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

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ABSTRACT

Background: In 2016, the International Consortium for Health Outcomes Measurement (ICHOM) defined an international consensus recommendation of the most important outcomes for lung cancer patients. 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 health-care.

Material and methods: An international, expert team of patient representatives, multidisciplinary healthcare professionals, academic researchers and pharmaceutical industry representatives (n = 17) reviewed potential outcomes generated through 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 expert multidisciplinary 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. The final lung cancer COS includes: 1) case-mix factors (n = 27); 2) PROs related to health-related quality of life (HRQoL) (n = 25); 3) clinical outcomes (n = 12). Patient-reported symptoms beyond domains included in the ICHOM lung cancer set in 2016 were insomnia, nausea, vomiting, anxiety, depression, lack of appetite, gastric problems, constipation, diarrhoea, dysphagia, and haemoptysis.

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Conclusions: We will implement the lung cancer COS in Europe within the H2O initiative by collecting the outcomes through a combination of clinician-reported measures and PRO measures. The COS will support the adoption and reporting of lung cancer measures in a standardized way across Europe and empower patients with lung cancer to better manage their health care.

1. 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, contributing to a low-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 targeted therapy and immunotherapy promise to improve the efficacy of lung cancer treatment and are labelled safe, the treatment-related side effects and their 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 improving patients' value. In VBHC, health outcomes are utilized to facilitate shared decision-making, enhance 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 the 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 supporting health care providers (HCPs) to 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, support communication between patients, physicians and other HCPs and align on the right course of action [14].

2. 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 steps include: 1) reviewing and critically appraising the existing standards using a literature review and discussions in a multidisciplinary expert team; 2) conducting a Delphi study with a broader reference group; and 3) holding final consensus meetings[14] (Fig. 1). The Core Outcome Measures in Effectiveness trials (COMET) handbook [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.

2.1. 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 (https://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 multidisciplinary expert team of patient(representative)s, HCPs, public researchers, and pharmaceutical industry representatives was established using 'snowball sampling'. We considered diversity, equity and inclusiveness, i.e. gender, sociodemographic, geographic, cultural background/ethnicity. In four online meetings convened in February-March 2021, the multidisciplinary expert 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 $\geq$ 50 % of respondents scored the outcome as critically important (score 7–9). Items were excluded if $\geq$ 50 % rated the outcome as of limited importance (score 1–3). In line with the COMET handbook, we used a less stringent consensus threshold of 50 % for the review by the expert team to reduce the likelihood that items would have been dropped that might have scored better by the stakeholders in the Delphi survey [15].

2.2. Delphi study

Members of the multidisciplinary expert 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.

Before the Delphi survey rounds, four lung cancer patient representatives reviewed the preliminary outcome list with outcome definitions, lay descriptions of each outcome, and domain names 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'. 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 multidisciplinary expert team on a 1–9 scale and were included in the second round if $\geq$ 50 % of respondents agreed that an outcome was critically important [7–9]. A less stringent consensus threshold of 50 % was used to reduce the likelihood that items were dropped that would be deemed relevant in round 2(15). The 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.

2.3. Consensus meetings

After completing the Delphi rounds, two online consensus meetings were organized with the multidisciplinary expert 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 team was enriched with interested Delphi participants from patient organizations and regulatory bodies to ensure the representation of all stakeholder groups. The pre-defined consensus threshold to include items in the final COS was $\geq$ 70 % (scores 7–9) in all four stakeholder groups. Outcomes were excluded if $\geq$ 15 % of participants in a stakeholder group rated it as not important [1–3]. We chose a more stringent consensus threshold of 70 % in the consensus meetings to reduce the number of items in the final outcome set [15]. The final COS was summarized and approved by the multidisciplinary expert team members.

3. Results

3.1. 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 literature search but were deemed as relevant by the multidisciplinary expert 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 multidisciplinary expert team.

An multidisciplinary expert 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 the literature review, 13 items (6 case-mix variables, 3 HRQoL outcomes and 4 clinical outcomes) were suggested by multidisciplinary expert 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 multidisciplinary expert team members on the preliminary outcomes set that were

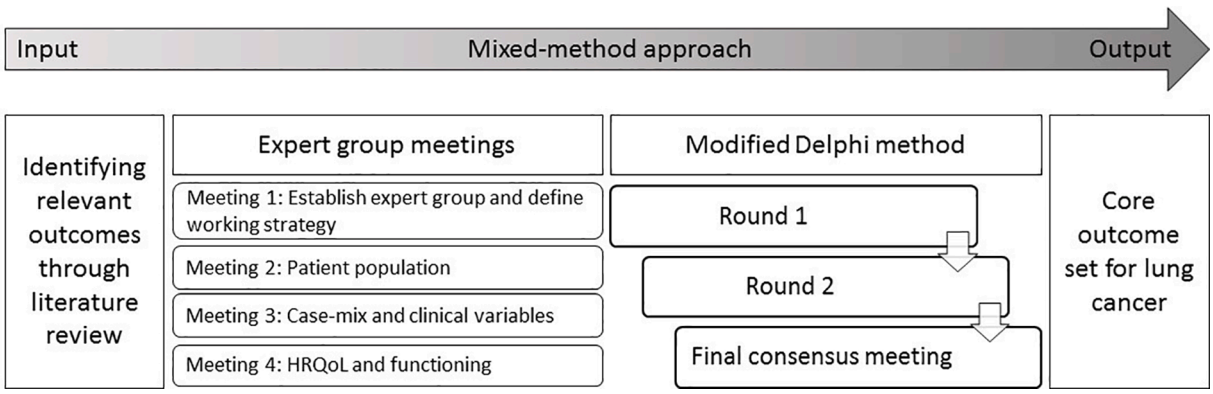

Fig. 1. Mixed-method approach for developing core outcome set for patients with lung cancer.

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	Drinking more than one alcoholic drink a day
6	Performance status*	Case-mix variables – patient-related	CRO	ECOG/WHO scale for performance status
7	Frailty	Case-mix variables – patient-related	CRO	Frailty stage using the Canadian study on Health Aging Clinical Frailty Scale
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)
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	PD-L1 or 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	Tumor Mutational Burden (TMB)
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	PRO-CTCAE
33	Depression	Health-related quality of life outcomes	PRO	PRO-CTCAE
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*		PRO	EORTC LC29

(*continued on next page*)

Table 1 (*continued*)

	Outcome	Domain	PRO/ CRO	Suggested measure
		Health-related quality of life outcomes		
38	Difficulty swallowing (dysphagia)	Health-related quality of life outcomes	PRO	EORTC LC29
39	Anorexia	Health-related quality of life outcomes	PRO	EORTC LC29
40	Nausea	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
41	Gastric problems	Health-related quality of life outcomes	PRO	EORTC item library
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	Pain*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
46	Fatigue*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
47	Social support	Health-related quality of life outcomes	PRO	EORTC item library
48	Financial impact	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
49	Health Related Quality Of Life Outcomes (General)*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
50	Physical Function*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
51	Physical activity	Health-related quality of life outcomes	PRO	Meeting WHO physical activity recommendation for adults
52	Hemoptysis	Health-related quality of life outcomes	PRO	EORTC LC29
53	Tumour response	Clinical outcomes - diagnostic	CRO	Complete response/ partial response / stable disease
54	Duration of tumor Response (DoR)	Clinical outcomes - diagnostic	CRO	Time from response to progression or death in number of days
55	Localization of metastases	Clinical outcomes - diagnostic	CRO	Intrapulmonary (inside the lungs) or extrapulmonary (outside the lungs)
56	Brain metastases	Clinical outcomes - diagnostic	CRO	Metastases in brain yes/ no
57	Treatment discontinuation due to side effects	Clinical outcomes – treatment related	CRO	Treatment has stopped yes/no
58	Treatment-related complications*	Clinical outcomes – treatment related	CRO	CTCAE version 5.0 grade III-IV complication, including name of the adverse event
59	Lung infection	Clinical outcomes – treatment related	CRO	Lung infection yes/no
60	Deep vein thrombosis	Clinical outcomes – treatment related	CRO	CTCAE version 5.0 grade III-IV vascular access complication
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 directly 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 LC29: European Organisation for Research and Treatment (EORTC) lung cancer module
PRO-CTCAE: Patient-reported outcomes version of the common terminology criteria for adverse events

subsequently included in the Delphi survey.

3.2. 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 multidisciplinary expert 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).

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

	Outcome	Domain	PRO/ CRO	Suggested measures
1	Ethnicity*	Case-mix variables – patient-related	PRO	Determined by country
2	Dose intensity of systemic treatment	Case-mix variables – treatment-related	CRO	Drug dose delivered per time unit (mg/m2 per week)
3	Dose reduction of systemic treatment	Case-mix variables – treatment-related	CRO	Reduction of the dose of systemic therapy drugs, yes/no
4	Dry mouth/sore mouth	Health-related quality of life outcomes	PRO	EORTC LC29
5	Body changes	Health-related quality of life outcomes	PRO	PRO-CTCAE
6	Social functioning*	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
7	Alternative 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
8	Role Function	Health-related quality of life outcomes	PRO	EORTC QLQ-C30
9	Activities to relieve psychological distress	Health-related quality of life outcomes	PRO	E.g. Yoga, meditation etc.
10	Return to work	Health-related quality of life outcomes	PRO	Ability and/or interest in returning/continuing to work
11	Lymphoedema	Health-related quality of life outcomes	PRO	PRO-CTCAE
12	Muscle pain (myalgia)	Health-related quality of life outcomes	PRO	PRO-CTCAE
13	Caregiver 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
EORTC QLQ-C30: European Organisation for Research and Treatment (EORTC) cancer core module
EORTC LC29: 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

3.3. 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 an 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 an 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 team despite 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; 25 HRQoL outcomes; 12 clinical outcomes), of which 30 items (5 case-mix and 25 HRQoL) are patient-reported, and 34 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 administering 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 (Fig. 2).

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 less than 60 % in the other stakeholder groups, were included in the optional set(15). An exception to this was the exclusion of a 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 their relevance to 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).

4. 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 a reference COS and was, among other COSs and outcome measures, reviewed by the multidisciplinary expert 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-

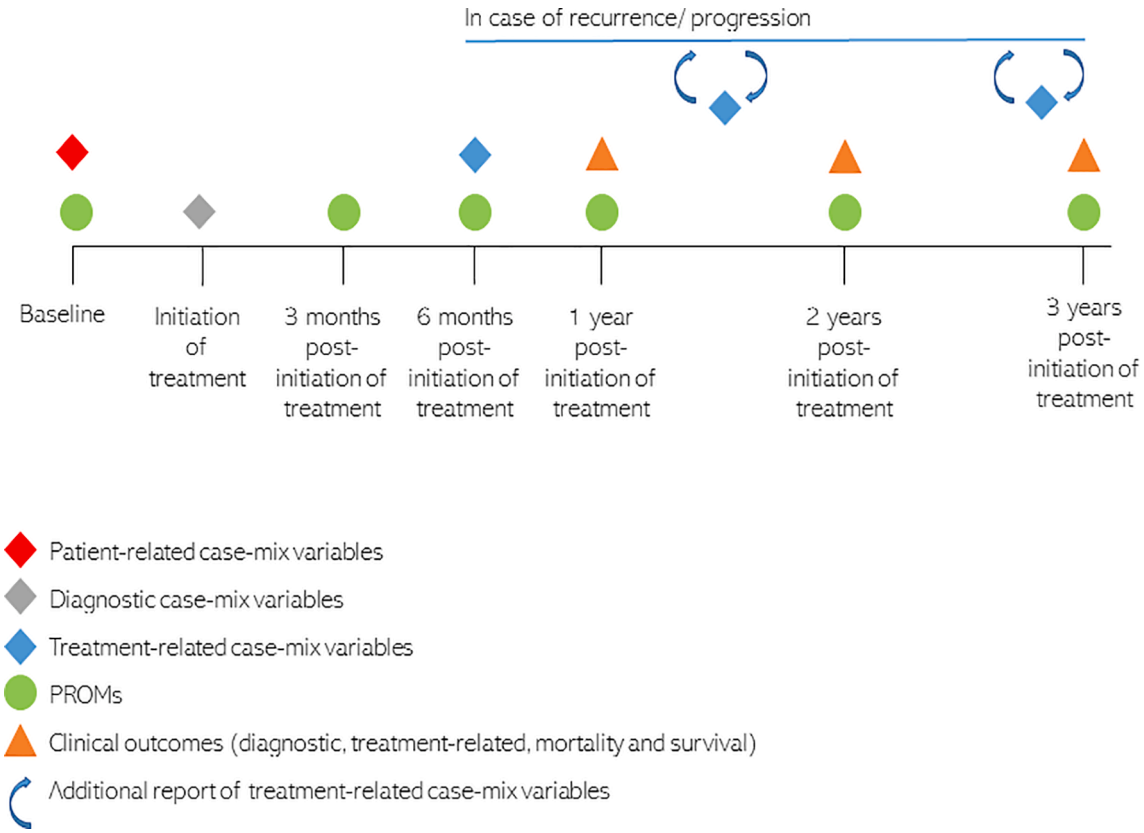

Fig. 2. Recommended timeline of measures, adapted from Mak et al. (ICHOM Lung Cancer Set, 2016).

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 multidisciplinary expert 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 team.

In contrast to the ICHOM lung cancer set, the expert 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 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 (less than20 %). 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, multidisciplinary expert 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. $\geq$ 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 hamper 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 our Delphi study aimed 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/

LC29, 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 for 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 multidisciplinary expert 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 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.

CRediT authorship contribution statement

Belle H. de Rooij: Conceptualization, Investigation, Methodology, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **Corina van den Hurk:** Conceptualization, Resources, Visualization, Writing – review & editing. **Veerle Smaardijk:** Conceptualization, Investigation, Methodology, Project administration. **Paz Fernandez-Ortega:** Resources, Writing – review & editing. **Arturo Navarro-Martin:** Resources, Writing – review & editing. **Lidia Barberio:** Resources, Writing – review & editing. **Matthias Guckenberger:** Resources, Writing – review & editing. **Severin Schmid:** Resources, Writing – review & editing. **Iris Walraven:** Resources, Writing – review & editing. **Susan Vallow:** Resources, Writing – review & editing. **Christina Kotsi:** Resources, Writing – review & editing. **Matthias Preusser:** Resources, Writing – review & editing. **Erika Mosor:** Resources, Writing – review & editing. **Jente M. Klok:** Resources, Writing – review & editing. **Annemarie Becker:** Resources, Writing – review & editing. **Alessandra Milani:** Resources, Writing – review & editing. **Lyudmil Ninov:** Resources, Writing – review & editing. **Lonneke V. van de Poll-Franse:** Resources, Writing – review & editing, Methodology, Supervision.

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Declaration of Competing Interest

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About IMI: The Innovative Medicines Initiative is a partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA). It is working to improve health by speeding up the next generation of medicines, particularly in areas with unmet medical or social needs. It works by facilitating collaboration between the key players involved in health research, including universities, research centers, pharmaceutical and other industries, small and medium-sized enterprises (SMEs), patient organizations, and medicines regulators. IMI is the world's most extensive public-private partnership (PPP) in the life sciences.

Disclaimer

References

[1] J. Ferlay, M. Colombet, I. Soerjomataram, D.M. Parkin, M. Piñeros, A. Znaor, et al., Cancer statistics for the year 2020: An overview, International Journal of Cancer (2021).
[2] C. Allemani, T. Matsuda, V. Di Carlo, R. Harewood, M. Matz, M. Nikšić, et al., Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries, The Lancet. 391 (10125) (2018) 1023–1075.
[3] N. Basumallik, M. Agarwal, Small cell lung cancer, StatPearls [internet]. (2020).
[4] T. Lu, X. Yang, Y. Huang, M. Zhao, M. Li, K. Ma, et al., Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades, Cancer management and research. 11 (2019) 943.
[5] N. Howlader, G. Forjaz, M.J. Mooradian, R. Meza, C.Y. Kong, K.A. Cronin, et al., The effect of advances in lung-cancer treatment on population mortality, New England Journal of Medicine. 383 (7) (2020) 640–649.
[6] X. Ai, X. Guo, J. Wang, A.L. Stancu, P.M. Joslin, D. Zhang, et al., Targeted therapies for advanced non-small cell lung cancer, Oncotarget. 9 (101) (2018) 37589.
[7] L. Liu, H. Bai, C. Wang, S. Seery, Z. Wang, J. Duan, et al., Efficacy and safety of first-line immunotherapy combinations for advanced NSCLC: a systematic review and network meta-analysis, Journal of Thoracic Oncology. 16 (7) (2021) 1099–1117.
[8] A. Calles, G. Aguado, C. Sandoval, R. Álvarez, The role of immunotherapy in small cell lung cancer, Clinical and Translational Oncology. 21 (8) (2019) 961–976.
[9] E. Aviki, S.M. Schleicher, S. Mullangi, K. Matsoukas, D. Korenstein, Value-based healthcare delivery models in oncology: A systematic review. American Society of, Clinical Oncology (2018).
[10] K.S. Mak, A.C. Van Bommel, C. Stowell, J.L. Abrahm, M. Baker, C.S. Baldotto, et al., Defining a standard set of patient-centred outcomes for lung cancer, European Respiratory Journal. 48 (3) (2016) 852–860.
[11] A.S. Tsao, G.V. Scagliotti, P.A. Bunn Jr, D.P. Carbone, G.W. Warren, C. Bai, et al., Scientific advances in lung cancer 2015, Journal of Thoracic Oncology. 11 (5) (2016) 613–638.
[12] S.S. Shaw, H.S. Jim, S. Eisel, A. Hoogland, D. LeDuc, A.P. Dicker, Patient reported toxicities: Development and validation of patient-reported symptom measure for lung cancer patients receiving immunotherapy. American Society of, Clinical Oncology (2019).
[13] A.R. Hansen, K. Ala-Leppilampi, C. McKillop, L.L. Siu, P.L. Bedard, A.R. Abdul Razak, et al., Development of the Functional Assessment of Cancer Therapy-Immune Checkpoint Modulator (FACT-ICM): A toxicity subscale to measure quality of life in patients with cancer who are treated with ICMs, Cancer. 126 (7) (2020) 1550–1558.
[14] T. Stamm, N. Bott, R. Thwaites, E. Mosor, M.R. Andrews, J. Borgdorff, et al., Building a Value-Based Care Infrastructure in Europe: The Health Outcomes Observatory, NEJM Catalyst Innovations in Care Delivery. 2 (3) (2021).
[15] Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, et al. The COMET Handbook: version 1.0. Trials. 2017;18(Suppl 3):280.

[16] A.C. Tricco, J. Antony, W. Zarin, L. Strifler, M. Ghassemi, J. Ivory, et al., A scoping review of rapid review methods, BMC medicine. 13 (1) (2015) 1–15.
[17] G.H. Guyatt, A.D. Oxman, R. Kunz, D. Atkins, J. Brozek, G. Vist, et al., GRADE guidelines: 2. Framing the question and deciding on important outcomes, Journal of Clinical Epidemiology. 64 (4) (2011) 395–400.
[18] R.B. Akins, H. Tolson, B.R. Cole, Stability of response characteristics of a Delphi panel: application of bootstrap data expansion, BMC Med Res Methodol. 5 (2005) 37.
[19] COMET. DelphiManager. COMET; 2016.
[20] Team R Core, A Language and Environment for Statistical, Computing (2013). https://www.R-project.org/2021.
[21] Escudero-Vilaplana V, Calles A, Collado-Borrell R, Belén Marzal-Alfaro M, Polanco C, Garrido C, et al. Standardizing Health Outcomes for Lung Cancer. Adaptation of the International Consortium for Health Outcomes Measurement Set to the Spanish Setting. Frontiers in oncology. 2020:1645. https://www.frontiersin.org/articles/10.3389/fonc.2020.01645/full.
[22] D. Howell, M. Fitch, D. Bakker, E. Green, J. Sussman, S. Mayo, et al., Core domains for a person-focused outcome measurement system in cancer (PROMS-Cancer Core) for routine care: a scoping review and Canadian Delphi Consensus, Value in health. 16 (1) (2013) 76–87.
[23] I. Ramsey, N. Corsini, A.D. Hutchinson, J. Marker, M. Eckert, A core set of patient-reported outcomes for population-based cancer survivorship research: A consensus study, Journal of Cancer Survivorship. 15 (2) (2021) 201–212.
[24] Milani A, Mauri S, Gandini S, Magon G. Oncology Nursing Minimum Data Set (ONMDS): can we hypothesize a set of prevalent Nursing Sensitive Outcomes (NSO) in cancer patients? ecancermedicalscience. 2013;7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3757958/.
[25] B.B. Reeve, M. McFatrich, L.C. Pinheiro, D.R. Freyer, E.M. Basch, J.N. Baker, et al., Cognitive interview-based validation of the patient-reported outcomes version of the common terminology criteria for adverse events in adolescents with cancer, Journal of pain and symptom management. 53 (4) (2017) 759–766.
[26] Y.B. Bouazza, I. Chiairi, O. El Kharbouchi, L. De Backer, G. Vanhoutte, A. Janssens, et al., Patient-reported outcome measures (PROMs) in the management of lung cancer: a systematic review, Lung Cancer. 113 (2017) 140–151.
[27] E. Veldhuijzen, I. Walraven, J. Belderbos, Selecting a Subset Based on the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events for Patient-Reported Symptom Monitoring in Lung Cancer Treatment: Mixed Methods Study, JMIR cancer. 7 (3) (2021), e26574.
[28] M. Van Leeuwen, O. Husson, P. Alberti, J.I. Arraras, O.L. Chinot, A. Costantini, et al., Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire, Health and quality of life outcomes. 16 (1) (2018) 1–15.
[29] W.L. Ong, M.G. Schouwenburg, A.C. Van Bommel, C. Stowell, K.H. Allison, K. E. Benn, et al., A standard set of value-based patient-centered outcomes for breast cancer: the International Consortium for Health Outcomes Measurement (ICHOM) initiative, JAMA oncology. 3 (5) (2017) 677–685.
[30] S. Oerlemans, M.C. Bennink, M.D. Levin, A. Broijl, M. Van der Klift, J. Van Deursen, et al., Development of a Patient Centered Outcome Set for Patients With Multiple Myeloma to be Used in Clinical Practice, HemaSphere. 4 (3) (2020).
[31] F. Conforti, L. Pala, V. Bagnardi, G. Viale, T. De Pas, E. Pagan, et al., Sex-based heterogeneity in response to lung cancer immunotherapy: a systematic review and meta-analysis, JNCI: Journal of the National Cancer Institute. 111 (8) (2019) 772–781.
[32] C. Radkiewicz, P.W. Dickman, A.L.V. Johansson, G. Wagenius, G. Edgren, M. Lambe, Sex and survival in non-small cell lung cancer: a nationwide cohort study, PloS one. 14 (6) (2019), e0219206.
[33] C. Cainap, O. Balacescu, S.S. Cainap, L.-A. Pop, Next Generation Sequencing Technology in Lung Cancer Diagnosis, Biology. 10 (9) (2021) 864.
[34] P.R. Williamson, D.G. Altman, J.M. Blazeby, M. Clarke, D. Devane, E. Gargon, et al., Developing core outcome sets for clinical trials: issues to consider, Trials. 13 (1) (2012) 1–8.
[35] M.A. Petersen, M. Groenvold, N.K. Aaronson, W.-C. Chie, T. Conroy, A. Costantini, et al., Development of computerised adaptive testing (CAT) for the EORTC QLQ-C30 dimensions–general approach and initial results for physical functioning, European Journal of Cancer. 46 (8) (2010) 1352–1358.