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Core outcome sets, developed collaboratively with patients, can improve the relevance and comparability of clinical trials.

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Tweetable abstract: #RCTs in #Respiratory Medicine require harmonisation. A core outcome set #COS is an agreed minimum set of outcomes that are critical for decision-making and should be evaluated in all future clinical trials.

Properly designed and conducted randomised controlled trials (RCTs) represent the gold standard study type for conclusively evaluating any efficacy, effectiveness, and/or safety of healthcare interventions. However, they are frequently associated with risks and burden to patients and require extensive resources[1]. These can only be considered acceptable if the RCTs fulfil their main objective, that is to inform guidelines and clinical practice and ultimately improve patients' health. Regrettably, RCTs are often less informative than they could be, owing to deficiencies in their design, and this may sometimes contribute to "research waste"[2,3]. This needs to be remedied by strengthening and harmonising trial methods, delivery, and reporting. This has implications across the breadth of clinical medicine.

Identification and assessment of outcomes that are most relevant to patients, carers and other healthcare stakeholders represent a crucial component of clinical trials methodology[4]. Trials often omit outcomes that are critical for decision-making therefore failing to translate trial efforts into patient benefits[5]. Moreover, there is often extensive heterogeneity across trials focusing on the same disease entity in terms of inclusion and exclusion criteria, chosen outcomes and their definitions[6], or instruments used to measure these outcomes. This substantially limits the ability to compare, contrast and combine data from various studies. In addition, the use of inappropriate or non-validated instruments reduces the interpretability of results. Inappropriate selection of clinical trial outcomes often limits the certainty in the available evidence that informs clinical practice guidelines and systematic reviews, while sometimes there are no data available around outcomes that are important to patients or health professionals[7-10].

Core outcome sets are developed to address these very issues. A core outcome set is an agreed minimum set of critically important outcomes that are required for decision-making and that should be evaluated in all future trials in a specific area of health care[4]. Furthermore, it is recommended that the most rigorously developed instrument for measuring each of the selected outcomes should be selected, based on an evidence-informed consensus[11]. This process leads to the development of a core outcome measurement instrument set. Plainly, the first defines *what* to measure and the latter describes *how* to measure it. Core outcome and measurement sets are informed by the best available evidence, but also by the views of patients, carers, clinicians, and other relevant stakeholders that have historically been excluded from the selection of research outcomes. A core outcome set does not limit the outcomes that a trial can measure but aims to ensure that the outcomes that are most critical to decision-making will be addressed. In other disease areas, established core outcome and measurement sets have promoted consistency in the selection and evaluation of outcomes, thus improving the comparability of efficacy, effectiveness and safety of health interventions and strengthening clinical recommendations[12,13].

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative and the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) have produced rigorous, standardised methodology for developing core outcome and measurement sets, respectively. This methodology adopts an evidence-informed consensus approach[4,14]. After clearly defining its scope, COMET recommends a three-step approach for developing a core outcome set (figure 1). First, a comprehensive list of outcomes relevant to the disease of interest should be set out. These outcomes should be informed by a rigorous

systematic review exploring all outcomes assessed in clinical trials; this process should be complemented by qualitative work exploring outcomes that are considered relevant to those with lived experience, including patients and carers, and other stakeholders, not necessarily captured in clinical trials. Thereafter, the most critical outcomes are prioritised through a consensus process, typically a multi-stakeholder Delphi survey, and based on prospectively defined thresholds for inclusion or exclusion of outcomes to the core outcome set. Finally, the selection of outcomes is finalised in a consensus meeting, that predominantly considers outcomes that need further discussion, i.e. those that have not reached the thresholds either for inclusion or exclusion. Both in the Delphi survey and consensus group, the views of different stakeholder groups are considered separately, and the participants should be representative of all relevant stakeholders, ideally internationally.

Based on the COSMIN methodology, to select a single, optimal measurement instrument for each core outcome, researchers should identify all available instruments and data around their measurement properties, including the internal structure, reliability, measurement error, criterion validity, construct validity, and responsiveness[15]. In addition, the acceptability of the instruments by patients and investigators, the resources required and feasibility of measuring them should be considered. It may also be important to consider how established various instruments are and how broadly they are already used across RCTs, since one of the main objectives is to promote consistency.

The European Respiratory Society (ERS) has already supported the development of two core outcome sets, while a third one is currently in development. Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA) were developed by the 3TR EU-IMI consortium and were informed by the core-Asthma core outcome set for moderate-to-

severe asthma[16-18] (figure 2). The ERS COPD Exacerbations Core Outcome Set and Core Outcome Measurement Instrument Set were developed by an ERS Task Force and have now been endorsed by 4 international respiratory societies[19-21] (box 1). Core outcome sets for the management of community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) are under development by an ongoing ERS task force. In parallel, independent groups have developed other high quality core outcome sets for clinical trials, observational studies, or clinical practice, including critical care ventilation trials[22], sarcoidosis[23], self-management interventions in COPD[24], moderate-to-severe asthma[18], or bronchiolitis[25]. Ongoing and completed core outcome sets are listed in the COMET initiative's registry (https://comet-initiative.org/).

While core outcome sets are developed predominantly for clinical trials, they are also important in other study types. Systematic reviews and meta-analyses of RCTs and clinical practice guidelines should also adhere to the relevant core outcome sets. For the same reason, it is important that these outcomes are considered in observational studies, for their findings to be comparable to RCT data. Finally, clinicians should also assess these outcomes, that are considered critical by patients and other stakeholders, in their clinical practice, to inform their judgements around disease activity or severity and their treatment decisions.

Factors other than core outcome sets and measurement sets impact on quality and comparability of RCTs in respiratory medicine. Lack of standardisation of the eligibility criteria limits comparability of the trial results. While very selective eligibility may be important in more exploratory trials, aiming to assess treatment efficacy, it is crucial that late phase trials adopt pragmatic criteria, to avoid excluding patient groups that will end up receiving these treatments[26]. Characteristically, trials have rarely tested treatment effects in

patients with COPD without a smoking history. Importantly, the populations assessed in RCTs were until recently limited by Oslerian diagnostic labels that group heterogeneous populations potentially responding diversly to treatments[27,28].

Overall, optimising the design of clinical trials should ensure that their results can drive the development and update of clinical practice guidelines leading to optimal patient care. Core outcome sets and measurement sets of high methodological rigour, and informed by global multi-stakeholder consensus, such as those endorsed by the ERS, can improve the quality and comparability of future RCTs. It is therefore strongly recommended that future RCTs should adhere to the agreed outcomes and instruments. Regulatory authorities, ethics boards, research funders, journal editors, and the pharmaceutical industry should support the implementation of core outcome sets and measurement sets, and they should consider ways to increase uptake, such as relevant regulations or guidelines, or specific questions within funding, ethics, or regulatory applications. Finally, consideration of existing core outcome sets should be used to highlight potential areas for future methodological or clinical research.

Box and Figure legends:Figure 1: Outline of the process for developing a core outcome set and a core outcome measurement instrument set. COSMIN: COnsensus-based Standards for the selection of health Measurement Instruments.

Figure 2. The paediatric (A) and adult (B) core outcome measure sets for severe asthma clinical trials. COMSA: Core Outcome Measures for paediatric and adult Severe Asthma.

3TR: Taxonomy, Treatments, Targets and Remission consortium. Reproduced from Khaleva et al. Eur Respir J 2023.

Box 1. Core Outcome Set for Clinical Trials Evaluating the Management of COPD Exacerbations. Reproduced from Mathioudakis et al. Eur Respir J 2022[21].

Box 1. Core Outcome Set for Clinical Trials Evaluating the Management of COPD Exacerbations. Reproduced from Mathioudakis et al 2022[21].

1. **Death**
    a. Death from any cause
    b. Death from a COPD exacerbation
2. **Treatment success**
3. **Need for higher level of care**
    a. Need for hospital admission for the presenting exacerbation
    b. Need for admission to the intensive care unit for the exacerbation
4. **Levels of oxygen and carbon dioxide in the blood (arterial blood gases)**
5. **Patient reported outcomes**
    a. Breathlessness
    b. Health related quality of life
    c. Activities of daily living
    d. Worsening of symptoms after the initial treatment
6. **Future Impact**
    a. Disease progression
    b. Future exacerbations
    c. Future hospital admissions
7. **Safety**
    a. Serious adverse events from treatments
    b. Development of resistant bacteria
    c. Development of pneumonia
8. **Treatment adherence**

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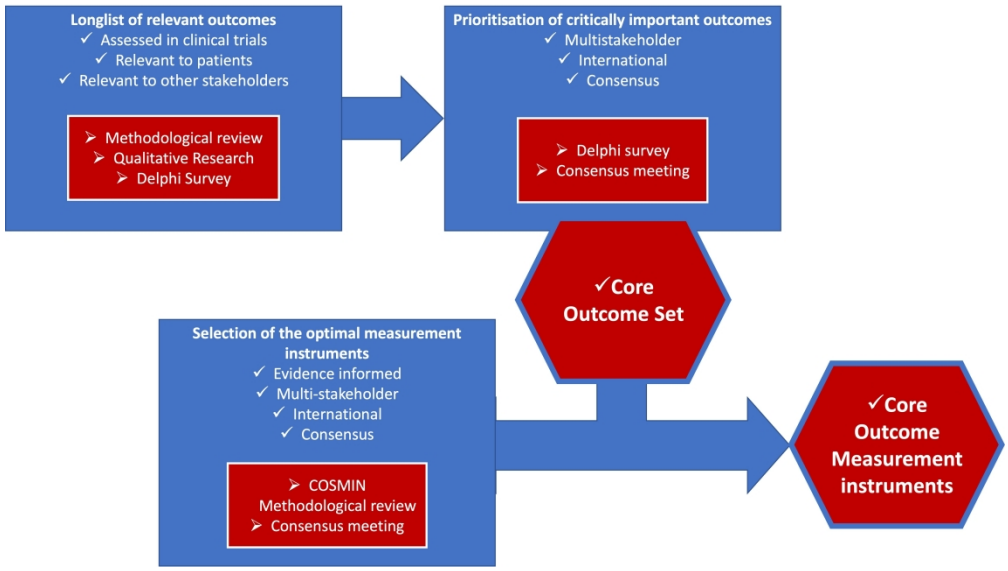

Outline of the process for developing a core outcome set and a core outcome measurement instrument set. COSMIN: COnsensus-based Standards for the selection of health Measurement Instruments.

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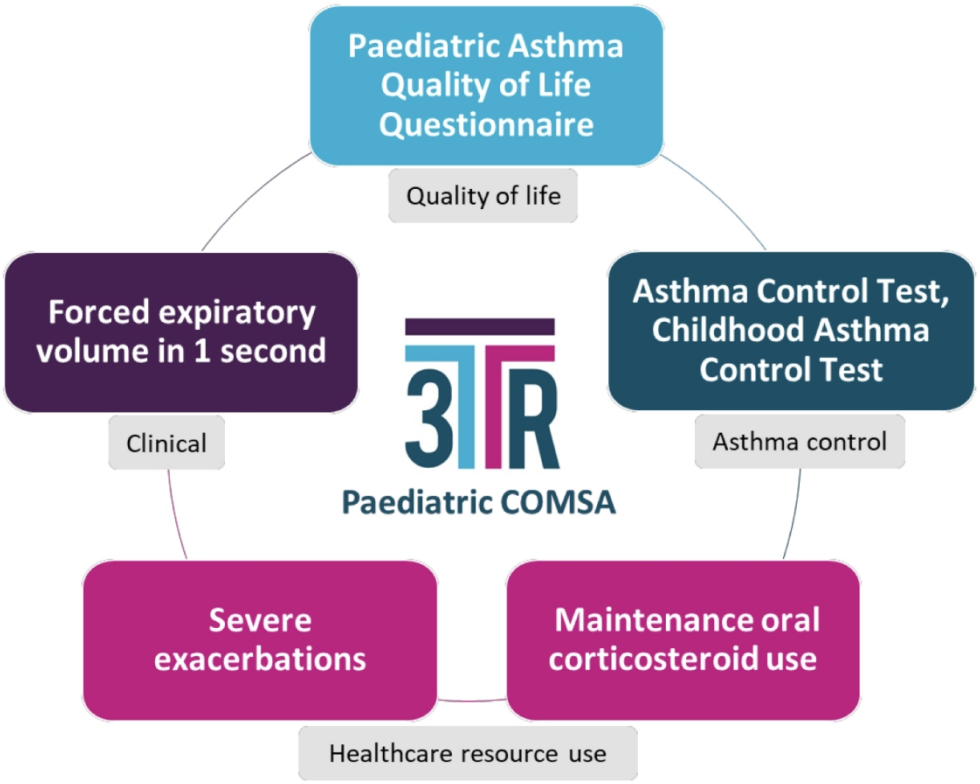

The paediatric (A) and adult (B) core outcome measure sets for severe asthma clinical trials. COMSA: Core Outcome Measures for paediatric and adult Severe Asthma. 3TR: Taxonomy, Treatments, Targets and Remission consortium. Reproduced from Khaleva et al. Eur Respir J 2023.

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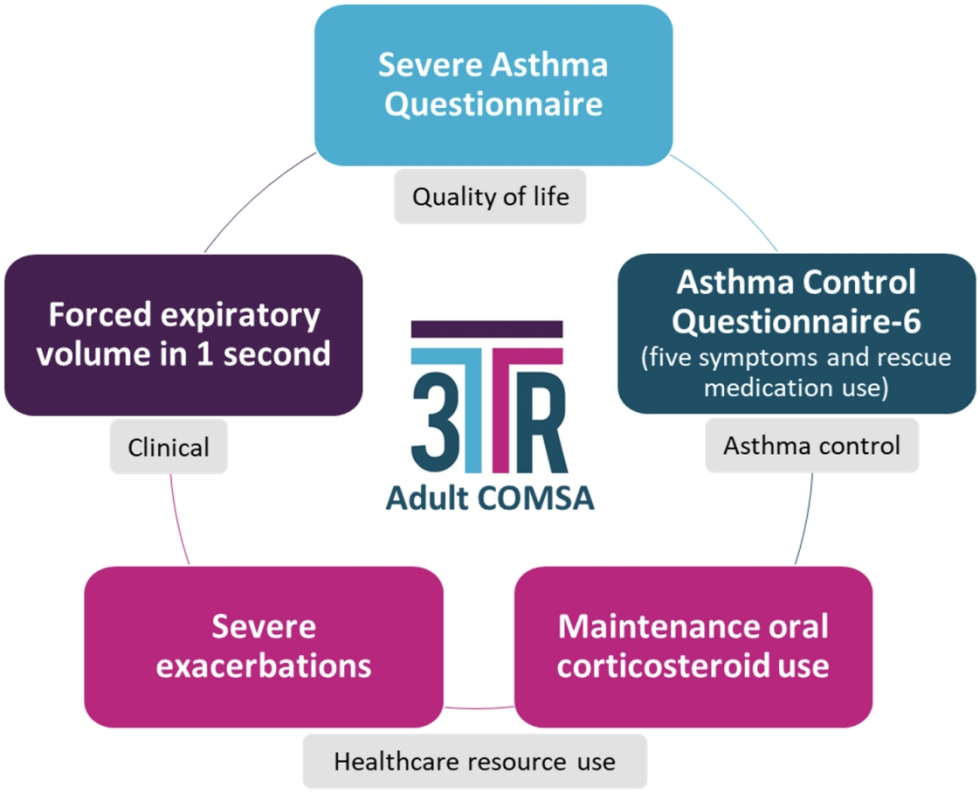

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