Development of an updated, standardized, patient-centered outcome set for lung cancer

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Abstract (max 250 words)

Background: The European Health Outcomes Observatory (H2O) initiative aimed to develop an updated patient-centered core outcome set (COS) for lung cancer, to capture the patient perspective of the impact of lung cancer and (novel) treatments using a combination of patient-reported outcome (PRO) instruments and clinical data as a means to drive value-based healthcare.

Material and methods: An international, multidisciplinary expert team (n=17) reviewed potential outcomes generated through a literature review. A broader group of patients/patient representatives (n=31), healthcare professionals / academic researchers (n=83), pharmaceutical industry representatives (n=26), and health authority representatives (n=6) participated in a Delphi study. In two survey rounds, participants scored the relevance of outcomes from a preliminary list. The threshold for consensus was defined as ≥70% of participants scoring an outcome as 'highly relevant'. In concluding consensus-meeting rounds, the multidisciplinary expert team finalized the COS.

Results: The preliminary list defined by the core group consisted of 102 outcomes and was prioritized in the Delphi procedure to 64 items. The final lung cancer COS includes: 1) case-mix factors (n=27); 2) PROs related to health-related quality of life (HRQoL) (n=26); 3) clinical outcomes (n=11). Patient-reported symptoms not included in the 2016 ICHOM lung cancer set were insomnia, nausea, vomiting, anxiety, depression, lack of appetite, gastric problems, constipation, diarrhoea, dysphagia, and haemoptysis.

Conclusions: The COS will support the adoption and reporting of lung cancer clinician-reported measures and PRO measures, in a standardized way across Europe and empower patients with lung cancer to better manage their health care.

Introduction

Lung cancer is the second most commonly diagnosed cancer type worldwide and remains the leading cause of cancer-related mortality, with 2.2 million new cases and 1.8 million deaths in 2020(1). Lung cancer is often detected at an advanced stage, which contributes to a poor overall 5-year survival rate of only 15% in developed countries (2). The two histological lung cancer types are small cell lung carcinoma (SCLC), in 15% of all lung cancers, and non-SCLC (NSCLC), in 85% of all lung cancers (3).

In the past decade, there have been significant advances in the treatment of NSCLC with gradual improvements in survival(4, 5). The discovery of oncogenic drivers of cancer allowed to develop targeted treatments for patients with specific molecular aberrations, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations, among others (6). Moreover, immune checkpoint inhibitors that target e.g. programmed death-1 (PD-1) or programmed death ligand-1 (PD-L1), have been approved by health regulatory authorities worldwide and are now commonly used to treat locally advanced and metastatic NSCLC (7). For SCLC, chemotherapy remains the standard treatment, but advances in immunotherapy for SCLC are on the rise (8). While both targeted therapy and immunotherapy hold promise to improve efficacy of lung cancer treatment and are labelled safe, the treatment-related side effects and its impact on health-related quality of life (HRQoL) require careful evaluation to improve care for a growing population of lung cancer patients.

With the increased popularity of value-based healthcare (VBHC), healthcare systems worldwide have shifted their focus to improve patients' value. In VBHC, health outcomes are utilized to facilitate shared decision making, improve quality of care and reduce healthcare costs (9). In 2016, the International Consortium for Health Outcomes Measurements (ICHOM) aimed to standardize measurements for VBHC in patients with lung cancer. A set of outcomes, corresponding baseline demographics and clinical and tumor characteristics was developed (10). The ICHOM lung cancer set was designed for all newly diagnosed lung cancer patients, including NSCLC and SCLC, treated with curative or palliative intent and all treatment modalities (10).

At the time of development of the 2016 ICHOM lung cancer set, the main first-line treatment modalities for lung cancer were surgery, radiotherapy and chemotherapy (11). Hence, (long-term) side effects included in the 2016 set are related to traditional therapies and only include fatigue, pain, dyspnea and cough (10). However, as immuno- and targeted therapies became standard of care for both first and second-line treatment of NSCLC in recent years, a broad range of treatment-related

sequelae are nowadays reported by lung cancer patients, such as joint and muscle pain, insomnia, back pain, itching and dry skin, and vision changes (12, 13).

We aimed to develop an updated, patient-centered Core Outcome Set (COS) for lung cancer, to capture the patient perspective of the impact of cancer and novel treatments including immunotherapy and targeted therapy, using a combination of patient-reported outcomes (PRO) and clinical outcomes (14). This study is part of the Health Outcomes Observatory (H2O) project. H2O has been designed to drive VBHC in Europe by improving the sustainability of health care systems and to help health care providers (HCPs) optimize care delivery and use their resources around outcomes that matter to patients. The updated lung cancer COS will form the basis of digital tools that allow patients to measure their symptoms and HRQoL in a standardized manner across Europe. The patient-reported data will be integrated with clinical outcomes and support the communication between patients, physicians and other HCPs and align on the right course of action (14).

Methods

As described previously (14), a modified Delphi methodology was developed within the H2O project by representatives from relevant stakeholder groups, including patients, HCPs, health authority representatives, researchers and pharmaceutical industry employees. The final agreed process include: 1) reviewing and critically appraising the existing standards using a literature review and discussions in an expert multidisciplinary team; 2) conducting a Delphi study with a broader reference group; and 3) holding final consensus meetings(14). The Core Outcome Measures in Effectiveness trials (COMET) protocol (15) was used to refine the procedure further and our protocol was publicly registered in the COMET database (https://www.cometinitiative.org/Studies/Details/1833).

Local execution of the Delphi study and consensus meeting was approved by the Netherlands Cancer Institutional Review Board (IRBd21-148). Formal ethical approval was not required for this study because the Dutch Medical Research (Human Subjects) Act did not apply.

Review of existing standards

Existing core outcome sets (COS) and outcome measures for lung cancer or cancer in general were identified and mapped through a rapid scoping review (16). The COMET database was used to search for studies published on COS for clinical practice in cancer populations (www.cometinitiative.org). In addition, MedLine and EMBASE were searched for lung cancer

specific and cancer generic outcome sets and measures, using the following search terms: 'lung cancer' OR 'cancer' AND 'outcome set' OR 'questionnaire' OR 'patient reported outcome' OR 'quality of life'. No limits on date, language, subject or (lung) cancer type were placed on the database search. The search was conducted in December 2020. Outcomes were summarized into three main domains: case-mix variables, HRQoL outcomes and clinical outcomes.

An international expert multidisciplinary team of patient(representative)s multidisciplinary HCPs, public researchers, and pharmaceutical industry representatives was established using 'snowball sampling'. We took into account diversity, equity and inclusiveness i.e. gender, sociodemographic, geographic, cultural background/ethnicity. In four online meetings convened in February-March 2021, the expert multidisciplinary team reviewed the outcomes list generated through the rapid scoping review. Prior to each meeting, team members scored the relevance of each item on a 9-point Likert scale on an Excel sheet (17). Consensus to include an outcome in the preliminary outcome list was reached if ≥50 % of respondents scored the outcome as critically important (score 7-9). Items were excluded if ≥50% rated the outcome as of limited importance (score 1-3).

Delphi study

Members of the expert multidisciplinary team and contributors of the H2O project representing the four countries where the COS will be initially implemented (i.e. Austria, the Netherlands, Germany and Spain) identified stakeholders from the four stakeholder groups described previously (14). As defined previously(14), in the Delphi study participated 1) patients/ patient representatives; 2) health care professionals / academic researchers; 3) pharmaceutical industry representatives; and 4) health authority representatives. We aimed to include at least 25 participants per stakeholder group to ensure stable outcomes of the Delphi rounds (18). The main focus was to include stakeholders from the H2O countries; however, another country of residence was not excluded.

Prior to the Delphi survey rounds, the preliminary outcome list with outcome definitions, lay descriptions of each outcome and domain names were reviewed by four lung cancer patient representatives for comprehensiveness and completeness. Stakeholders were approached via e-mail to participate in a two-round Delphi exercise. The web-based DelphiManager software program (19) was used to obtain online informed consent, collect background data of participants (age, sex, country of residence, experience with outcomes, educational level, year of diagnosis [only for patients] and years of working experience [for the other stakeholder groups]) and administer the

Delphi voting rounds. The Delphi survey was available in English, Dutch, German and Spanish. The outcome list was translated from English to the other languages using a translation program and was checked for accuracy and adapted by native speakers. Each Delphi round was open for four weeks, and reminders were sent via e-mail to non-responders after one week.

In the first Delphi voting round, participants were asked to rate all outcomes based on their importance on a 9-point Likert scale, with scores 1-3 indicating 'not that important', scores 4-6 indicating 'important but not critical', and scores 7-9 indicating 'critical' (17). If participants felt that they did not have the expertise to score a particular outcome, they could select 'unable to score'. Participants were also provided with the opportunity to add new outcomes they thought were missing from the list(15). The suggested outcomes were then rated by the expert multidisciplinary team on a 1-9 scale and were included in the second round if ≥50% of respondents agreed that an outcome was critically important (7-9). These new outcomes were also translated into the respective languages. In the second Delphi voting round, participants' own ratings from the first round were shown and the ratings in each stakeholder group were presented in histograms created in R (20). Participants were asked to review their own ratings from the first Delphi round, and optionally change their ratings while keeping in mind the ratings of the other stakeholders. Participants were also asked to rate the new outcomes that were added in the first round.

Consensus meetings

After completing the Delphi rounds, two online consensus meetings were organized with the expert multidisciplinary team to reach a final agreement on the outcomes to be included in the COS. We also considered overlapping items and discussed the ideal frequency of measuring patient-reported and clinical outcomes. The initial expert multidisciplinary team was enriched with interested Delphi participants from patient organizations and regulatory bodies to ensure representation of all stakeholder groups. The pre-defined consensus threshold to include items in the final COS was ≥70% (scores 7-9) in all four stakeholder groups (15). The final COS was summarized and approved by the expert multidisciplinary team members.

Results

Review of existing standards

Our searches in the COMET database, Medline and Embase retrieved two lung-cancer specific COS(10, 21), and three generic COS for cancer patients(22), cancer survivors (23)and nursing

patients(24). In addition, a PRO-CTCAE development for adolescents (25), and a review of patient-reported outcome measures (PROMs) for lung cancer (26) were found. Further, a lung-cancer specific subset of the PRO version of the common terminology criteria for adverse events (PRO-CTCAE)(27) and PROM development of an EORTC survivorship module (28) were not yet published at the time of the of the literature search but were deemed as relevant by the expert multidisciplinary team. Because of our parallel development of a COS for metastatic breast cancer within the H2O project (https://www.cometinitiative.org/Studies/Details/1833), non-cancer specific items from those searches were also considered for standardization purposes (29, 30). All outcomes retrieved from the COS and PROMs were summarized with removal of duplicate items. A total of 167 items (36 case-mix variables, 118 HRQoL outcomes and 13 clinical outcomes) were included in a draft outcome list for review by the expert multidisciplinary team.

An expert multidisciplinary team of 17 members, including patient representatives (n=3), pulmonologists (n=2), radiation oncologists (n=2), a lung surgeon (n=1), a medical oncologist (n=1), nurse specialists (n=2) academic researchers (n=4) and pharmaceutical industry representatives (n=2) was established, representing 7 European and 1 non-European countries. In addition to the outcomes obtained through literature review, 13 items (6 case-mix variables, 3 HRQoL outcomes and 4 clinical outcomes) were suggested by expert multidisciplinary team members in the meetings. Through review by the team, 79 items (37 case-mix variables; 35 HRQoL outcomes and 7 clinical outcomes) were included in the preliminary outcome list to be used in the Delphi study. Table 1 summarizes the ratings of the expert multidisciplinary team members on the preliminary outcomes set that were subsequently included in the Delphi survey.

Delphi study

A total of 146 stakeholders participated in the first Delphi round, of whom 31 patients/ patient representatives (21%), 83 health care professionals/ academic researchers (70 HCPs, 48%; 13 academic researchers, 9%), 26 pharmaceutical industry representatives (18%), and 6 representatives from health authority/ regulatory agencies (4%), representing 8 European and 4 non-European countries. Overall, the mean age of participants was 56.2 years, the majority (64%) were female, almost half had much experience with health outcomes (46%), and nearly a third (31%) participated in one of the working groups of the H2O project. Patients were diagnosed on average 5.2 years ago, and the other stakeholders had 13.7 years of professional experience in the current field (Supplementary Table 1). One-hundred-nineteen stakeholders (82%) also participated in the second

Delphi round (26 patients/patient representatives, 84%; 66 HCPs/ academic researchers, 80%; 22 pharmaceutical industry representatives, 85% and 5 health authority/regulatory representatives, 83%).

The Delphi survey ratings with relevance scores of 7-9 by stakeholder group are summarized in Supplementary Table 2. In the first round, consensus (≥70%) was reached in all stakeholder groups for 19 items (13 case-mix variables; 1 HRQoL outcome; 5 clinical outcomes). In addition, 32 new outcomes were suggested by Delphi participants, of which 24 (5 case-mix variables; 15 HRQoL outcomes; 4 clinical outcomes) were deemed as relevant (≥50%) by the expert multidisciplinary team (Table 1). In the second round, consensus (≥70%) was reached in all stakeholder groups for 35 items (22 case-mix variables; 3 HRQoL outcomes; 10 clinical outcomes).

Consensus meetings

In two concluding consensus meetings, a multidisciplinary stakeholder group (n=15), of patient representatives (n=3); HCPs (n=4); researchers (n=4), industry representatives (n=2) and health authority/regulatory representatives (n=2) agreed to ease the consensus criterion to agreement (≥70% in and ≥15% out) in the three main stakeholder groups because of a very small (n=6) stakeholder group of health authority and regulatory representatives. Furthermore, because of the patient-centeredness of the H2O project, it was agreed to include all HRQoL outcomes with agreement in patients/ patient representatives ≥70% if there was also ≥60% agreement in any of the other larger stakeholder groups (i.e. HCP/academics or pharmaceutical industry representatives). There were a few notable exceptions: the inclusion of gender (sex) as this case-mix variable was deemed as highly relevant by the expert multidisciplinary team in spite of the low agreement (round 2: 44%, 48%, 67% and 60% respectively); the inclusion of financial impact because of its high relevance to patients (round 2: 80%); and the exclusion of ERCC1 and RRM1 genes because of a lack of relevance for lung cancer and no routine measurement in centres participating in the project. Furthermore, ‘mental health’ and ‘perceived mobility’ were excluded because of overlap with ‘emotional functioning’ and ‘mobility’, respectively.

In total, 64 outcomes were included in the lung cancer COS (27 case-mix variables; 26 HRQoL outcomes; 11 clinical outcomes), of which 31 items (5 case-mix and 26 HRQoL) are patient-reported and 33 are clinician-reported. The final COS with supporting descriptions is shown in Table 1.

It was also agreed to adapt the timeline for frequency of measures from the 2016 ICHOM set (10) to standardize the measurements for all treatment schedules. It also states to administer treatment-related case-mix variables at 6 months after treatment initiation and repeatedly when treatment changes or in case of new lines of therapy for standardization purposes within the H2O project (Figure 1).

In addition, it was agreed to define an optional set (Table 2), which could be optionally implemented in addition to the COS if resources are available. HRQoL outcomes with >70% consensus in the patients/ patients representatives group, but no other group, was included in the optional set. An exception to this was the exclusion of family history of lung cancer because of difficulties in measurement. Also, thyroid dysfunction was excluded because of its low prevalence in lung cancer patients. Ethnicity and alternative or complementary therapy were added because of its relevance for patients. Moreover, dose intensity and dose reduction of systemic treatment were included as optional because these outcomes were deemed relevant but at the moment not routinely measured or available in most clinical practises (Table 3).

Discussion

We developed an updated, enriched and comprehensive COS for lung cancer that captures the patient perspective of the impact of cancer and novel treatments, including immunotherapy and targeted therapy. A consensus-based approach was used in a large international, multidisciplinary group of stakeholders. The COS consists of 64 outcomes, nearly half of them patient-reported. It will be implemented in Europe as part of the H2O initiative.

The ICHOM lung cancer set published in 2016 (10) was used as reference COS and was, among other COSs and outcome measures, reviewed by the expert multidisciplinary team for the development of the Delphi survey. Our Delphi exercise enriched the 2016 ICHOM set mostly with PROs, such as additional HRQoL outcomes and patient-reported symptoms, in alignment with our patient-centred approach (14). Hence, a considerable number of patient-reported symptoms beyond those included by ICHOM in 2016 (i.e. fatigue, pain, cough, shortness of breath (10)) were included in our COS, such as insomnia, nausea, vomiting, anxiety, depression, lack of appetite, gastric problems, constipation, diarrhoea and dysphagia and haemoptysis. Its similarity with the recently published lung cancer subset of the PRO-CTCAE (27) emphasizes the inclusiveness of recent lung cancer therapies and its relevance to lung cancer patients. Conversely, symptoms more exclusively

related to immuno- and targeted therapy such as muscle pain and skin problems (12, 13) were only included in the optional set because these issues were not recognized by stakeholder groups other than patients or their representatives. However, pain was included in our COS to cover various sources of pain, including joint and muscle pain, following the changing landscape of lung cancer therapies.

Regarding the case-mix variables included in the 2016 ICHOM set, both gender and education were deemed less relevant by the Delphi participants. Whereas gender was included in the Delphi survey rather than (biological) sex for inclusiveness, the outcome description may have distracted from its relevance for research and treatment(31, 32), and was therefore included by the expert multidisciplinary team nevertheless. The decision to exclude education was guided by low agreement in all stakeholder groups and was also deemed as less impactful for clinical practise by the expert multidisciplinary team.

In contrast to the ICHOM lung cancer set, the expert multidisciplinary team decided to include next-generation sequencing (NGS) instead of specifically targeted aberrations such as ALK and EGFR because of the rapid developments in the discovery of biomarkers that are relevant for lung cancer treatment (33). NGS allows to assess a large number of mutations in a short time at low cost and is therefore considered the gold standard as well as a solid basis of current and future developments in molecular cancer research (33) and was also deemed as feasible because of routine NGS in participating in H2O. The fast-paced developments in this field are further emphasized by the agreement within our multidisciplinary expert multidisciplinary team to not include ERCC1 and RRM1 expression and CEA/CYFRA 21- biomarker signature determination because of its lack of relevance at the time of development of our COS nor in the near future, whereas these biomarkers were included in a COS for lung cancer developed in Spain only two years ago(21).

We deployed a rigorous Delphi process in a large and international representation of key stakeholders, with availability of the Delphi survey in four languages to accommodate a large outreach, and low drop-out rates (<20%). However, our study was limited by a rapid scoping review to identify existing COS and outcome measures, which may have omitted literature on novel treatments that were not yet included due to the time lag. Therefore, both expert multidisciplinary team members and Delphi participants had the opportunity to add new outcomes. Further, we had a limited (n=6) representation of health authority and regulatory representatives resulting in less stable

stakeholder ratings in this group (18). Therefore, their perspectives were not included in our consensus threshold (i.e. ≥70% agreement in the larger stakeholder groups) but were only used as additional guidance during our consensus meeting. Furthermore, we had two Delphi survey rounds with the option to add new outcomes in the first round, resulting in single-time voting for outcomes that were added, which may hampered the consensus process (34). However, each of these outcomes was deliberately discussed in our consensus meeting. Lastly, our pre-defined consensus threshold was, for HRQoL outcomes, changed during the consensus meeting, which may have induced bias (34). However, this was justified by our patient-centred approach to avoid excluding HRQOL outcomes that were deemed as highly relevant by patients.

Although the aim of our Delphi study was to identify outcomes and not measures, the latter was discussed in our consensus meetings. For clinical implementation, we recommend that PRO questionnaires with their support of their validity would be included such as the European Organisation for Research and Treatment (EORTC) QLQ-C30 and LC13, NCSCLC-SAQ, Functional Assessment of Cancer Therapy (FACT)-G and -L, Patient-reported Outcomes Measurement Information System (PROMIS), Patient Global Impresssion of Severity of Symptoms or a combination of these. Yet, most of these questionnaires cover more outcomes than included in our COS, except single items selected from item banks. However, as an example, we found a combination of the EORTC-QLQC30 and EORTC-LC13/LC29, supplemented with PRO-CTCAE items to cover all PROs in our lung cancer COS, which was deemed acceptable by the patients and patient representatives in our expert multidisciplinary team, and support the ultimate goal to measure outcomes that are important to them. Furthermore, computer adaptive testing (CAT) could minimize reporting burden for patients (35).

Our updated COS for lung cancer will be implemented in clinical centres across Europe, initially in Austria, Germany, the Netherlands and Spain, as part of the H2O project(14). The technological tools that are developed within the project will allow for easy and efficient outcome tracking, feedback of data and visualization, in a standardized way across H2O clinics to maximize uptake and utilization of outcomes in clinical care and decision making. The H2O public-private consortium strives to maximize value for patients through the establishment of an ecosystem to collect and incorporate PROs and other health outcomes into health care decision(14). Patients will be provided with digital tools to track their own outcomes and control their data flows. They might consent sharing their data to develop new treatments, devices, products and therapies. Standardized data

collection across Europe further enables rich data comparisons on an aggregated level to improve research and treatment for lung cancer patients. International, patient-centred initiatives such as H2O contribute to the ultimate goal of driving better outcomes for patients.

Declarations of interest

MP has received honoraria for lectures, consultation or advisory board participation from the following for-profit companies: Bayer, Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, BMJ Journals, MedMedia, Astra Zeneca, AbbVie, Lilly, Medahead, Daiichi Sankyo, Sanofi, Merck Sharp & Dome, Tocagen, Adastra, Gan & Lee Pharmaceuticals.

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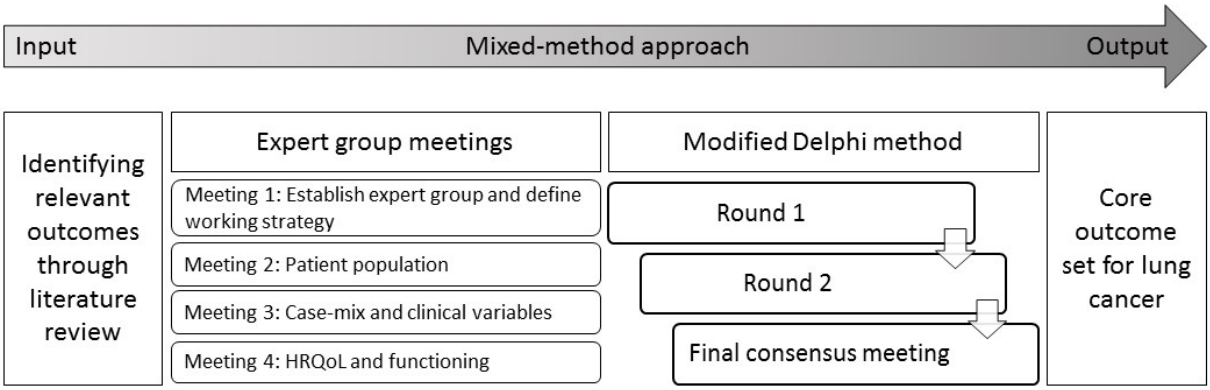
Figure 1 Mixed-method approach for developing core outcome set for patients with metastatic breast cancer



Supplementary table 1: Baseline characteristics of Delphi participants

	(Former) patients/ patient representatives n=31	Health care professionals/ academic researchers N=83 *(70 HCPs; 13 academic researchers)*	Pharmaceutical industry representatives n=26	Health authority/ regulatory representatives n=6	Total n=146
Mean age (SD)	56.2 (9.3)	44.9 (10.7)	44.9 (9.2)	53.3 (13.9)	56.2 (9.3)
Gender					
Male	13 (42)	21 (25)	13 (50)	5 (83)	52 (36)
Female	18 (58)	62 (75)	13 (50)	1 (17)	94 (64)
Country of residence					
Argentina	1 (3)	4 (5)	3 (12)	1 (17)	9 (6)
Austria	1 (3)	7 (8)	2 (8)	1 (17)	11 (8)
Canada	0 (0)	0 (0)	1 (4)	0 (0)	1 (1)
Cyprus	1 (3)	0 (0)	0	0 (0)	1 (1)
Germany	3 (10)	5 (6)	4 (15)	1 (17)	13 (9)
Italy	0 (0)	3 (4)	1 (4)	0 (0)	4 (3)
Netherlands	10 (32)	14 (5)	4 (15)	0 (0)	28 (19)
Norway	0 (0)	0 (0)	1 (4)	0 (0)	1 (1)
Spain	15 (48)	48 (59)	1 (4)	3 (5)	67 (46)
Switzerland	0 (0)	2 (2)	2 (8)	0 (0)	4 (3)
Turkey	0 (0)	0 (0)	1 (4)	0 (0)	1 (1)
United States of America	0 (0)	0 (0)	6 (7)	0 (0)	6 (4)
Are you involved in the H2O project?					
Yes	6 (19)	27 (33)	11 (42)	1 (17)	45 (31)
No	25 (81)	56 (67)	15 (58)	5 (83)	101 (69)
Are you familiar with health-related outcomes?					
Not at all	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
A little	6 (19)	14 (17)	0 (0)	1 (17)	21 (14)
Quite a bit	19 (61)	41 (49)	16 (62)	3 (50)	79 (54)
Very much	6 (19)	28 (34)	10 (38)	2 (33)	46 (32)
Years since diagnosis, M (SD)	5.2 (4.6)				
Years of professional experience, M (SD)	N/A	14.5 (9.3)	11.5 (6.7)	12.8 (9.7)	13.7 (8.9)

Supplementary table 2: Relevance scores (% of participants that scored 7-9), by stakeholder group and round (expert multidisciplinary team meeting, Delphi round and consensus meeting)

Outcomes	Expert team meeting	Delphi Round 1				Delphi Round 2				Consensus meeting
	Overall (n=11)	Patients (n=31)	HCPs/ academics (n=83)	Industry (n=26)	HA/HR (n=6)	Patients (n=26)	HCPs/ academics (n=66)	Industry (n=22)	HA/HR (n=5)	Overall decision (n=16)
Case mix variables										
Gender/sex*	100	40	51	69	67	44	48	67	60	Include
Age*	100	68	72	89	83	60	70	95	80	Include
Educational level*	45	15	28	28	0	12	15	0	0	Exclude
Relationship status	36	21	21	20	0	24	8	0	0	Exclude
Living situation	36	34	35	28	0	40	25	10	0	Exclude
Children at home	27	32	31	31	0	41	19	15	0	Exclude
Working/employment situation	36	50	38	39	17	52	39	39	0	Exclude
Ethnicity*	55	19	35	57	17	32	27	43	0	Optional
Monthly income	Added by EG	18	15	23	0	12	7	10	0	Exclude
Health insurance	Added by EG	47	24	46	0	54	23	43	0	Exclude
Comorbidities*	73	74	94	96	100	82	97	96	100	Include
Height and weight	64	42	61	50	34	30	51	48	40	Exclude
Nutritional status	55	63	87	44	51	62	77	45	40	Exclude
Smoking status*	91	82	90	85	83	87	83	86	80	Include
Alcohol use	Added by EG	66	83	51	67	71	83	76	60	Include
Performance status*	100	61	78	80	33	70	77	91	0	Include
Frailty	Added by EG	80	93	84	84	88	94	86	100	Include
Date of diagnosis	75	60	76	80	83	54	78	90	80	Include
Type of lung cancer*	82	99	98	96	84	100	97	100	100	Include
Clinical cancer stage*	91	100	99	99	100	100	98	100	100	Include
Pathological cancer stage*	100	100	95	88	83	100	99	100	100	Include
Lung function*	64	93	86	72	100	91	96	95	100	Include
PD-L1 expression	100	91	90	80	83	96	95	95	80	Include
ERCC1 and RRM1 expression	50	82	63	67	67	88	72	75	60	Exclude
Next generation sequencing	Added by EG	95	77	75	83	100	93	90	80	Include
Second primary tumour	50	96	89	66	84	99	95	85	80	Include
Time from diagnosis to treatment	Added by EG	91	89	65	83	91	92	82	100	Include
Standard therapy versus experimental/clinical trial therapy	75	85	83	66	80	95	90	76	80	Include
(Neo)adjuvant radiotherapy*	100	88	85	65	100	90	86	76	100	Include

Fractions and dose of radiotherapy		63	86	73	49	100	90	78	70	100Include
(Neo)adjuvant chemotherapy*		100	85	86	69	80	87	93	86	100Include
Immunotherapy*	Added by EG		96	90	81	80	95	95	96	80Include
Targeted therapy*		100	96	92	80	83	95	95	95	100Include
Sessions of systemic therapy		63	86	75	68	84	89	84	80	80Include
Surgery*		88	92	90	70	83	91	93	91	80Include
No therapy		88	92	87	76	75	91	90	90	80Include
Alternative or complementary therapies		63	59	53	42	60	72	46	62	50Optional
Family history of lung cancer	Added after R1	N/A	N/A	N/A	N/A		70	37	58	0Exclude
Number of mutations	Added after R1	N/A	N/A	N/A	N/A		95	83	80	100Include
Dose intensity of systemic treatment	Added after R1	N/A	N/A	N/A	N/A		75	65	75	75Optional
Dose reduction of systemic treatment	Added after R1	N/A	N/A	N/A	N/A		79	54	64	75Optional
Combination treatments	Added after R1	N/A	N/A	N/A	N/A		94	84	85	100Include
Health-related quality of life outcomes										
Subjective well-being/health-related quality of life		70	84	82	95	66	87	83	95	60Include
Cognitive functioning*		100	81	82	69	33	88	90	72	40Include
Mental health		60	91	77	77	33	91	83	77	20Exclude
Emotional functioning*		100	81	75	77	67	92	77	85	60Include
Patients personal beliefs and expectations about their illness		60	74	73	65	84	83	77	80	80Include
Anxiety		90	94	75	62	66	87	81	81	60Include
Depression		90	81	78	62	50	79	86	86	40Include
Insomnia		60	72	67	69	34	83	62	62	20Include
Mobility		70	84	72	70	50	84	76	81	40Include
Perceived mobility	Added after R1		77	69	50	17	75	70	53	0Exclude
Falls		30	65	61	46	17	66	67	53	0Exclude
Shortness of breath/chest tightness*		100	84	88	84	67	96	91	86	60Include
Coughing problems*		90	80	81	77	83	92	78	81	80Include
Dry mouth/sore mouth		30	73	60	53	17	79	55	53	20Optional
Difficulty swallowing (dysphagia)		50	87	80	61	50	92	80	68	40Include
Anorexia		60	81	86	61	84	87	92	71	80Include

Increased appetite	Added by PAB		53	39	44	17	45	36	34	0Exclude
Nausea		80	79	70	70	17	88	76	72	0Include
Gastric problems		40	72	61	69	17	75	66	68	0Include
Vomiting		60	77	75	73	34	92	82	81	20Include
Constipation		70	69	65	58	17	74	65	52	0Include
Diarrhea		80	75	67	65	17	84	77	57	0Include
Deep vein thrombosis		50	83	74	64	51	91	78	70	40Include
Body changes	Added by EG		72	46	49	34	71	56	50	40Optional
Pain*		100	91	95	92	67	100	94	95	60Include
Fatigue*		100	78	76	85	50	87	85	90	40Include
Thyroid dysfunction	Added by PAB		79	48	54	40	87	56	60	25Exclude
Skin (problems)		40	63	42	48	20	66	44	49	0Exclude
Social support		70	75	61	52	66	79	62	62	60Include
Social functioning*		80	56	55	64	34	54	48	58	20Optional
Relationship/marital problems		50	60	49	32	33	45	36	29	20Exclude
Sexual pleasure		20	34	27	36	17	24	8	15	0Exclude
Sexual interest		20	43	26	36	17	32	10	15	0Exclude
Sexual functioning		70	43	28	40	17	37	15	20	0Exclude
Financial impact		60	72	47	58	34	80	51	67	20Include
Health Related Quality Of Life Outcomes (General)*	Added after R1	N/A	N/A	N/A	N/A		87	74	90	50Include
Physical Function*	Added after R1	N/A	N/A	N/A	N/A		86	64	91	50Include
Role Function	Added after R1	N/A	N/A	N/A	N/A		75	49	68	0Optional
Physical activity	Added after R1	N/A	N/A	N/A	N/A		82	61	91	50Include
Activities to relieve psychological distress	Added after R1	N/A	N/A	N/A	N/A		78	53	52	25Optional
Ability to perform household activities	Added after R1	N/A	N/A	N/A	N/A		69	47	76	25Exclude
Return to work	Added after R1	N/A	N/A	N/A	N/A		53	45	77	50Optional
Hemoptysis	Added after R1	N/A	N/A	N/A	N/A		80	72	69	33Include
Hoarseness (dysphonia)	Added after R1	N/A	N/A	N/A	N/A		37	47	34	25Exclude
Numbness/Tingling (peripheral Neuropathy)	Added after R1	N/A	N/A	N/A	N/A		57	53	62	50Exclude
Rash	Added after R1	N/A	N/A	N/A	N/A		58	35	48	0Exclude
Lymphoedema	Added after R1	N/A	N/A	N/A	N/A		75	50	55	25Optional
Muscle pain (myalgia)	Added after R1	N/A	N/A	N/A	N/A		73	48	43	50Optional
Caregiver tasks	Added after R1	N/A	N/A	N/A	N/A		77	49	55	25Optional

Clinical outcomes

Lung infection	Added by EG	88	94	73	67	96	91	81	60Include
Overall survival*	100	81	90	92	83	95	96	96	80Include
Death attributed to lung cancer*	75	67	87	81	83	88	90	96	80Include
Tumour response	88	100	96	85	83	100	100	96	80Include
Localization of metastases	Added by EG	100	90	84	83	100	95	95	100Include
Brain metastases	75	100	95	88	100	100	98	95	100Include
Treatment-related complications	88	100	88	85	83	95	95	100	100Include
Progression Free Survival	Added after R1	N/A	N/A	N/A	N/A	91	85	100	75Include
Duration of tumor Response	Added after R1	N/A	N/A	N/A	N/A	85	86	75	100Include
Treatment discontinuation due to side effects	Added after R1	N/A	N/A	N/A	N/A	99	98	91	100Include
Medication compliance/adherence	Added after R1	N/A	N/A	N/A	N/A	91	85	76	100Include

Table 1: Core outcome set with supporting information

	Outcome	Domain	PRO/CRO	Suggested measure
1	Gender/sex*	Case-mix variables – patient-related	PRO	Male/female/other/prefer not to say
2	Age*	Case-mix variables – patient-related	PRO	Age at time of diagnosis
3	Comorbidities*	Case-mix variables – patient-related	PRO	Modified SCQ
4	Smoking status*	Case-mix variables – patient-related	PRO	Smoking status at diagnosis
5	Alcohol use	Case-mix variables – patient-related	PRO	Number of alcoholic drinks per week
6	Performance status*	Case-mix variables – patient-related	CRO	ECOG/WHO scale for performance status
7	Frailty	Case-mix variables – patient-related	CRO	Frailty Index
8	Date of diagnosis	Case-mix variables – diagnostic	CRO	Date of diagnosis determined based on tissue examination (histology)
9	Lung cancer histology*	Case-mix variables – diagnostic	CRO	Lung cancer type determined based on tissue examination (histology): small cell carcinoma, adenocarcinoma, squamous cell carcinoma, large cell carcinoma, other types
10	Clinical cancer stage*	Case-mix variables – diagnostic	CRO	TNM stage Per UICC / IASLC / AJCC 8th edition based on results of tests done before surgery
11	Pathological cancer stage*	Case-mix variables – diagnostic	CRO	TNM stage per UICC / IASLC / AJCC 8th edition based on what is found during surgery
12	Lung function*	Case-mix variables – diagnostic	CRO	Absolute and predicted FEV-1 (forced expiratory volume in one second)
13	PD-L1 expression	Case-mix variables – diagnostic	CRO	Tumor Proportion Score (TPS)
14	Next generation sequencing	Case-mix variables – diagnostic	CRO	Results of next generation sequencing (NGS), yes/no; if yes: broad NGS testing vs. list of lung cancer actionable targets
15	Second primary tumour	Case-mix variables – diagnostic	CRO	New lung cancer or other cancer diagnosis
16	Time from diagnosis to treatment	Case-mix variables – treatment-related	CRO	Time between date of diagnosis (based on tissue examination; histology) and start date of first treatment
17	Standard therapy versus experimental/clinical trial therapy	Case-mix variables – treatment-related	CRO	Treatment received according to the guidelines, therapy other than guideline or as part of a clinical trial
18	(Neo)adjuvant radiotherapy*	Case-mix variables – treatment-related	CRO	Received (neo)adjuvant radiotherapy, yes/no
19	Fractions and dose of radiotherapy	Case-mix variables – treatment-related	CRO	Number of treatment sessions (#) and dose (Gy) with radiation received
20	(Neo)adjuvant chemotherapy*	Case-mix variables – treatment-related	CRO	Received (neo)adjuvant chemotherapy, yes/no
21	Immunotherapy*	Case-mix variables – treatment-related	CRO	Received immunotherapy, yes/no
22	Targeted therapy*	Case-mix variables – treatment-related	CRO	Received targeted therapy, yes/no

23	Sessions of systemic therapy	Case-mix variables – treatment-related	CRO	Number (#) of sessions of chemo-, immuno-, or targeted therapy received
24	Surgery*	Case-mix variables – treatment-related	CRO	Received surgery, yes/no
25	No therapy	Case-mix variables – treatment-related	CRO	Received no cancer therapy that is part of medical care, yes/no
26	Number of mutations	Case-mix variables – treatment-related	CRO	Number of genetic mutations
27	Combination treatments	Case-mix variables – treatment-related	CRO	Received two or more kinds of therapies, yes/no
28	Subjective well-being/health-related quality of life	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
29	Cognitive functioning*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
30	Emotional functioning*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
31	Patients personal beliefs and expectations about their illness	Health-related quality of life outcomes	PRO	EORTC item library
32	Anxiety	Health-related quality of life outcomes	PRO	EORTC item library
33	Depression	Health-related quality of life outcomes	PRO	EORTC item library
34	Insomnia	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
35	Mobility	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
36	Shortness of breath/chest tightness*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
37	Coughing problems*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
38	Difficulty swallowing (dysphagia)	Health-related quality of life outcomes	PRO	EORTC QLQ-LC13
39	Anorexia	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
40	Nausea	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
41	Gastric problems	Health-related quality of life outcomes	PRO	PRO-CTCAE
42	Vomiting	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
43	Constipation	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
44	Diarrhea	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
45	Deep vein thrombosis	Health-related quality of life outcomes	PRO	PRO-CTCAE
46	Pain*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
47	Fatigue*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
48	Social support	Health-related quality of life outcomes	PRO	EORTC item library
49	Financial impact	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
50	Health Related Quality Of Life Outcomes (General)*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
51	Physical Function*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
52	Physical activity	Health-related quality of life outcomes	PRO	Meeting WHO physical activity recommendation for adults

53	Hemoptysis	Health-related quality of life outcomes	PRO	EORTC QLQ-LC13
54	Tumour response	Clinical outcomes - diagnostic	CRO	Complete response/ partial response / stable disease
55	Duration of tumor Response (DoR)	Clinical outcomes - diagnostic	CRO	Time from response to progression or death in number of days
56	Localization of metastases	Clinical outcomes - diagnostic	CRO	Intrapulmonary (inside the lungs) or extrapulmonary (outside the lungs)
57	Brain metastases	Clinical outcomes - diagnostic	CRO	Metastases in brain yes/no
58	Treatment discontinuation due to side effects	Clinical outcomes – treatment related	CRO	Treatment has stopped yes/no
59	Treatment-related complications*	Clinical outcomes – treatment related	CRO	CTCAE version 5.0 complication, including name of the adverse event
60	Lung infection	Clinical outcomes – treatment related	CRO	Lung infection yes/no
61	Medication compliance/adherence	Clinical outcomes – treatment related	CRO/PRO	Taking medication as prescribed, yes/no
62	Overall survival*	Clinical outcomes – mortality and survival	CRO	Date of diagnosis to date of death
63	Progression Free Survival	Clinical outcomes – mortality and survival	CRO	Date of diagnosis to date of progression or date of death
64	Cause of death*	Clinical outcomes – mortality and survival	CRO	Death attributed to lung cancer, yes/no

PRO: patient-reported outcome
CRO: clinician-reported outcome
**included in ICHOM lung cancer COS, 2016*
ECOG: Eastern Cooperative Oncology group
WHO: World Health Organization
SCQ: Self-administered comorbidity questionnaire
EORTC QLQ-C30: European Organisation for Research and Treatment (EORTC) cancer core module
EORTC LC-13: European Organisation for Research and Treatment (EORTC) lung cancer module
PRO-CTCAE: Patient-reported outcomes version of the common terminology criteria for adverse events

Table 2: Optional (add-on) set with supporting information

Outcome	Domain	PRO/CRO	Suggested measures
1Ethnicity*	Case-mix variables – patient-related	PRO	Determined by country
2Dose intensity of systemic treatment	Case-mix variables – treatment-related	CRO	Drug dose delivered per time unit (mg/m2 per week)
3Dose reduction of systemic treatment	Case-mix variables – treatment-related	CRO	Reduction of the dose of systemic therapy drugs, yes/no
4Dry mouth/sore mouth	Health-related quality of life outcomes	PRO	EORTC QLQ-LC13
5Body changes	Health-related quality of life outcomes	PRO	PRO-CTCAE
6Social functioning*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
7Alternative or complementary therapies	Health-related quality of life outcomes	PRO	Received therapies that aren't usually part of medical care in Europe, such as yoga, meditation, acupuncture and homeopathy
8Role Function	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
9Activities to relieve psychological distress	Health-related quality of life outcomes	PRO	E.g. Yoga, meditation etc.
10Return to work	Health-related quality of life outcomes	PRO	Ability and/or interest in returning/continuing to work
11Lymphoedema	Health-related quality of life outcomes	PRO	PRO-CTCAE
12Muscle pain (myalgia)	Health-related quality of life outcomes	PRO	PRO-CTCAE
13Caregiver tasks	Health-related quality of life outcomes	PRO	EORTC QLQ-C30

PRO: patient-reported outcome
CRO: clinician-reported outcome
**included in ICHOM lung cancer COS, 2016*
ECOG: Eastern Cooperative Oncology group
WHO: World Health Organization
SCQ: Self-administered comorbidity questionnaire
QLQ-C30: European Organisation for Research and Treatment (EORTC) cancer core module

LC-13: European Organisation for Research and Treatment (EORTC) lung cancer module
B-IPQ: Brief illness perceptions questionnaire
NSCLC-SAQ: Non-small cell lung cancer symptom assessment questionnaire
NFLSI-17: Functional Assessment of Cancer Therapy Lung Cancer Symptom Index
PRO-CTCAE: Patient-reported outcomes version of the common terminology criteria for adverse events

Figure 1: Recommended timeline of measures, adapted from Mak et al. (ICHOM Lung Cancer Set, 2016)