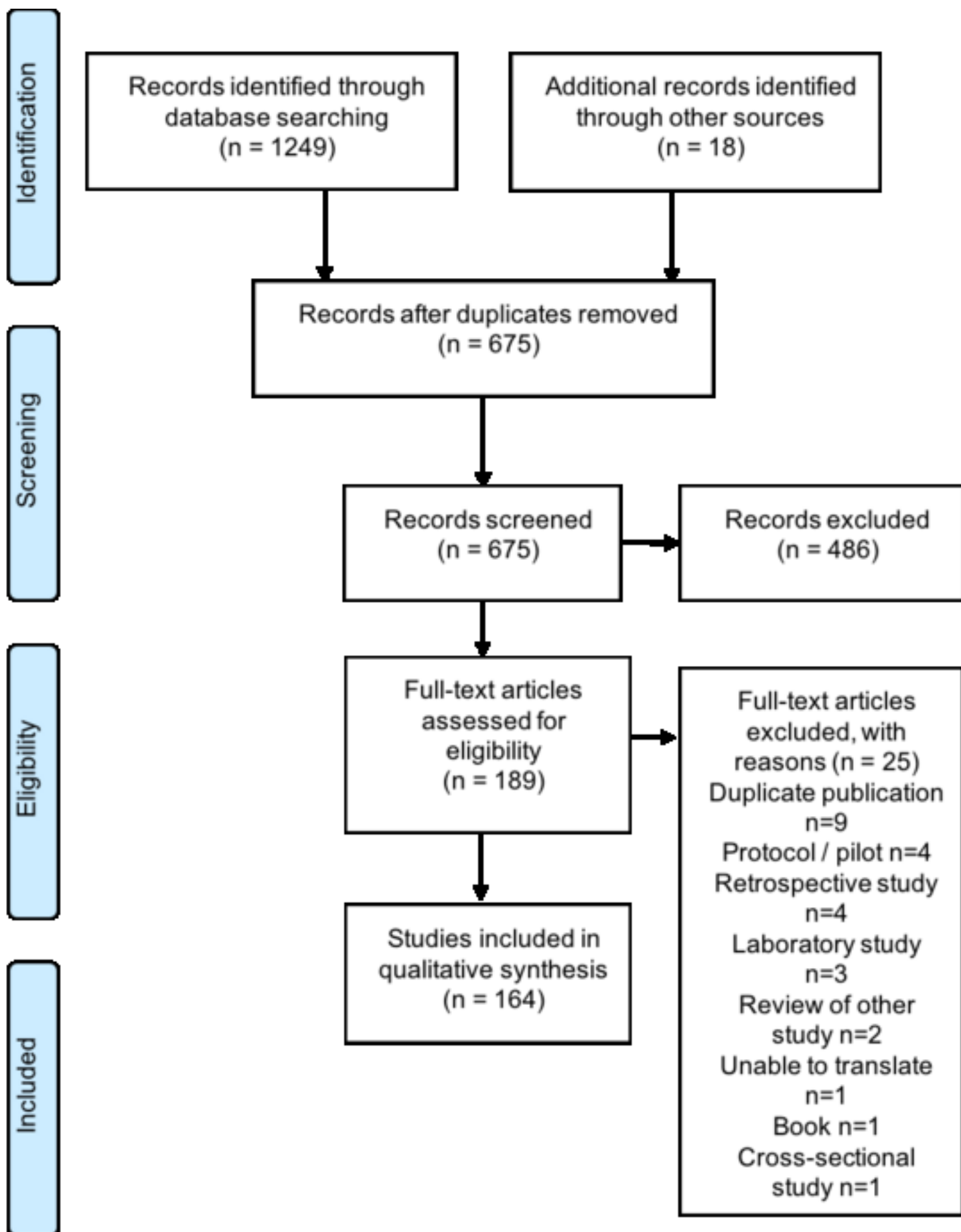


Figure 2
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