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ORIGINAL ARTICLE

Clinical trials of pneumonia management assess heterogeneous outcomes and measurement instruments

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Abstract

Objectives: To inform clinical practice guidelines, randomized controlled trials (RCTs) of the management of pneumonia need to address the outcomes that are most important to patients and health professionals using consistent instruments, to enable results to be compared, contrasted, and combined as appropriate. This systematic review describes the outcomes reported in clinical trials of pneumonia management and the instruments used to measure these outcomes.

Study Design and Setting: Based on a prospective protocol, we searched MEDLINE/PubMed, Cochrane CENTRAL and clinical trial registries for ongoing or completed clinical trials evaluating pneumonia management in adults in any clinical setting. We grouped reported outcomes thematically and classified them following the COMET Initiative's taxonomy. We describe instruments used for assessing each outcome.

Results: We found 280 eligible RCTs of which 115 (41.1) enrolled critically ill patients and 165 (58.9) predominantly noncritically ill patients. We identified 43 distinct outcomes and 108 measurement instruments, excluding nonvalidated scores and questionnaires. Almost all trials reported clinical/physiological outcomes (97.5). Safety (63.2), mortality (56.4), resource use (48.6) and life impact (11.8) outcomes were less frequently addressed. The most frequently reported outcomes were treatment success (60.7), mortality (56.4) and adverse events (41.1). There was significant variation in the selection of measurement instruments, with approximately two-thirds used in less than 10 of the 280 RCTs. None of the patient-reported outcomes were used in 10 or more RCTs.

Conclusion: This review reveals significant variation in outcomes and measurement instruments reported in clinical trials of pneumonia management. Outcomes that are important to patients and health professionals are often omitted. Our findings support the need for a

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rigorous core outcome set, such as that being developed by the European Respiratory Society.

Keywords: Pneumonia; Community-acquired pneumonia; Hospital-acquired pneumonia; Ventilator-associated pneumonia; Outcomes; End points; Core outcome set; Clinical trials; Systematic reviews; Evidence-based medicine

1 Introduction

Pneumonia, an inflammatory condition of the lungs usually caused by bacteria, viruses or other microorganisms, accounts for almost three million deaths annually worldwide [1,2]. It is also associated with considerable morbidity, health-care expenditure and resource use [3]. Depending on the timing and location of infection, pneumonia is usually classified as community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP) [4]. Some authors also suggest a fourth category of pneumonia for patients not hospitalized, but with a significant exposure to the health-care system: healthcare-associated pneumonia [4], which has been debated intensively throughout the last decades [5].

Despite our expanding understanding of mechanisms that underlie pneumonia, available treatments remain suboptimal and pneumonia still causes unacceptable morbidity and mortality [3,6]. Randomized controlled trials (RCTs) represent the optimal study design for assessing the safety and clinical effectiveness of novel therapeutics, but the design, conduct and reporting of clinical trials investigating pneumonia management is complicated due to the acute nature and heterogeneity of the condition [7]. Ad hoc recruitment of patients upon presentation for an acute condition is challenging. Furthermore, potential participants may not be able or willing to give informed consent while they are acutely ill and unwell [7]. This is further complicated by multiple causative pathogens, a divergent host-response, heterogeneity in study populations that may suffer from various comorbidities and be using intercurrent medications, resulting in distinct clinical trajectories. In parallel, the main characteristics of therapeutic trials reporting on pneumonia management lack standardization, with significant variation in the diagnostic criteria [8,9], outcomes and outcome measurement instruments used [10,11].

To ensure that clinical trials inform clinical guidelines and practice effectively [12], they must address outcomes that are most relevant to both patients and health-care professionals [7,12,13]. It is also crucial to consistently evaluate critically important outcomes using the same, optimal measurement instruments, allowing findings to be easily compared, contrasted, and combined in systematic reviews and clinical practice guidelines. Use of a core outcome set (COS), an agreed minimum set of critically important outcomes required for decision-making that should be evaluated in all future trials in a specific area of health care, can resolve these problems [7,13]. Indeed, in other disease areas, COS have improved the quality of subsequent RCTs, ensuring that these have addressed the most pertinent outcomes, making them more comparable, and thus more likely to inform policy and clinical practice [14 16].

To date, the European Respiratory Society (ERS) has supported the development of two COSs, the ERS Chronic Obstructive Pulmonary Disease (COPD) Exacerbations Core Outcome Set [17 19], and the Core Outcome Measures Sets for Pediatric and Adult Severe Asthma [7,20]. More recently, the ERS has formed a task force aiming to develop COSs for CAP, HAP, and VAP.

The specific aim of this systematic review was to identify the outcomes evaluated in RCTs reporting on the management of pneumonia in adults, along with their corresponding measurement instruments, which will inform the development of the ERS Pneumonia COS.

2 Materials and methods

This methodological systematic review was based on a prospectively registered protocol (PROSPERO, ID: CRD42019147411). It was conducted in line with guidance from Cochrane and the Core Outcome Measures in Effectiveness Trials (COMET) Initiative [13,21] and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses [22].

Eligible studies included ongoing or completed RCTs evaluating any pharmacological or nonpharmacological intervention, including precision medicine interventions, for pneumonia management, either CAP, HAP, or VAP in adults. We accepted any established definitions and diagnostic criteria for the various types of pneumonia, but excluded studies assessing a combination of clinical presentations extending beyond pneumonia (e.g., lower respiratory tract infections). We also excluded RCTs focusing on Coronavirus Disease 2019 (COVID-19), as these were not included in the review protocol and have been addressed in a separate review [23]. We only included trial protocols and/or the main trial publications; we excluded secondary publications or reports of post-hoc RCT analyses. We only included reports in English.

We identified potentially relevant RCTs using a structured search strategy consisting of controlled vocabulary and free search terms describing pneumonia, along with filters that included the Cochrane sensitivity and precision maximising filter for RCTs (available in the online appendix). We searched MEDLINE/PubMed, the Cochrane Register of Controlled Trials (CENTRAL), the U.S. National Library

What is new?

Key Findings

- This systematic review assessed the outcomes and measurement instruments tested in 280 ongoing or completed RCTs of pneumonia management.
- The most frequently reported outcomes were treatment success (60.7), mortality (56.4) and adverse events (41.1).
- With the exception of treatment success and mortality, all other outcomes were assessed in less than half of the included studies, highlighting a significant variation in the selection of outcomes.

What this adds to what was known?

- Clinical trials of pneumonia management assess heterogeneous outcomes and measurement instruments. Outcomes that are important to patients, health professionals and other stakeholders are often omitted. This limits the interpretability and comparability of trial results.

What is the implication and what should change now?

- These findings underscore the necessity of establishing a core outcome set for future pneumonia management RCTs, to enhance their quality and comparability. A core outcome set is a minimum agreed set of outcomes that will be assessed in all future RCTs of pneumonia management. The European Respiratory Society has initiated a task force to develop a core outcome set that will be informed by this methodological systematic review and international, multi-stakeholder consensus.

of Medicine Clinical Trials Register (clinicaltrials.gov) and the World Health Organisation (WHO) International Clinical Trials Registry Platform for articles published from 1st January 2010 to 13th December 2021.

Search results were screened for eligibility by two investigators independently (from among AGM, MF, JH, FH, AK) at title and abstract level, followed by full-text assessment of all potentially eligible studies. Disagreement in this and following steps were resolved by discussion or adjudication by a third reviewer. A risk of bias assessment of the included studies was beyond the scope of this review, given the focus on assessing the outcomes evaluated in pneumonia trials rather than the results of those trials. Eligible studies were grouped into those evaluating exclusively patients admitted to an intensive care unit (ICU, which we defined as ''critically ill patients'') vs. studies looking predominantly at patients who were not in ICU (which we defined as ''predominantly noncritically ill patients''), given our experience that outcomes relevant to these patient groups will differ considerably. One reviewer extracted relevant study characteristics of all eligible studies in a standardised form and a second reviewer cross-checked the extracted data for accuracy (from among AGM, MF, JH, RCR, FH, TW, AK). More specifically, we captured information regarding the study population, participant age, recruitment setting, blinding, interventions, sponsor, and geographic distribution of participating sites. All outcomes reported in each study alongside the outcome measurement instruments used to evaluate them were recorded verbatim.

After assessing the outcomes in a random sample of 20 studies from the critically ill and from the predominantly noncritically ill groups and drawing on our experience in previous systematic reviews evaluating the outcomes of other acute respiratory conditions, namely COVID-19 and COPD exacerbations [23,24], we developed an initial list of outcome domains that were classified following the taxonomy proposed by the COMET Initiative [25]. Two reviewers independently categorized each of the extracted verbatim outcome descriptions into a single outcome domain (from among AGM, MF, JH, RCR, FH, TW, AK). The list was expanded as needed after discussion among the extractors upon identification of additional outcome domains that were not initially included. Our findings are described narratively and in tabulated format. The unit of interest for this report is the trial. We assessed each trial once and collated data from multiple eligible reports of the same trial.

3 Results

3.1. Included studies

Following deduplication, our searches retrieved 4,492 records, of which 358, reporting on 280 RCTs, were considered eligible. These included 181 (64.6) completed RCTs with published results, and 99 (35.4) studies without published results, the majority of which are still ongoing. Characteristics of the included trials are described in Supplementary Table 1.

3.2. Patient populations, disease groups and interventions

There were 115 (41.1) RCTs that enrolled critically ill patients, with a median study size of 82 participants (range: 4 1,200). Of these RCTs, 79 (68.7) included only patients with VAP, 14 (12.2) only patients with CAP, one (0.9) only patients with HAP, while the remaining 21 (18.3) accepted a combination of CAP, VAP and/or HAP. The most frequently assessed interventions in these trials were antibiotics (*n* 72, 62.6); precision medicine interventions (*n* 10, 8.7); and steroids, anti-inflammatories or immunomodulating agents including biologics (*n* 8, 7.0).

There were 165 (58.9) RCTs that recruited patients who were predominantly noncritically ill, with a median study size of 172 participants (range: 5 7,100). Solely patients with CAP were recruited in 124 (75.2) and only patients with HAP were recruited in four (2.4) trials, while the rest accepted combinations of CAP, HAP, and/or VAP. Antibiotics (*n* 77, 46.7) were the most frequently assessed intervention, followed by steroids, anti-inflammatories or immunomodulating agents (*n* 19, 11.5) and traditional medicine interventions (*n* 12, 7.3).

3.3. Trial outcomes

Our review identified 43 outcome domains and 108 measurement instruments, excluding nonvalidated scores and questionnaires (Fig. 1). The definitions of the various outcomes, the frequencies of their reporting, and the corresponding instruments used to measure them in the included RCTs are presented in Supplementary Tables 2 and 3 A primary outcome was defined in 226 (80.7) of the RCTs, with similar proportions for trials focusing on critically ill (*n* 92, 80.0) and predominantly noncritically ill (*n* 134, 81.2) patients.

The included RCTs reported on a median of five outcome domains [interquartile range: 3 7], with up to 16 domains assessed (Fig. 2). These figures did not differ between studies assessing critically ill (5 [4 8]) or predominantly noncritically ill (5 [3 7]) patients. There was no clear association between the number of participants and number of outcome domains evaluated (Fig. 3). Although some trials reported a larger number of outcomes, for the purpose of this analysis, we reclassified based on our 43 identified domains.

Classification of outcomes into the COMET taxonomy revealed that 97.5 of all trials assessed at least one clinical/physiological outcome, while 65.0 defined a primary

Fig 1 Sunburnt plot summarising the frequency that outcomes are reported in pneumonia RCTs outcomes reported in ≤2 trials are not labeled in this figure). For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

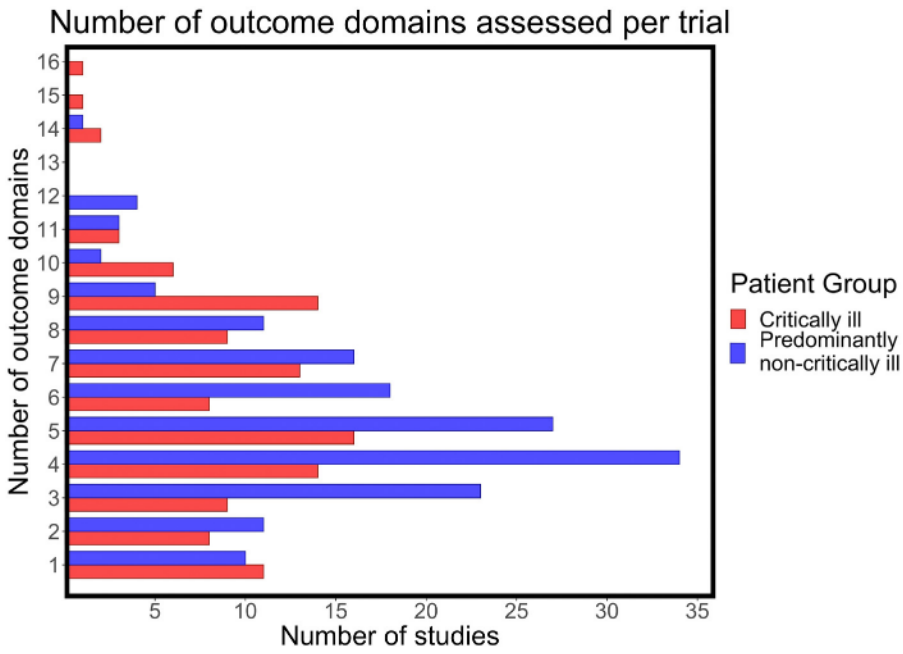

Fig 2 Number of outcome domains assessed per trial. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

outcome from this category. Safety outcomes were addressed in 63.2 of all trials, but were rarely selected as primary outcomes (3.6). Mortality/survival, resource use and life impact were assessed less frequently, in 56.4 , 48.6 and 11.8 of all trials, respectively, and were infrequently selected as primary outcomes (13.6 , 6.1 , 1.4 respectively). Overall, the most frequently reported outcomes were treatment success (60.7), followed by mortality (56.4) and adverse events (41.1). It is worth noting that treatment success and mortality were the only outcomes assessed in more than half of the included studies. In trials evaluating critically ill patients, mortality was the most frequently used outcome (62.6), followed by adverse events (60.9) and treatment success (56.5). Conversely, trials looking at noncritically ill patients reported most frequently on treatment success (63.6), followed by mortality (52.1) and adverse events (49.1).

3.4. Measurement instruments to assess outcomes

There was significant variation in the selection of instruments used for assessing the various outcomes, with a total of 108 different instruments used across all included trials (Supplementary Table 2). Of note, 73 (67.6) of the included instruments were used in 10 RCTs or less. Importantly, none of the patient-reported instruments were used in 10 or more RCTs.

4 Discussion and conclusion

This systematic review describes the outcomes and outcome measurement instruments tested in 280 ongoing or completed RCTs evaluating interventions for pneumonia management. There was significant variability in the reported outcomes. Outcomes that are important to patients, health professionals, and policy makers were often omitted. One in three trials did not report on safety, while four in ten did not assess mortality or the overall outcome of the infection (treatment success). With the exception of the aforementioned three outcomes, all other identified outcomes were assessed in less than half of the included studies. We also detected wide variation in the instruments used to assess outcomes such as treatment success, disease severity, signs, symptoms, or health status. Although subjective and patient reported outcomes are often reported, less than half the included RCTs were double-blind, raising concerns around potential risk of bias.

The included studies were grouped into those assessing critically ill patients and those including predominantly noncritically ill patients, as we expected that the outcomes and measurement instruments might differ across these categories. The (ongoing) need for ICU admission or invasive ventilation, duration of antibiotics, disease severity or trajectory were more frequently assessed in studies focusing on critically ill patients. In addition, the instruments used to assess some of the outcomes varied across the two groups of studies. For example, in critically ill patients, safety was more often assessed by laboratory testing, whereas studies of noncritically ill patients commonly relied on clinical indices. Studies of critically ill patients assessed the duration of ICU admission or mechanical ventilation, while those of noncritically ill patients used the requirement for intensive care as an outcome. Interestingly, studies evaluating critically ill patients with CAP selected

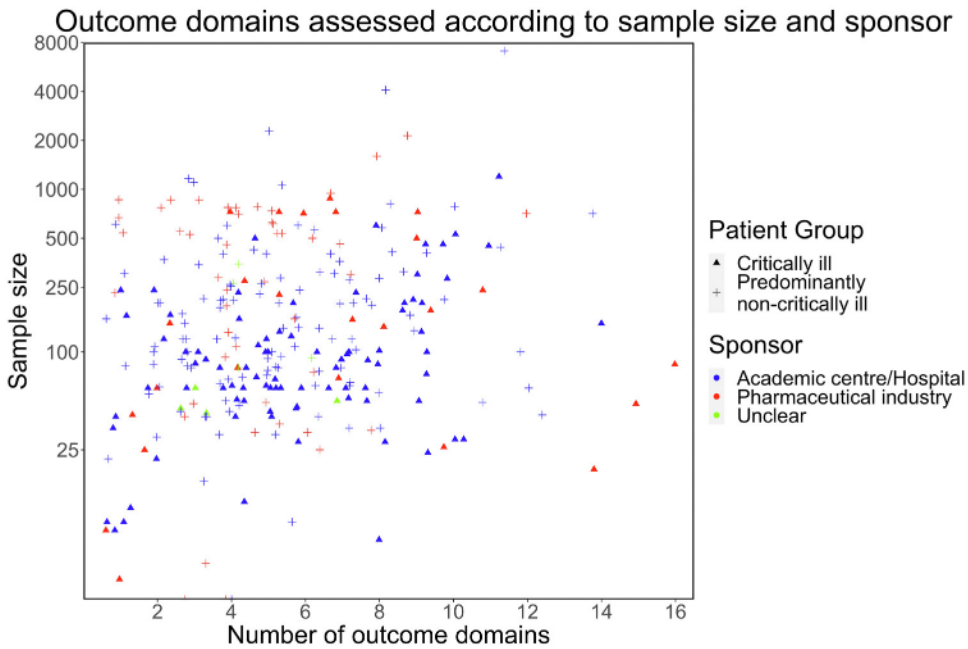

Fig 3 Number of outcome domains assessed according to the study sample size. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

similar outcomes to studies looking at VAP, perhaps suggesting the need for two COSs, focusing on the treatment setting, rather than the classification of pneumonia.

Despite being the most frequently assessed outcome across the included RCTs, there are no established and validated tools for assessing treatment success or failure in pneumonia or other acute respiratory conditions [26]. This outcome is defined as an overall assessment of whether pneumonia was treated successfully or not. Broadly, there are three different groups of instruments evaluating this outcome, but they are defined differently across various RCTs, leading to significant inconsistency and poor comparability. Descriptive instruments define treatment success or failure based on qualitative or semi-quantitative descriptions of the patients' clinical status with regards to the pneumonia, as judged by the responsible health-care professional. For example, in descriptive tools, cure is often defined as a complete or nearly complete resolution of all signs and symptoms of the pneumonia, with some trials also requiring the normalisation of laboratory and radiological findings. Treatment failure is defined as a lack of improvement or deterioration of the clinical condition of the patient, while intermediate status might be labeled as ''clinical improvement'' or ''marked clinical improvement''. The second group of instruments usually defines treatment success or failure as a composite outcome consisting of several desirable or undesirable scenarios, together defining an overall favourable or unfavourable outcome. For example, treatment failure might be defined as the need for supplemental oxygen, hospital admission, extension of the consolidation on imaging, or death. The third group of instruments focuses on the need for additional unplanned treatments, and mainly the need for additional antibiotics beyond the predefined course. In this group, treatment success is typically defined as an improved clinical condition of the patient who does not require any further antibiotics. For the purposes of this work, we presented these three broad instrument categories. However, the inconsistent definition of treatment success and the frequent inclusion of highly subjective measurement tools is a key finding of this review and there is an urgent need for a rigorously validated tool.

Microbiological cure or eradication has also been assessed in 3/10 studies, with equal distribution between those looking at critical or not necessarily critical outcomes. This outcome did not fulfill our definition of treatment success/failure, so it was reported separately. Microbiological cure is a surrogate outcome predicting the clinically important outcomes. It was only assessed in 31.1 of all trials, but that is probably because patients were followed-up until clinical cure, that is more important to patients and clinicians.

Patient-reported outcome measures (PROM) were evaluated infrequently. More specifically, symptoms, quality of life and health status were only considered in 14.6 , 5.7 and 1.8 of the whole sample of RCTs, while the respective proportions for studies assessing critically ill patients were even lower (7.0 , 6.1 and 0.0). This will need to be addressed, especially given the long-term sequelae that severe pneumonia has on the health and well-being of patients. There are no PROMs validated in HAP but two, well validated, CAP specific PROMs exist [27,28]. However, most CAP trials used nonvalidated instruments. The creation, validation and consistent use of

PROMs should be emphasized when agreeing a COS for pneumonia trials.

Recent methodological reviews of the outcomes evaluated in other acute respiratory presentations, namely acute exacerbations of COPD and COVID-19 revealed similar findings and limitations [23,24]. Both the outcomes and measurement instruments that are used in all three disease areas vary widely and are drawn from the same pool described in this paper. There is little focus on the longitudinal impact of acute events on the health and well-being of patients and this may need to be revisited given that these domains were prioritised in the COPD Exacerbations COS, that was based on global, multi-stakeholder consensus with strong patient involvement [19].

Our findings suggest that several RCTs on the management of pneumonia cannot adequately inform clinical recommendations and practice because their results cannot be properly compared, contrasted, and combined. These findings confirm the need for COSs for trials on the management of various types of pneumonia, to ensure that future trials address the most critical outcomes in a standardized way, thus improving their quality and comparability.

Two previous consensus documents have prioritized outcomes for evaluation in clinical trials of CAP [11] and HAP/VAP [10]. Both recommended the evaluation of safety, mortality, and treatment success; which were most frequently assessed outcomes in RCTs in this study. They also encouraged the use of other outcomes that are less frequently tested in clinical trials, such as quality of life, severity scores, and, for studies assessing CAP, the need for ICU admission. Although the CAP document was published almost 20 years ago, trial adherence to the recommended outcomes remains limited. The HAP/VAP document is newer, and adherence cannot be appreciated yet. Uptake of such documents is key to their success. The planned ERS Pneumonia COSs are being developed following rigorous methodology proposed by the COMET initiative, which is based on thorough methodological systematic reviews (such as this one) and international, multistakeholder involvement and consensus [29,30]. It is anticipated that the core outcomes will be endorsed by the ERS. We hope that these strengths, along with a rigorous dissemination strategy will maximise the likelihood of success.

The main limitation of this review is that we were not able to classify trials according to their trial phase. It is generally acceptable for phase 2 trials to have more exploratory or preliminary outcomes [31]. However, a significant proportion of the included trials did not report on their phase and classification was not possible. Moreover, we did not address the timepoints at which various outcomes were measured, or the exact methods for analysing various outcomes and instruments, as these were beyond the scope of our work. These important parameters will need to be addressed in future work. Indeed, assessing mortality only during ICU stay or hospital admission can be misleading, as it overlooks the substantial mortality occurring within 6 12 months post the acute event. Furthermore, this approach may introduce bias due to variations in the length of ICU/hospital stays mong different treatment groups or participants. Likewise, the analysis of treatment success can be conducted either at as specific timepoint or based on time-to-treatment success. The latter strategy generally provides a more robust analysis with greater power to identify differences. Another potential limitation of this work is that we only included studies reported in the English language. However, the number and broad geographic distribution of the included studies reassures that we have not missed outcomes.

The main strengths of this systematic review are the rigorous literature review that revealed 280 eligible studies, including ongoing and completed RCTs, allowing us to capture the frequency at which relevant outcomes and measurement instruments are assessed in RCTs of pneumonia management. Characteristically, after extracting data from approximately 15 and 60 of the included studies, we reached saturation of outcomes and measurement instruments, respectively.

It should be noted that for completeness we have included all outcomes evaluated in the included studies. Some of these outcomes, such as guidelines adherence or satisfaction of health professionals are not patient health outcomes, and will therefore be excluded from the COS development. Moreover, the ERS COS will focus on late phase efficacy and effectiveness trials and will not consider pharmacodynamics and pharmacokinetics, that are more relevant to early phase trials, while cost-effectiveness analyses will not be considered either. Although biomarkers are often assessed as surrogates to patient important outcomes, it is still debated whether they should be considered as outcomes, especially in effectiveness trials.

In summary, this methodological review identifies the outcomes and outcome measurement instruments reported in trials on the management of pneumonia, quantifying how frequently they are used. These findings will inform the development of the ERS Pneumonia COSs.

CRediT authorship contribution statement

Study conception: AGM, MF, JV, TF. Study design: AGM, MF, PD, PRW, JV, TF. Methodological expertise: AGM, PRW. Screening, study selection, data extraction: AGM, MF, JH, RCR, FH, TW, AK. Analysis: AGM, TF. Manuscript drafting: AGM, MF, TF. Interpretation of findings: All authors. Critical revision of the manuscript: All authors.

Data availability

This is a systematic review. Data are available from the original publications that have been included and cited.

Declaration of competing interest

The authors declare no conflict of interest related to this work.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2023.10.011.

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