ORIGINAL ARTICLE

Assessing the Uptake of the Lung Cancer Core Outcome Set: A Cross-Sectional Analysis

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ABSTRACT

Introduction: A core outcome set (COS) helps standardize outcome measurements across clinical trials. Although lung cancer is the leading cause of cancer-related deaths, research exploring COS implementation across lung cancer trials remains limited. We aim to analyze the uptake of the lung cancer COS and identify potential gaps in COS adherence.

Methods: On June 26, 2023, we conducted a cross-sectional analysis of clinical trials that evaluated lung cancer interventions. Our sample consisted of studies registered on ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform between September 2011 and June 2023. In a masked and duplicate fashion, investigators extracted data regarding trial characteristics and COS adoption. An interrupted time series analysis was conducted to evaluate the adherence of lung cancer COS before and after its publication.

Results: Of the 626 observed trials, we found no overall significant difference in lung cancer COS uptake pre- and post-publication (0.01%, 95% confidence interval: −0.16% to 0.19%, p=0.85). The most frequently measured outcomes were "overall survival" (91.69%%) and "treatment-related mortalities" (54.69%). Health-related quality of life questionnaires were typically used to evaluate outcomes in the "Degree of health" domain (49.20%). Outcomes related to "time from diagnosis to treatment" (0%), "place of death" (0.16%), and "duration of time spent in the hospital at the end of life" (1.60%) were rarely measured.

Conclusions: Despite the advantages of COS implementation, adherence across lung cancer clinical trials remains alarmingly low—which could compromise data reliability and patient care. Our findings showcase these inconsistencies and emphasize the need for proactive approaches to improve uptake.

Keywords: Lung cancer; Core outcome sets; Clinical trials; Adherence; Uptake

Introduction

Lung cancer stands as a formidable global health challenge, with reported cases exceeding two million in 2020, making it the leading cause of cancer-related deaths worldwide.[1,2] The prognosis for patients is significantly influenced by the stage at which the disease is diagnosed, with later-stage diagnoses associated with a notable 40% decrease in five-year survival rates compared with early-stage diagnoses.[3] This disease not only presents major health complications but also imposes a significant financial burden, exemplified by the staggering $23.8 billion national expenditure on lung cancer care in the

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United States according to the 2020 National Institutes of Health Cancer Trend Progression Report.[4,5]

Lung cancer represents a significant and pressing problem in public health, necessitating rigorous research methodologies like randomized controlled trials (RCTs) to develop innovative treatments and medications. Nevertheless, the validity of RCTs has been called into question because of inconsistencies in outcome measurements, leading to unreliable, ambiguous, and potentially inaccurate data being published.[6] A 2020 assessment of systematic reviews revealed that 40% of Cochrane Review Group editors reported problems with outcome inconsistencies across various health-related topics.[7] Moreover, MacLennan et al.[8] and Waters et al.[9] came to the same conclusion when they found inconsistency and variability in urological and oropharyngeal cancer clinical trial outcomes. The imperative for improved treatments is hindered by inadequate reporting of outcome measures, highlighting the urgent need for standardized approaches in RCTs to ensure data reliability and comparability. Given the profound impact of lung cancer on global health, standardization is particularly crucial in lung cancer trials to facilitate meaningful advancements in patient care and treatment strategies.

In addressing the variability of outcomes measured in clinical trials, core outcome sets (COS) have emerged as a solution.[10,11] A COS specifies a minimum set of outcomes that should be measured in all clinical trials, thus ensuring comparability and generalizability of results.[10] Development of a COS using a wide array of stakeholders can further help standardize result measurements, reduce the risk of reporting bias, and identify clinically relevant outcomes.[12]

Considering the severity of all aspects of lung cancer, it is critical that clinicians are able to easily understand and compare the results across clinical trials to make informed medical decisions when caring for patients. The Lung Cancer Working Group of the International Consortium for Health Outcomes Measurement established a COS for lung cancer in September 2016, which specifies outcomes that should be measured by all trials.[13] A standard set of 19 outcome measurements across five main domains was developed.[13] Ideally, strict adherence to the COS would increase transparency and reduce bias across lung cancer clinical trials.[13] This study aims to analyze the inclusion of the recommended outcomes in published lung cancer clinical trials, identify the prevalence and characteristics of COS used in the research, and evaluate any gaps in adherence to the COS.

Materials and Methods

Reproducibility and Study Design

We conducted a pilot test of search strategies, inclusion criteria, and data extraction materials a priori to this study. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 checklist[14] to ensure our findings were comprehensively reported. In this investigation, we evaluated the outcomes measured and adoption of the lung cancer COS by RCTs using a methodology similar to that of Kirkham et al.[15] Our methodology was strictly followed and made publicly available on the Open Science Framework (OSF) to ensure reproducibility and transparency.[16] The protocol was submitted to the Institutional Review Board, which determined that our study did not use human research subjects.

Search String

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative is an organization that brings stakeholders together to develop a standardized COS.[10] The COMET Initiative's COS database was used to identify "Defining a standard set of patient-centered outcomes for lung cancer" published by Mak et al.[13] for uptake analysis.[10,13] On June 26, 2023, we searched ClinicalTrials.gov,[17] which provides information on over 450,000 clinical trials.[18] Our study focused on trials that evaluate the efficacy and effectiveness of interventions; therefore, only phase 3 and phase 4 trials were included. The following filters were applied to the ClinicalTrials.gov database: "conditions: lung cancer," "study type: interventional studies," "phase: 3 and 4," "date: 09/01/2011 to 06/26/2023." This time frame ensured an adequate portrayal of lung cancer clinical trials before and after the lung cancer COS publication. No restrictions were applied regarding recruitment status. In addition, the ClinicalTrials.gov search also included terms associated with the "conditions: lung cancer" filter (see Supplementary Data 1).

To ensure comprehensive coverage of international trials and mitigate potential selection bias, we incorporated a secondary clinical trial registry database, the WHO International Clinical Trials Registry Platform (ICTRP),[19] into our data collection process. The ICTRP search portal was subjected to specific filters, including "title: lung cancer," "recruitment status: ALL," "phases are: 3 and 4," and "date: 01/09/2011 to 26/06/2023."

Trials identified through ICTRP that were also listed on ClinicalTrials.gov or had an associated National Clinical Trial number were classified as "duplicate" and subsequently excluded from our sample. By implementing this criterion, we ensured the integrity of our data set and minimized redundancy in our analysis.

Training

To ensure consistency and promote reliability in data extraction, all investigators received training on general

COS principles.[20] Once completed, the principal investigator arranged a presentation on COS uptake, which included a complete review of the COMET Initiative handbook[10] and group discussions to further prepare the authors.

Screening & Eligibility Criteria

The following criteria for inclusion were applied: (1) trial subjects were patients diagnosed with SCLC or NSCLC, (2) the trial was registered five years before the publication of the COS to June 26, 2023, and (3) the trial assessed the effectiveness or efficacy of interventions according to the COS.[13] Trials that did not meet these criteria were excluded. Such ineligible trials included those not exclusively focused on lung cancer, non-randomized trials, trials focused on diagnostic test accuracy, trials solely focused on drug pharmacokinetics or pharmacodynamics, trials with patients who had other types of lung cancer such as mesothelioma or carcinoid tumors, and single-group assignment trials.

The rationale behind excluding trials solely focused on drug pharmacokinetics or pharmacodynamics was to maintain a focus on studies evaluating the effectiveness or efficacy of interventions as per the COS. While pharmacokinetic and pharmacodynamic studies are valuable in drug development, they typically do not directly assess the clinical effectiveness or efficacy of interventions in treating patients with lung cancer. Therefore, we opted to exclude such trials from our analysis to ensure relevance to our research objectives.

The RCTs identified from the comprehensive search were compiled into a Google Sheet. In the initial screening, two authors (AVT and BD) independently evaluated the clinical trial registry of all search results in a masked duplicate fashion to assess their inclusion within the study. In this study, "masked duplicate fashion" refers to a procedure where the investigators independently assessed the trial registry without knowledge of each other's evaluations. This approach aims to minimize potential biases that may arise from mutual influence or preconceived notions. By conducting the evaluation independently and "masked" from each other, the integrity of the data extraction process is upheld, and the risk of bias is mitigated. Once their initial evaluation of the registry was completed, both authors reconciled decisions regarding study inclusion/exclusion.

In cases where consensus could not be reached, a third investigator (MR) played a role in resolving discrepancies. The involvement of the third investigator served two purposes: first, MR independently re-evaluated the extracted data for the specific trials in question. This re-evaluation involved a thorough review of the trial characteristics and relevance to the study criteria. Second, MR actively participated in discussions between the first two investigators, offering insights and perspectives to facilitate resolution.

Throughout this process, the aim was to ensure that all decisions regarding study inclusion/exclusion and data extraction were based on a comprehensive and objective assessment of the available information. By involving a third investigator, the research team sought to minimize potential biases and enhance the reliability of the extracted data.

Data Extraction

A similar masked duplicate approach was employed to extract data regarding general study characteristics and the completeness of COS uptake. The two investigators (AVT and BD) utilized a pilot-tested Google Form to collect relevant data, ensuring consistency and accuracy in the extraction process.

The following general characteristics were recorded for each RCT: year of trial start date, National Clinical Trial number, trial continent affiliation(s), if before/after COS publication, phase of trial, recruitment status, sponsor, enrollment number, trial duration, and type of intervention. In addition, the Google Form included the domains and outcomes defined by the authors of the lung cancer COS,[13] encompassed essential parameters such as "acute complications of treatment," "degree of health," "survival," and "quality of death" (Supplementary Data 2). The method and timing of collection were recorded in the Google Form for all previously mentioned outcome measures.

If trialists used an established screening instrument (e.g., European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires-Core 30 [EORTC QLQ-C30], Functional Assessment of Cancer Therapy-Lung, Lung Cancer Symptom Scale, etc.), authors consulted the questionnaire to determine if relevant outcome measures were included. It is important to note that the use of these instruments may serve various purposes within the trials, including assessing quality of life, symptom severity, or other aspects of patient-reported outcomes.

Both investigators extracted data independently from the first five RCTs within the sample for training purposes and subsequently resolved any discrepancies. Investigators then completed data extraction for the remaining RCTs within the sample. Any inconsistencies during the extraction process were reconciled by a third investigator (MR).

Statistical Analysis

Our primary analysis used an interrupted time series analysis to assess the uptake of the COS before and after

its publication. An interrupted time series analysis is a statistical method used to assess the effect of an intervention or event on a particular outcome over time. In our study, the intervention of interest was the publication of the COS, and the outcome of interest was the adherence to the COS-defined outcomes in lung cancer clinical trials.

Interrupted time series analysis involves analyzing longitudinal data collected at multiple time points, with a clear point in time where an intervention or event occurs. By comparing the trend in the outcome variable before and after the intervention, interrupted time series analysis allows us to assess whether there is a significant change in the outcome associated with the intervention.

To measure adherence to the COS, we calculated the percentage adherence for each trial. This was determined by dividing the number of COS outcomes measured in the trial by the total number of possible outcomes as defined in the published COS. Mathematically, the formula for calculating percentage adherence is as follows:

$$Percent\ Adherence\ (COS-defined\ outcomes) = \frac{Number\ of\ COS\ Outcomes\ Measured}{Total\ Number\ of\ Possible\ COS\ Outcomes} \times 100\%$$

The mean percentage of adherence was calculated per month for all trials, allowing for only one data point per time period. To account for any potential uptake after the publication of the COS, we allocated a one-year period post-COS publication for analysis. This time frame was chosen to capture any changes or trends in adherence to COS-defined outcomes in lung cancer clinical trials.

We utilized the Newey-West method to estimate standard errors in our interrupted time series analysis. This method is well-suited for time series data analysis, as it adjusts standard errors to accommodate potential autocorrelation and heteroscedasticity in the data. By employing the Newey-West method, we aimed to ensure the accuracy and reliability of our statistical inferences regarding COS adherence trends over time.

In addition, a secondary analysis was performed using a one-way analysis of variance to assess the effects of "Continent," "Funding Type," and "Recruitment Status" on the variation in the percent of COS-defined outcomes measured. For this exploratory analysis, an alpha value of less than 0.001 was determined to be the significant threshold.

Furthermore, we calculated the Pearson correlation effect size between "Enrollment Number" and the percent of COS outcomes measured. This analysis allowed us to assess any potential relationship between trial enrollment size and the extent to which COS-defined outcomes were included in the trials.

These methodological approaches were selected to provide a comprehensive assessment of COS adherence in lung cancer clinical trials and to capture potential factors influencing adherence levels. Our statistical analyses were performed using Stata/BE 17.0 (StataCorp, LLC, College Station, TX), R (version 4.2.1), and RStudio. All original data, final reconciled data, and statistical analysis approaches were uploaded to OSF.[16]

Results

Trial Inclusions and Exclusions

Our initial search of ClinicalTrials.gov yielded a total of 11,183 clinical trials, while the ICTRP retrieved 16,794 clinical trials. Subsequent filtration on the basis of trial phase and date criteria led to the identification of 1982 RCTs. Further screening led to the exclusion of an additional 1356 trials, with 191 exclusions attributed to single-group assignment trials, the most prevalent reason for exclusion. Of the trials excluded, 166 were categorized as "wrong disease," referring to those not specifically centered on lung cancer, the primary disease of interest in the COS. These trials might have been related to different medical conditions or diseases unrelated to lung cancer. Therefore, they were deemed irrelevant to our research objectives and consequently omitted from our final sample.

Ultimately, our final data set comprised 626 eligible trials for analysis (Fig. 1).

Trial Characteristics

Our sample noted a median enrollment of 334 (interquartile range: 190–549) individuals and a median trial duration of 54 months (interquartile range: 36–79). Within our final sample, 553 studies (553 of 626;

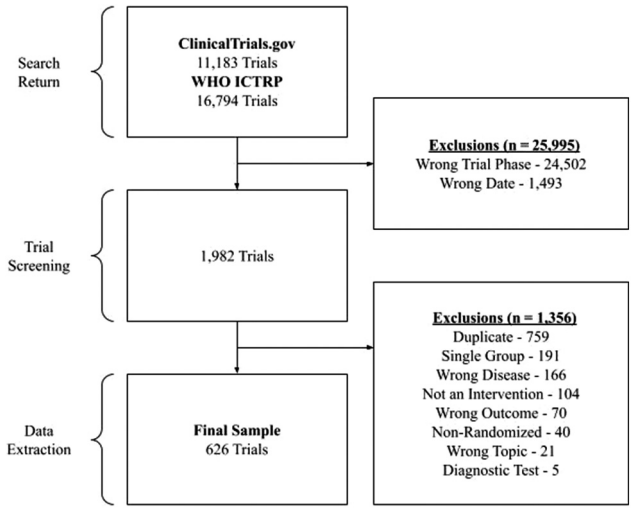

Figure 1. Study selection flow diagram. WHO ICTRP, WHO International Clinical Trials Registry Platform.

Table 1. Trial Characteristics

Characteristics	N = 626, n (%)
Year	
2020	67 (10.70)
2019	67 (10.70)
2018	63 (10.06)
2015	63 (10.06)
2021	57 (9.12)
2016	53 (8.47)
2014	49 (7.83)
2022	48 (7.67)
2017	47 (7.51)
2013	39 (6.23)
2012	32 (5.11)
2023	25 (4.00)
2011	16 (2.56)
Phase	
3	553 (88.34)
4	73 (11.66)
Continent	
Asia	291 (46.49)
Multiple	194 (30.99)
Not listed	47 (7.51)
North America	46 (7.35)
Europe	44 (7.03)
South America	2 (0.32)
Africa	1 (0.16)
Australia	1 (0.16)
Recruitment status	
Recruiting	165 (26.36)
Active, but no recruiting	121 (19.33)
Completed	114 (18.21)
Unknown	96 (15.34)
Not yet recruiting	79 (12.62)
Terminated	34 (5.43)
Withdrawn	9 (1.44)
Suspended	6 (0.96)
Enrolling by invitation	2 (0.32)
Sponsor type	
Industry	358 (57.19)
Hospital	93 (14.86)
Multiple without industry	60 (9.58)
Multiple with industry	44 (7.03)
Government	24 (3.83)
University	23 (3.67)
Nonprofit	11 (1.76)
Individual	8 (1.28)
Private	5 (0.80)
Median enrollment number (IQR)	334 (190-549)
Unknown	2
Median trial duration in mo (IQR)	54 (36-79)
Unknown	50
Type of intervention	
Multiple	326 (52.08)
Chemotherapy	203 (32.43)
Immunotherapy	38 (6.07)
Other[a]	20 (3.19)
Radiotherapy	20 (3.19)
Surgical	13 (2.08)
Targeted therapy	6 (0.96)

[a]Other: biological, nonchemotherapy, nonsurgical, or nonradiation interventions.
IQR, interquartile range.

88.34%) were phase 3 trials, while the rest (73 of 636; 11.66%) were phase 4. The most frequent enrollment status was "Recruiting" (165 of 262; 26.36%). The least common enrollment status was "Enrolling by Invitation" (two of 626; 0.32%). Many trials had an industry sponsor as the primary source of funding (358 of 626; 57.19%), with the next most common being hospital sponsorship (93 of 626; 14.86%). There were 326 trials (326 of 626; 52.08%) that used "Multiple" types of interventions, whereas only six trials focused on "Targeted Therapy" (six of 626; 0.96%). Additional information regarding trial characteristics can be found in Table 1.

Analysis of COS Uptake

We evaluated trials from September 2011 to June 2023. In the beginning (September 2011), trialists measured an average of 21.89% of the outcomes specified by the COS. Before the publication of the lung cancer COS, a significant monthly increase in COS-defined outcome measurement was noted (0.20%, 95% confidence interval [CI]: 0.01%–0.38%, p=0.04). After the publication of the lung cancer COS, there was a nonsignificant monthly decrease in COS-defined outcome measurement (0.01%, 95% CI: −0.16% to 0.19%, p=0.85). Figure 2 illustrates these findings, with a one-year grace period to allow for the uptake of the COS.

Of the 626 trials in our sample, none measured all of the COS outcomes (zero of 626; 0.00%). We found that 308 (308 of 626; 49.20%) trials used a patient-reported health-related quality of life (HRQoL) questionnaire to assess outcomes in the "Degree of Health" domain. The most frequently measured outcome was "overall survival" (574 of 626; 91.69%), followed by "treatment-related mortalities" (342 of 626; 54.63. The least-measured outcomes were: "duration of time spent in the hospital at the end of life" (10 of 626; 1.60%), "place of death" (one of 626; 0.16%), and "time between diagnosis and treatment" (zero of 626; 0.00%). Additional information regarding outcome measurements is provided in Table 2. The average percentage of measured outcomes per year stayed consistently below 50% (Fig. 3).

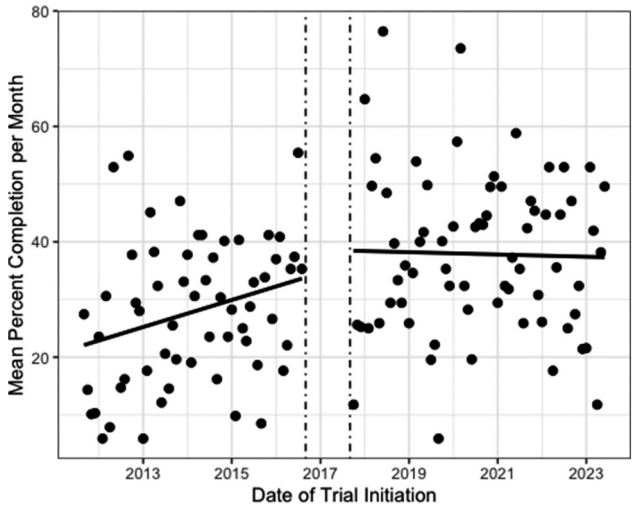

Figure 2. Interrupted time series analysis of COS-defined outcomes before and after publication, by month (September 2011–June 2023). COS, core outcome set.

Relationship Between Trial Characteristics and Outcome Selection

Our secondary analysis found a significant difference in COS-defined outcome measurements across "Continent" ($p<0.001$), "Recruitment Status" ($p<0.001$), and "Funding Type" ($p<0.001$). The effect sizes (η^2) indicate that approximately 1.4% of the variation was because of the differences between "Continent," 4% was because of the differences between "Funding Type," and 7% was because of differences between "Recruitment Status."

In addition, we performed a Pearson correlation analysis to assess the strength and direction of the relationship between "Enrollment Number" and the frequency of COS outcome measurements. The Pearson correlation coefficient indicated a significant positive correlation (r=0.19, *t*-statistic = 4.83, $p<0.001$), suggesting that as the "Enrollment Number" increases, the frequency of COS outcome measurements also increases

Table 3 provides a detailed summary of these analyses. For each characteristic, the mean and SD of COS-defined outcomes are reported, along with the *F*-statistic, *p* value, and effect size (η^2) for the one-way analysis of variance. The table also includes the *t*-statistic, *p* value, and correlation coefficient for the Pearson correlation analysis.

Discussion

Despite the establishment of the COS, our study found adherence to the COS-defined outcomes in lung cancer trials has remained consistently below 50% throughout the entire study period, from September 2011 to June 2023, highlighting the need for improvement. Our investigation found a widespread lack of adherence by trialists, with no trials measuring the outcome "time between diagnosis and treatment" and only one trial measuring "place of death." Prior research has reported the multiple potential benefits of COS adherence,[15,21,22] yet most of our observed clinical trials still overlooked some aspects of the established COS.

The significant differences observed in COS-defined outcome measurements across various trial characteristics—such as "Continent," "Recruitment Status," and "Funding Type"—highlight the influence of contextual factors on outcome selection in lung cancer trials. These findings suggest that regional differences and trial recruitment strategies may play a role in shaping the prioritization and inclusion of COS outcomes. In addition, the positive correlation between "Enrollment Number" and the frequency of COS outcome measurement indicates a potential relationship between study size and the comprehensiveness of outcome assessment. Exploring the underlying reasons behind these correlations, such as cultural or organizational differences across continents, funding influences on outcome selection, and the impact of trial scale on outcome measurement strategies, would provide valuable insights into the dynamics of outcome selection in lung cancer research.

A wide array of HRQoL questionnaires was evident in our sample, with some being more prevalent than others, likely because of their comprehensive nature or broader scope. This variation stems from the lack of standardization across lung cancer clinical trials, resulting in the development of multiple questionnaires aiming to measure the same outcomes.[23] Three frequently used questionnaires—EORTC QLQ-C30, Functional Assessment of Cancer Therapy-Lung, and the Lung Cancer Symptom Scale— had overlapping coverage of some COS measurements in our study. Outcomes in the "Degree of Health" domain—such as "HRQoL," "social functioning," "emotional functioning," "physical functioning," and "dyspnea"—were measured across all three questionnaires.[24–26] The only difference between the three surveys is that the EORTC QLQ-C30 measures the "cognitive function" outcome. The redundancy stemming from using multiple questionnaires places an unnecessary burden on the patients participating in clinical trials.[27] This burden can result in missing data owing to increased complexity in data entry management, reduced statistical power of trials, and increased patient fatigue.[27] While adopting standardized questionnaires is critical for capturing consistent patient-centered outcomes, it is also important to ensure that data is accurate and organized, thereby encouraging reliable comparisons across trials.[13] Therefore, future trials may benefit from adopting a singular and comprehensive HRQoL questionnaire that integrates elements from the COS.

The adoption of a standardized method for data collection, such as a COS, has been shown to significantly

Table 2. Frequency of Core Outcomes Measurements in Lung Cancer Randomized Controlled Trials

Outcome Set Domain	Specific Outcome Measure	N = 626
Acute complications of treatment	**Major surgical complications, n (%)**	
	Yes	21 (77.78)
	No	6 (22.22)
	Unknown	599
	Major radiation complications, n (%)	
	Yes	60 (83.33)
	No	12 (16.67)
	Unknown	554
	Major systemic therapy complications, n (%)	
	Yes	404 (68.82)
	No	183 (31.18)
	Unknown	39
Degree of health	**ECOG/WHO performance status, n (%)**	
	Yes	25 (3.99)
	No	601 (96.01)
	Global health/quality of life, n (%)	
	Yes	308 (49.20)
	No	318 (50.80)
	Fatigue, n (%)	
	Yes	197 (31.47)
	No	429 (68.53)
	Social functioning, n (%)	
	Yes	215 (34.35)
	No	411 (65.65)
	Physical functioning, n (%)	
	Yes	237 (37.86)
	No	389 (62.14)
	Emotional functioning, n (%)	
	Yes	225 (35.94)
	No	401 (64.06)
	Cognitive function, n (%)	
	Yes	185 (29.55)
	No	441 (70.45)
	Pain, n (%)	
	Yes	219 (34.98)
	No	407 (65.02)
	Dyspnea, n (%)	
	Yes	218 (34.82)
	No	408 (65.18)
	Cough, n (%)	
	Yes	162 (25.88)
	No	464 (74.12)
Survival	**Cause of death, n (%)**	
	Yes	296 (47.28)
	No	330 (52.72)
	Overall survival, n (%)	
	Yes	574 (91.69)
	No	52 (8.31)
	Treatment-related mortality, n (%)	
	Yes	342 (54.63)
	No	284 (45.37)
Quality of death	**Place of death, n (%)**	
	Yes	1 (0.16)
	No	625 (99.84)
	Duration of time spent in hospital at end of life, n (%)	
	Yes	10 (1.60)
	No	614 (98.40)
	Not applicable	2
Other	**Time from diagnosis to treatment, n (%)**	
	Yes	0 (0.00)
	No	626 (100.00)

enhance lung cancer research.[28] These enhancements manifest in more consistent and comparable data across trials, which in turn facilitate better analyses and more robust conclusions. By ensuring that key outcomes are consistently measured and reported, this standardized approach empowers physicians to deliver optimal care to patients. Nevertheless, despite the evident benefits of COS implementation, there remains a question of why trialists often overlook these standards in lung cancer research. For instance, a recent systematic review found a broad spectrum of domains and measurement timelines were used in outcome sets for women's and newborn health trials.[29] Such lack of standardization makes it difficult to compare results across trials.[29] Therefore, future lung cancer trials should prioritize the adoption of COS outcome measurements to ensure that data is consistent, comparable, and comprehensive. This strategic approach not only enhances research quality but also contributes to better patient care outcomes.

Prior studies have proposed likely reasons for poor COS adherence by clinical trial researchers, such as lack of awareness, disagreement on outcome measures, and lack of enforcement by a governing body.[30–34] A survey of pediatric postoperative pain RCT authors found that one-third of the authors were familiar with the COS for acute pediatric pain.[33] This same article hypothesized that authors did not believe the suggested COS was appropriate for their study, and therefore less likely to adhere to the

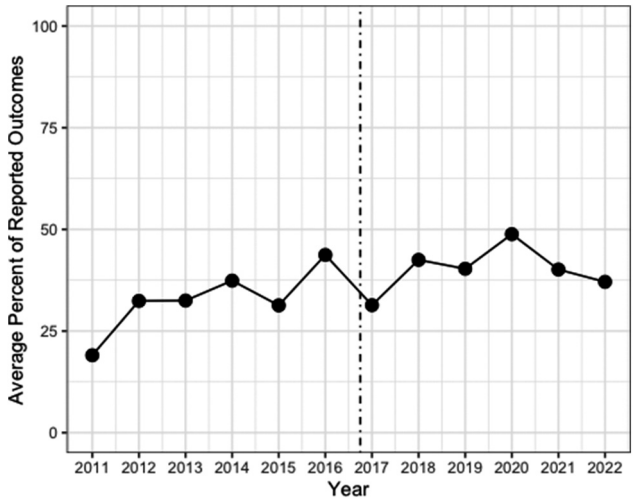

Figure 3. Mean percentage of outcomes measured, by year (2011–2023).

COS.[33] Reaching a consensus on measurable outcomes is a prominent concern in clinical trials.[29] To address this issue, Mease et al.[35] highlight the importance of inputs from both experts and patients by means of a Delphi study. Using this approach, a COS with domains encompassing aspects relevant to all parties can be developed.[35] One of the most common reasons for not following the proposed COS was the lack of regulatory guidance.[36] Previous literature has found that the proportion of trials measuring the entire rheumatoid arthritis COS rose shortly after Federal Drug Administration and European Medicines Agency regulations were introduced, which recommended measuring the same outcome points within the COS.[34,36] To combat the lack of awareness, the COMET Initiative's website lists all COS publications.[30] Addressing the concerns above and making subsequent changes to the COS is pivotal for improving adherence.

Several areas exist where COS uptake could be improved, and all parties are capable of implementing changes necessary for meaningful improvement. To provide more informed treatment decisions, it is crucial to balance the perspectives of all stakeholders, including clinicians and patients.[37] Nevertheless, when testing the efficacy of lung cancer interventions, trials tend to focus on objective measurements for disease progression—such as those in the "Survival" domain—rather than the patient-reported outcomes published in the COS. While these "Survival" outcomes are essential measurements for evaluating an intervention's efficacy and effectiveness,[13] most trials lack the valuable patient-reported outcomes that are crucial for understanding the patient's overall health.[37,38] Therefore, by emphasizing the use of patient-reported outcomes, clinical trials can capture more unique patient-centered data – ultimately leading to improved medical decisions by both the clinician and patient.[38] In addition, we suggest that Institutional Review Board members are aware of the standardized COS in their respective fields and reject any trials that do not strictly adhere to them.[33] This change will incentivize trials to observe outcomes that are not typically measured—such as those in the "Quality of Death" domain. To further improve adherence to the less frequently measured outcomes, government agencies—such as the Federal Drug Administration and European Medicines Agency—can encourage the uptake of the COS, as prior research has shown its effectiveness.[34,36] In theory, this principle could be applied to future lung cancer clinical trials, thus promoting adherence to the COS and improving clinical decision-making.

In addition, ethical concerns might arise if the lack of adherence to the COS leads to inadequate measurement of patient-centered outcomes, potentially impacting patients' well-being and the quality of their care. If certain outcomes are consistently omitted from clinical trials, it could result in biased reporting and a limited understanding of treatment effects for certain patient groups. This lack of diversity in outcomes might raise concerns about equitable access to effective treatments. Therefore, ensuring comprehensive measurement of outcomes not only enhances the reliability and validity of research findings but also upholds ethical standards by prioritizing patients' interests and facilitating informed decision-making in healthcare

Strengths and Limitations

Our study has multiple strengths with some limitations. First, we performed this study in a masked, duplicate fashion to minimize potential bias and data extraction errors.[39] Second, the investigators attended the same rigorous training sessions before starting the data extraction process. Third, an unbiased third party was consulted to resolve any discrepancies regarding data collection. Fourth, to promote reproducibility and transparency, we made our protocol, raw data, analysis scripts, and Google Form publicly available on OSF. Finally, our sample of RCTs consists of studies that date back to 2011, allowing for a fair representation of data before and after COS publication.

Although our study has major strengths in methodology, there are also some limitations that must be acknowledged. Given the focus on evaluating the uptake of the lung cancer COS, our study did not include a direct control or comparison group. While this approach aligns with the study's objectives, the lack of a control group limits our ability to draw direct comparisons and infer causality. In addition, our inclusion criteria were restricted to phase 3 and 4 trials, potentially excluding relevant data from earlier phases. This limitation may impact the generalizability of our findings to all stages of clinical trial development.

Table 3. Association Between Trial Characteristics and COS-Defined Outcomes

Characteristics	N = 626[a]	F-statistic[b]	*p* value[b]	Effect Size (η^2)[b]
Continent		14.69	**<0.001**	0.014
Africa	72.22 (NA)			
Australia	72.22 (NA)			
Multiple	47.85 (25.93)			
South America	35.29 (41.59)			
Europe	31.38 (25.50)			
Not Listed	32.51 (22.53)			
North America	30.88 (21.90)			
Asia	26.74 (21.43)			
Sponsor type		3.61	**<0.001**	0.04
Industry	38.78 (26.72)			
University	33.53 (19.96)			
Multiple without industry	32.46 (22.37)			
Government	29.81 (21.06)			
Private	29.48 (24.34)			
Multiple with industry	28.63 (22.80)			
Hospital	26.06 (20.63)			
Individual	24.89 (24.42)			
Nonprofit	23.92 (21.41)			
Recruitment status		5.40	**<0.001**	0.07
Active, but no recruiting	43.82 (26.56)			
Withdrawn	42.30 (23.42)			
Recruiting	38.07 (25.77)			
Terminated	35.23 (26.80)			
Completed	29.88 (23.19)			
Enrolling by invitation	29.41 (33.28)			
Not yet recruiting	27.25 (23.02)			
Unknown	28.64 (21.21)			
Suspended	13.51 (8.58)			

Characteristics	t-statistic[c]	*p* value[c]	Correlation Coefficient Value (r)[c]
Enrollment number	4.83	**<0.001**	0.19

Note: Boldface values represent significant *p* values.
[a]Mean (SD).
[b]One-way ANOVA.
[c]Pearson correlation coefficient.
ANOVA, analysis of variance; COS, core outcome sets.

Furthermore, we recognize the potential for misclassification in trial phases by clinical trial registries, where trials categorized under phase 1 and phase 2 may actually belong to phase 3 and phase 4. Although we implemented rigorous screening to minimize such errors, occasional misclassification may have occurred, potentially influencing the composition of our final data set. In addition, it is important to note that some trials may not be included in our study because they were not listed in the two registries we utilized. Nevertheless, considering the extensive international coverage of both the ICTRP registry and the ClinicalTrials.gov registries, the probability of significant omissions is minimal.

Conclusion

The findings of our study shed light on the formidable challenges faced in standardizing lung cancer clinical trials despite the implementation of the COS. Our analysis revealed a concerning trend of inconsistent trial adherence, resulting in significant variations in measured outcomes. These discrepancies not only hinder the reliability of data but also impact patient outcomes and the advancement of effective treatments.

Moving forward, it is imperative for all stakeholders involved in lung cancer research to adopt proactive measures toward enhancing COS uptake. This includes promoting transparency, fostering collaboration among researchers and clinicians, and advocating for standardized reporting practices. By embracing these strategies, we can pave the way for improved data reliability, enhanced comparability of trial results, and ultimately, better outcomes for patients with lung cancer.

Our study underscores the urgent need for concerted efforts to address the challenges in COS adoption and adherence within the realm of lung cancer clinical trials.

This call to action is crucial in shaping the future of research practices and ensuring the delivery of high-quality, evidence-based care to individuals battling lung cancer.

CRediT Authorship Contribution Statement

Andrew V. Tran: Investigation, Writing - original draft, Writing - review & editing, Visualization (submission of images for figure preparation).

Brody Dennis: Investigation, Writing - original draft.

Matthew Rashid: Investigation, Writing - original draft.

Kyle Fitzgerald: Conceptualization, Methodology, Software, Formal analysis, Data curation.

Garrett Jones: Conceptualization, Methodology.

Kimberly Magana: Conceptualization, Methodology.

Jay Modi: Conceptualization, Methodology.

Trevor Magee: Conceptualization, Methodology.

Shaelyn Ward: Conceptualization, Methodology.

Griffin Hughes: Software, Formal analysis, Data curation.

Alicia Ito Ford: Supervision.

Matt Vassar: Supervision, Project administration.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2024.100713.

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