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Defining a standard set of patient-centred outcomes for lung cancer

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ABSTRACT In lung cancer, outcome measurement has been mostly limited to survival. Proper assessment of the value of lung cancer treatments, and the performance of institutions delivering care, requires more comprehensive measurement of standardised outcomes.

The International Consortium for Health Outcomes Measurement convened an international, multidisciplinary working group of patient representatives, medical oncologists, surgeons, radiation oncologists, pulmonologists, palliative care specialists, registry experts and specialist nurses to review existing data and practices. Using a modified Delphi method, the group developed a consensus recommendation ("the set") on the outcomes most essential to track for patients with lung cancer, along with baseline demographic, clinical and tumour characteristics (case-mix variables) for risk adjustment.

The set applies to patients diagnosed with nonsmall cell lung cancer and small cell lung cancer. Our working group recommends the collection of the following outcomes: survival, complications during or within 6 months of treatment and patient-reported domains of health-related quality of life including pain, fatigue, cough and dyspnoea. Case-mix variables were defined to improve interpretation of comparisons.

We defined an international consensus recommendation of the most important outcomes for lung cancer patients, along with relevant case-mix variables, and are working to support adoption and reporting of these measures globally.

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#ICHOM Lung Cancer Standard Set of patient-centred outcomes: aligning global efforts to improve lung cancer care http://ow.ly/bFDR300EhY7

Introduction

Lung cancer is the most frequently diagnosed cancer worldwide, with an estimated 1.8 million new cases in 2012, comprising 12.9% of all cancers [1]. The disease accounted for an estimated 1.6 million deaths worldwide in 2012, representing the leading cause of cancer-related mortality (19.4%) [2]. While lung cancers are heterogeneous in histology and genetic profile [3, 4], the majority are advanced by the time of diagnosis. Survival is poor, with 5-year survival <20% [5, 6]. A variety of management approaches including surgery, radiation and systemic therapies may be used in lung cancer, depending on histology, stage at diagnosis and patient fitness. Both the disease and treatment can lead to symptoms with profound effects on patients' physical, social and emotional functioning. While survival outcomes are frequently collected in registries, the impact of the disease and its treatment on patients' quality of life is rarely assessed routinely.

The lack of routinely collected outcomes for lung cancer patients limits the development of value-based healthcare, where value is defined as the health outcomes achieved relative to the costs incurred. In the United States, the move towards value has been placed on an aggressive time schedule [7], and in other advanced economies, similar reforms are underway. The success of this transition depends on comprehensive measurement of outcomes to inform what works best for whom and at what cost. To date, no standard set of data exists by which to answer these questions. There are selected initiatives which are pioneering the integration of quality of life measures into routine practice [8], but these are rare. Establishment of an international standard to align existing and newly developing initiatives would ease implementation and unlock far greater global collaboration to deliver better health at lower cost.

To address this need, we convened an international multidisciplinary working group to define a recommended standard set of outcomes and corresponding baseline demographic, clinical and tumour characteristics (case-mix variables) for patients with lung cancer.

Materials and methods

The working group was convened and organised by the International Consortium for Health Outcomes Measurement (ICHOM), a nonprofit organisation focused on the development of standard sets of outcomes and case-mix variables for multiple medical conditions. ICHOM is supported by patient advocacy groups, specialty societies, hospitals, payers and governments (online supplementary material, appendix 1). The 19 members of the working group consisted of patient representatives, specialist nurses, registry experts, surgeons, medical oncologists, pulmonologists, radiation oncologists and palliative care specialists. They were invited to participate by a smaller project team (KSM, ACMvB, CS and MDP), which coordinated and guided the group's activities. Working group members represented academic centres, large teaching hospitals, registries and patients from North America, Europe, Brazil and Australia.

The goal was to define a core set of outcomes and related case-mix variables, the Lung Cancer Standard Set, that would serve as a guide for aligning existing and newly developing outcome measurement initiatives internationally. The project team performed a literature search in MEDLINE to identify outcomes and case-mix measures to guide discussions of the working group (online supplementary material, appendices 2–4). From July to December 2014, the group convened for six structured teleconferences to share evidence and expert opinions, including scope and outcome domains; outcome definitions; outcome measures including clinical data and patient-reported outcome measures (PROMs); case-mix domains; and case-mix measures. Five surveys were sent to the working group to gather feedback and make decisions on points discussed during the teleconference calls. In the survey, a structured, consensus-driven modified-Delphi method was used to debate proposals from the project team (online supplementary material, appendix 4). Using a two-thirds (66%) majority as the threshold for inclusion, the group determined which outcomes and case-mix variables were essential, and reached consensus on their precise definitions and methods for their measurement. Outcomes and case-mix variables not meeting the threshold of 66%, but >40% were discussed in the next call after the survey. A second round of voting was conducted during the call after an open discussion. If needed, additional discussion occurred before a third vote during the call. Most outcomes were decided in one or two rounds, and a minority required a

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maximum of three rounds. ICHOM had access to all the data during the project, but neither ICHOM, its funders nor the funders of this project had editorial control over the final publication.

Results

Condition scope and treatments covered

The Lung Cancer Standard Set was designed for all patients with newly diagnosed lung cancer, including nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC), treated with curative or palliative intent (including best supportive care). While treatment modalities and prognosis may vary with respect to NSCLC *versus* SCLC, we felt that both NSCLC and SCLC patients would value outcomes such as survival, degree of health and treatment toxicity. Creating a common standard set for use with both NSCLC and SCLC would also allow future analyses that could compare the relative importance of key outcomes by histology. In addition, from a practical point of view of inspiring institutions and lung cancer clinicians to adopt the set, it was deemed more practical to create one instead of multiple specific sets for each histological subtype of lung cancer. Based on epidemiological data, we expect that this scope includes 1.9 million individuals with lung cancer worldwide [1]. Treatments include surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy (table 1). For surgery and radiotherapy, treatments are specified by site, with distinctions between the primary tumour, brain metastases and metastases of other sites. Only details felt to be essential for the analysis of subgroups of patients were included.

Lung Cancer Standard Set: outcomes

Survival

Duration of survival is crucial for patients with lung cancer, a disease with high mortality rates due to both tumour burden and morbid therapies [9]. Our working group reached consensus that overall survival, cause of death and treatment-related mortality were essential measures of survival for the Lung Cancer Standard Set (table 2 and online supplementary material, appendix 4). Although progression-free survival is an intermediate end-point commonly collected in the clinical trial setting as a measure of disease control, this outcome was excluded from the set as it was deemed potentially unreliable in routine practice due to ascertainment bias [10], and ultimately less important than overall survival. Ideally, survival outcomes would be routinely collected throughout the course of care, but annual querying of national death indices where available is recommended to validate local statistics (figure 1).

Complications

Treatment complications are a significant cause of morbidity and mortality in lung cancer, and can profoundly impact patient preferences, outcomes and costs [11]. Our working group reviewed treatment-related toxicity scales in common practice today. For patients treated with surgery, the consensus was to use the Clavien–Dindo classification [12]. We selected a simplified version of the Common Terminology Criteria for Adverse Events version 4 for patients receiving systemic therapy and/or radiotherapy [13]. This platform was designed as a comprehensive grading system for identifying adverse effects of cancer treatment and indicating their severity, and is commonly used in clinical trials. We propose a modified version to simplify and expedite data collection, which assigns the event to a general category (constitutional, skin, bone marrow suppression, infection, cardiovascular, lung, gastrointestinal, hepatic, renal, neurological or other). We recommend collecting all grade 3 or higher toxicities that occur during or within the first 6 months following the initiation of each treatment course for lung cancer (figure 1).

Degree of health

Performance status is a strong independent predictor of survival in lung cancer [14]. Our working group recommends measuring performance status per the Eastern Cooperative Oncology Group (ECOG) and World Health Organization (WHO) scoring method, ranging from 0 to 5, as it provides clinician-reported data to correlate with patient-reported outcomes. Baseline, pretreatment performance status will also be captured as a case-mix variable, allowing detection of change in performance status over time.

Given the importance of health-related quality of life (HRQoL) in patients with lung cancer [15] and its prognostic impact [16], PROMs have been increasingly developed and implemented [17]. Lung cancer is associated with burdensome symptoms, and often requires treatments associated with significant toxicity. General HRQoL domains that we advocate collecting include global health status/quality of life, pain, fatigue and physical, social, emotional and cognitive function (table 2 and online supplementary material, appendix 4). Lung cancer-specific HRQoL domains deemed essential included dyspnoea and cough.

Common existing PROMs that cover these domains were reviewed by the group (online supplementary material, appendix 5). PROM selection was thoroughly deliberated, as was our goal to provide clear advice to newly developing initiatives, with the hope of ultimately aligning existing measurement efforts. Our consensus recommendation included one general and one lung cancer-specific instrument to adequately

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TABLE 1 Summary of International Consortium for Health Outcomes Measurement Lung Cancer Standard Set of treatment approaches and case-mix variables

	Patient population	Measure	Supporting information	Timing	Data source[#]
Treatment approaches included	All patients	Surgery Radiotherapy Chemotherapy Targeted therapy Immunotherapy Other		Update at least annually	Clinical
Case-mix variables					
Demographic factors	All patients	Age	Date of birth	Baseline	Clinical or patient-reported
		Sex	Sex at birth		Patient-reported
		Ethnicity	Determined by country		
		Educational level	Level of schooling completed[¶]		
Baseline clinical factors	All patients	Weight loss	Unintentional weight loss[+]		
		Comorbidities	Modified SCQ[§]		
		Patient-reported health status	Tracked *via* EORTC QLQ-C30 and EORTC QLQ-LC13		
		Smoking status	Smoking status at diagnosis[f]		
		Performance status	ECOG/WHO scale for performance status		Clinical
	Patients undergoing surgery	Pulmonary function	Absolute and predicted FEV_1		
Baseline tumour factors	All patients	Basis of diagnosis	Diagnosis by clinical, histological or cytological assessment		
		Histology	Lung cancer histology (including small cell lung cancer, adenocarcinoma, squamous cell carcinoma)		
		ALK translocation	Presence of ALK translocation		
		EGFR mutation	Presence of activating *EGFR* mutation		
		Clinical stage	Clinical stage per UICC/IASLC/AJCC 7th edition		
		Pathological stage	Pathological stage per UICC/IASLC/AJCC 7th edition	After biopsy/surgery	
Treatment factors	All patients	Treatment intent	Curative or palliative treatment intent[##]	At time of treatment decision	
		Completed treatment	Completed treatment with or without dose reduction	After treatment	

SCQ: Self-administered Comorbidity Questionnaire; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: core quality of life questionnaire; QLQ-LC13: lung cancer-specific quality of life questionnaire; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; FEV_1: forced expiratory volume in 1 s; ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; UICC: Union for International Cancer Control; IASLC: International Association for the Study of Lung Cancer; AJCC: American Joint Committee on Cancer. [#]: reflects the way case-mix variables and outcomes are collected: clinical data include data abstraction and clinician reports; patient-reported data include patient-reported outcome measures (*e.g.* EORTC QLQ-C30 and EORTC QLQ-LC13) and other relevant patient-reported questions; [¶]: level of schooling defined in each country as per the International Standard Classification of Education; [+]: any unintentional weight loss preceding the lung cancer diagnosis; [§]: "Have you ever been told by a doctor that you have any of the following? I have no other disease, heart disease (*e.g.* angina, heart attack or heart failure), high blood pressure, leg pain when walking due to poor circulation, lung disease (*e.g.* asthma, chronic bronchitis or emphysema), diabetes, kidney disease, liver disease, problems caused by stroke, disease of the nervous system (*e.g.* Parkinson's disease or multiple sclerosis), other cancer (within the last 5 years), depression, arthritis (select all that apply)"; [f]: never-smoker (<100 cigarettes in lifetime), ex-smoker (stopped ⩾1 year before diagnosis) or current smoker; [##]: palliative treatment includes best supportive care or treatment for oligometastatic disease.

cover the prioritised domains. The heterogeneous nature of lung cancer presentations challenged us to pick from a variety of well-validated PROMs and outcome definitions, many of which captured the most important domains. Our working group ultimately selected the European Organisation for the Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) [18] and its corresponding lung cancer-specific module (QLQ-LC13) [19], since these best covered the domains we considered most important. These

TABLE 2 Summary of International Consortium for Health Outcomes Measurement Lung Cancer Standard Set of outcomes

Outcome category	Patient population	Measure	Supporting information	Timing	Data source[#]
Other	All patients	Time from diagnosis to treatment	Diagnosed using pathology: starting first treatment	When treatment begins	Clinical
Acute complications of treatment	All patients receiving surgical resection	Major surgical complications	Presence or absence of grade ⩾3 event by Clavien–Dindo classification	Update at least annually	Clinical
	Patients with radiation therapy	Major radiation complications	Presence or absence of grade ⩾3 CTCAE version 4 complication, including name of the adverse event		
	Patients with systemic therapy	Major systemic therapy complications	Presence or absence of grade ⩾3 CTCAE version 4 complication, including name of the adverse event		
Degree of health	All patients	ECOG/WHO performance status	ECOG/WHO scale for performance status	1 year post-initiation of treatment; tracked annually for life	Clinical
		Global health status/ quality of life	Tracked *via* EORTC QLQ-C30	Baseline; 3 months post-initiation of treatment; 6 months post-initiation of treatment; 1 year post-initiation of treatment; tracked annually for life	Patient-reported
		Fatigue			
		Social functioning			
		Physical functioning			
		Emotional functioning			
		Cognitive function			
		Pain	Tracked *via* EORTC QLQ-C30 and EORTC QLQ-LC13		
		Dyspnoea	Tracked *via* EORTC QLQ-LC13		
		Cough			
Survival	All patients	Cause of death	Death attributed to lung cancer on death certificate	1 year post-initiation of treatment tracked annually for life	Administrative data (death registry)
		Overall survival	Date of death		
		Treatment-related mortality	Death attributable to lung cancer treatment within 30 or 90 days		Clinical
Quality of death	All patients	Place of death	Where patient died	1 year post-initiation of treatment; tracked annually for life	Administrative data (death registry)
	All patients with end-stage disease	Duration of time spent in hospital at end of life	Number of days patient spent in hospital or ICU in last 30 days		Clinical

CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: core quality of life questionnaire; QLQ-LC13: lung cancer-specific quality of life questionnaire; ICU: intensive care unit. [#]: reflects the way case-mix variables and outcomes are collected: clinical data include data abstraction and clinician reports; patient-reported data include patient-reported outcome measures (*e.g.* EORTC QLQ-C30 and EORTC QLQ-LC13) and other relevant patient-reported questions.

validated instruments are internationally recognised, widely used in a variety of languages, feasible to implement and well studied, with scores that can be clinically interpreted [20, 21]. While the EORTC has a separate questionnaire assessing the HRQoL of patients in the palliative care setting (QLQ-C15-PAL) [22], the same domains are captured in the EORTC QLQ-C30 and therefore it was felt to be sufficient.

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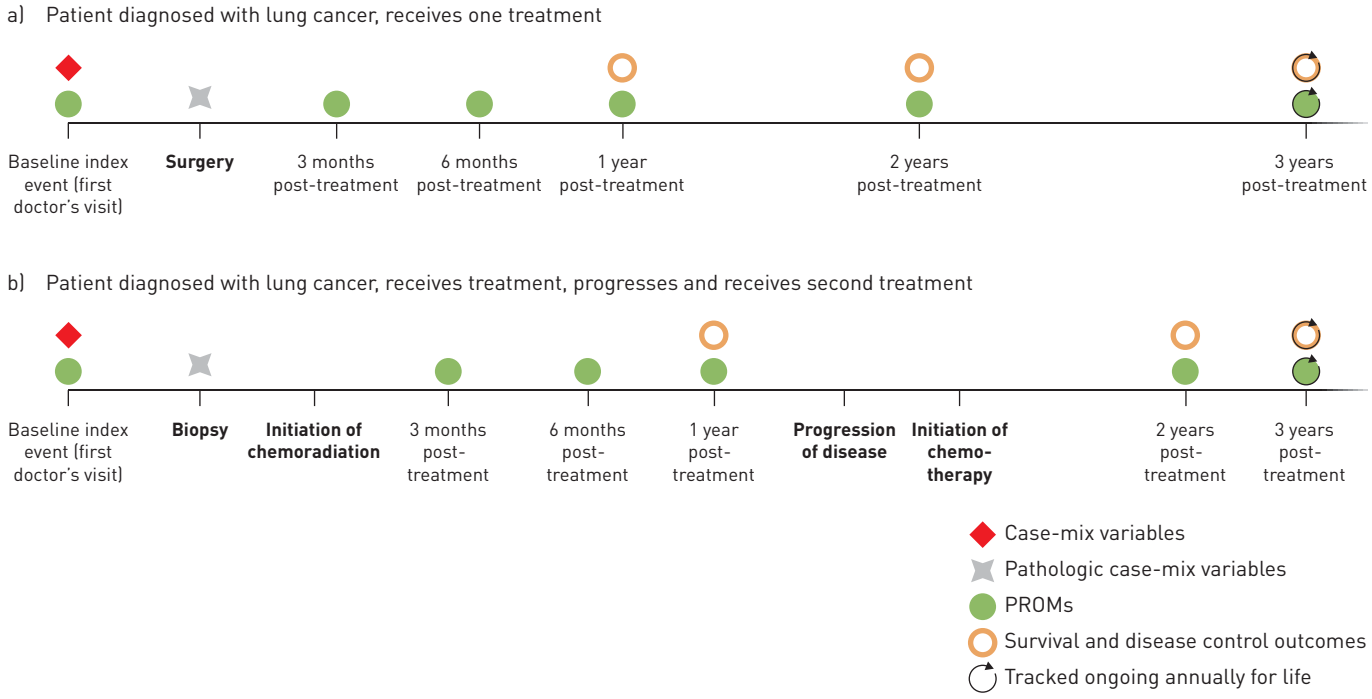

FIGURE 1 Sample timelines illustrating when case-mix variables and key outcomes should be collected for patients treated with different modalities, including a) surgery or b) multiple treatments with definitive chemoradiation followed by chemotherapy after disease progression. These timelines are intended to represent the outcome data collection points for possible treatment paths and not to advocate any particular treatment approach. PROMs: patient-reported outcome measures.

For institutions with compelling reasons to use other validated PROMs, our recommendation is to collect data on the equivalent domains at the same time points. We eagerly anticipate the development of algorithms enabling conversion of commonly used lung cancer PROMs to a standard scoring system, as has been achieved in other diseases [23].

We recommend assessing patient-reported outcomes prior to treatment as a baseline (or at diagnosis if no treatment was pursued), at 3, 6 and 12 months following initiation of treatment, and then annually (figure 1). We recognise that the burden of answering 43 items from EORTC QLQ-C30 and EORTC QLQ-LC13 at each interval may be significant for some patients. However, both the clinical and patient representatives in the working group felt that all these domains were essential and if used in the process of clinical care, would be accepted by patients. This position is bolstered by research suggesting that respondent satisfaction is more directly linked to the salience of questions than their length [24]. We also anticipate that in time computer-adaptive PROMs will decrease respondent burden while providing similar domain coverage [25].

The working group recognised that patient wellbeing can change rapidly and profoundly in this population with frequently advanced cancer. Thus, where feasible, we encourage more routine measurement of PROMs in clinical practice as regularly as possible to complement the defined time points.

Other outcomes

Previous studies have demonstrated that treatment delays are prognostic in lung cancer [26, 27]. We therefore recommend collecting the time from diagnosis of lung cancer to initiation of treatment. For consistency, we recommend defining the date of diagnosis in accordance with the hierarchy established by the European Network of Cancer Registries, with date of hospital admission or outpatient consultation being used in cases where no histological or cytological confirmation of malignancy was obtained [28].

Quality measures at the end of life

Quality of end-of-life care is an important consideration in lung cancer. Outcomes such as frequent hospitalisations and intensive care unit (ICU) admissions near the end of life have been assessed, and suggest improper use of aggressive intervention [29]. It is less clear whether any treatment near the end of life should be considered a marker of poor quality, as some procedures or therapies may be effective in palliating distressful symptoms. Appropriate palliative care has been shown to be associated with improved

quality of life and a reduced likelihood of aggressive care [30]. We reviewed existing measures used to assess the quality of the death and dying process. Although we desired a patient- or caregiver-reported measure, existing options were not found to be suitable for widespread use [31]. As a proxy, our group recommends capturing place of death, *i.e.* in a hospital, care home, hospice or the patient's own residence as well as the duration of time spent in hospital, including in the ICU, in the last 30 days of life.

Case-mix variables

Baseline demographic, clinical and tumour factors are associated with survival and other outcomes in lung cancer. As outlined in table 1, the working group identified the baseline case-mix variables thought to be essential for risk adjustment to enable meaningful comparisons between patients. Given the number of potential variables associated with clinical outcomes following treatment for lung cancer, the group focused on the most established essential demographic, clinical and tumour factors (online supplementary material, appendix 4). Where applicable, we recommend that these case-mix variables be collected prior to treatment initiation.

Specifically, we recommend collecting the following demographic factors: age, sex, ethnicity and education level. While a key determinant of health outcomes in the lung cancer population [32], socioeconomic status (SES) is difficult to capture and quantify for a variety of reasons, including patient reluctance to disclose financial details and the challenge of accurately encapsulating a complex, multifactorial determinant of health within a single metric [33]. We recommend collecting the patient-reported highest level of education as a surrogate measurement of SES [33], as patients generally feel comfortable reporting this information and it can be compared across countries using the International Standard Classification of Education [34].

The working group also recommends that ethnicity data be collected, deferring to local standards for its definition, given the variance in population characteristics globally.

We advocate the collection of the following clinical factors: baseline ECOG/WHO performance status, unintentional weight loss, smoking status (defined as never smoker (<100 cigarettes in lifetime), ex-smoker (stopped $\geqslant$1 year before diagnosis) or current smoker) and pulmonary function as measured by the absolute and predicted forced expiratory volume in 1 s, baseline patient-reported health status as measured by the EORTC QLQ-C30 and QLQ-LC13 and comorbidities (table 1). Our working group endorsed the use of the Modified Self-Administered Comorbidity Questionnaire (SCQ) [35] to collect a list of comorbid diseases. The SCQ has been shown to predict functional outcomes as well as the medical record based Charlson Comorbidity Index, and better predict quality of life [36].

Baseline tumour factors to be recorded are clinical and pathological stage, histology, activating epidermal growth factor receptor mutation status, anaplastic lymphoma kinase translocation status and clinical *versus* pathological (histological or cytological) basis of diagnosis.

For patients undergoing treatment, our working group recommends collecting additional data on treatment intent (curative *versus* palliative, with the latter including best supportive care) and whether treatment was completed. We recognise that therapies for oligometastatic disease may not clearly constitute curative *versus* palliative treatment, and recommend that this type of treatment be classified as palliative for consistency in data collection.

Data collection

The long-term goal of ICHOM is to facilitate the collection and aggregation of outcomes and case-mix data across international institutions and registries to support quality improvement, cost reduction and comparative effectiveness research. To improve the consistency in which international institutions and registries collect these data, we have recommended data sources for each outcome and case-mix variable, along with data specifications (response options, coding instructions, *etc.*). A reference guide including sample questionnaires and a data dictionary that further describes each measure, its precise definition, inclusion and exclusion criteria, numerical and categorical response options and potential data sources is freely available on the ICHOM website (www.ichom.org/project/lung-cancer/).

Most countries currently lack the national infrastructure to collect all or part of this dataset. We suggest that individual institutions take the first step in piloting data collection and focus step-wise on including the full set of recommended outcome domains over time. The ICHOM experience in localised prostate cancer, which began implementation within select institutions and registries and now forms the base of a global outcomes collaborative facilitated by the Movember Foundation, suggests how this can be achieved [37].

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Discussion

Transparent measurement of outcomes and costs has the potential to align patients, providers and payers towards a common goal of improving the value of care for lung cancer patients. A current barrier to the adoption of value-based healthcare is the absence of standardised outcomes that are meaningful to patients [38]. This international multidisciplinary working group defined a standard set of patient-centred outcomes, along with corresponding case-mix variables, which can enable providers to measure the value of care they deliver for their patients.

The recommendations of the set reflect the opinion of a selected group of experts and patient representatives. Using extensive literature reviews, and applying a Delphi technique to document our decision-making process, we strived to achieve a high level of transparency. However, it is important to recognise that a different group of participants could have agreed on different recommendations. In a similar vein, the conclusion of which outcome domains are the most important to be tracked in lung cancer patients was informed primarily by the experience of the two patient representatives and working group members, with some augmentation by the patient-reported outcome literature. It is important to note that the set is a foundation and should not limit the inclusion of additional treatment-related and process details to support local research and quality improvement efforts.

This recommendation is a starting point, and time and experience will be needed to refine the set towards a true global standard. Although many aspects of the set have been validated and implemented in research settings (*e.g.* the EORTC questionnaires), the set as a whole has not yet been implemented or validated. Members of this working group have begun pilot phase adoption, and their implementation experience, alongside others, will inform regular revisions of the set. A steering committee, composed of these pilot implementers among others from the working group, will govern the set, clarify definitions as appropriate and review and approve proposed revisions on an annual basis. We already anticipate several key topics to be addressed in the future: new prognostic biomarkers and therapies based on new molecular targets [39], improved measures for assessing the quality of death and dying, new PROMs that improve precision while maintaining domain coverage, and feedback of feasibility and reliability of data definitions by early implementers.

It is important to note that in in many settings, particularly in low- and middle-income countries, the scope of this dataset is large and feels far from feasible. For this reason, the working group considers the set as a future goal, rather than a threshold by which other initiatives are deemed inadequate. We recognise the importance of learning from early adopters to address validation, feasibility and data analysis to guide subsequent adoption. These efforts will be supported by continued progress in information and communication technology that is already making similar data collection more streamlined and affordable [40].

We also recognise the protection and privacy concerns of international data aggregation, and are reassured by multinational clinical trials that commonly address this issue successfully. Pilot efforts of aggregating data collected in registries or routine care are currently underway in localised prostate cancer, hip and knee osteoarthritis and cataracts, the former led by the Movember Foundation and the two latter by ICHOM, which will inform the feasibility of future efforts.

We have defined here a consensus recommendation of outcomes and case-mix variables to be collected for lung cancer patients in routine clinical practice. We believe this set is an important step in enabling more institutions internationally to measure, compare and improve the outcomes of their lung cancer care.

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