Research White Paper

Standardized Library of Lung Cancer Outcome Measures

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This report is based on research conducted by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers' Methods Workgroup. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help EPCs and AHRQ understand health-systems need and use of evidence to inform their decisionmaking. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new healthcare technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality. The reports undergo peer review prior to their release as a final report.

If you have comments on this Methods Research Project they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Introduction

Significant variation exists in both the types and definitions of outcome measures used in patient registries, even within the same clinical area. This variation reduces the utility of registries, making it difficult to compare, link, and aggregate data across the spectrum of clinical care and reporting. To address these limitations, the Agency for Healthcare Research and Quality (AHRQ) developed the Outcome Measures Framework (OMF), a conceptual model for classifying outcomes that are relevant to patients and providers across most conditions; it is intended to serve as a content model for developing harmonized outcome measures for specific clinical areas.[1]

AHRQ is assessing the feasibility of using the OMF to develop standardized libraries of outcome measures in five clinical areas, including (1) Atrial fibrillation, (2) Asthma, (3) Depression, (4) Lung cancer, and (5) Lumbar spondylolisthesis.[2] These clinical areas represent diverse populations and care settings, different treatment modalities, and varying levels of harmonization. For each clinical area, the relevant registries and observational studies are identified, and registry sponsors, informaticists, and clinical subject matter experts are invited to participate in a registry group that focuses on harmonizing outcome measures through a series of in-person and web-based meetings. A stakeholder group, including payers, patient representatives, Federal partners and health system leaders, is also assembled to discuss challenges and provide feedback on the harmonization effort.

A key goal of this effort is to standardize the definitions of the components that make up the outcome measures, so users can understand the level of comparability between measures across different systems and studies. As a final step in the harmonization process, clinical informaticists map the narrative definitions (generated by the workgroups) to standardized terminologies to produce a library of common data definitions.

This document describes the technical approach used to prepare the Standardized Library of Lung Cancer Outcome Measures workbook. For reference, the narrative definitions for the minimum set of outcome measures produced by the Lung Cancer Workgroup are included in Appendix A.

[1] Gliklich RE, Leavy MB, Karl J, et al. A framework for creating standardized outcome measures for patient registries. Journal of Comparative Effectiveness Research. 2014;3(5):473-80.

[2] This work was supported by the Office of the Secretary Patient-Centered Outcomes Research Trust Fund under Interagency Agreement #16-566R-16.

Approach to Representing an Outcome Definition

For each measure, the accompanying workbook (Appendix B), contains the narrative definition and recommended reporting period (timeframe), the initial population for measurement (e.g., all lung cancer patients), the outcome focused population (patients who experienced the outcome of interest), and the data criteria and value sets.

Electronic Health Record (EHR) data often will not contain all the requisite components of an outcome definition that would allow for the computational confirmation of that outcome. The approach used for this project is to gather the clinician's assertion of an outcome condition and as much supporting evidence as possible, so that even where the expression logic cannot computationally confirm an outcome, some structured evidence might still be available.

Relationships between events raise a challenge because relationships are often not directly asserted in an EHR. Thus, where possible, relationships have been inferred based on time stamps and intervals. Where this is not possible (e.g., cause of death), the logic requires an asserted relationship.

For each outcome, the following have been defined:

- *An object representing the outcome condition itself:* In many cases, the only structured data will be an assertion of an outcome, with all the supporting evidence being present in the narrative.
- *Fast Healthcare Interoperability Resources (FHIR) resources for evidence for the outcome:* These include labs, diagnostic imaging, etc.
- *FHIR resources for additional relevant events:* These might include procedures, encounters, etc.
- *Temporal aspects for all events:* These allow for inferred relationships.

Approach to Identifying Overlaps

A key goal of this project is to leverage existing resources and build connections across initiatives, where possible. To support that goal, the following sources were searched for overlap:

- https://ecqi.healthit.gov/: Primarily looking for overlapping criteria
- https://vsac.nlm.nih.gov/: Primarily looking for overlapping value sets
- C-CDA: Primarily looking for overlapping data representations
- https://www.nlm.nih.gov/cde/: Primarily looking for overlapping data element definitions

Each website has a specific, unique purpose, and data representations vary, so while there are some direct comparisons with similar use cases, there are also important differences both in terms of data structures and use cases. Results of the comparisons are provided below.

- https://ecqi.healthit.gov/; https://vsac.nlm.nih.gov/:
    - Overlapping value sets identified in VSAC:
        - Acute Respiratory Failure (2.16.840.1.113883.3.464.1003.102.12.1018)
        - ECOG Performance Status (2.16.840.1.113762.1.4.1116.162)
        - Endotracheal Intubation (2.16.840.1.113762.1.4.1045.69)
        - Lung Cancer (2.16.840.1.113762.1.4.1116.89)
        - Lung Resection (2.16.840.1.113883.3.1434.1022)
        - Need for Ventilator (2.16.840.1.113762.1.4.1045.82)
        - Pneumonia (2.16.840.1.113883.3.666.5.752)
        - Respiratory Distress (2.16.840.1.113762.1.4.1111.53)
        - Respiratory failure acute or chronic (2.16.840.1.113883.3.666.5.2319)
    - Reasons for differences may include:
        - Different use cases
        - +/- inclusion of retired codes
        - Different groups find different codes
        - +/- inclusion on non-billable ICD codes
        - Lack of intensional rules makes comparison difficult
    - eCQMs are based on the National Quality Forum's Quality Data Model, as expressed as HL7 QRDA templates, whereas this project is based on FHIR version

1.8.0 objects[3]. The HL7 Clinical Quality Improvement committee is actively harmonizing QDM and FHIR resources, and a FHIR-based quality reporting format is expected to be balloted soon.

    - VSAC does not at this time provide intensionally-defined value sets. Therefore, comparisons are done based on enumerated lists.

- C-CDA:
    - There are no lung cancer-specific templates or value sets in C-CDA.
- https://www.nlm.nih.gov/cde/:
    - We were unable to identify any data elements that laid out specific criteria for any of the lung cancer outcomes. CDEs generally look for presence/absence of a condition, and may associate a condition with a code system or value set. As a result, there was minimal overlap between any lung cancer outcome and existing CDEs.

[3] http://hl7.org/fhir/2017Jan/index.html

Challenges and Lessons Learned

The workgroup participants agreed on a minimum set of outcome measures and harmonized definitions to capture the domains of Survival, Clinical Response, Events of Interest, and Resource Utilization. However, the workgroup was unable to reach consensus on a recommendation for capturing patient-reported outcomes (PROs). As seen in Appendix A, the workgroup agreed that capture of PROs is important, but did not reach consensus on which domains should be captured nor which instruments should be used. Instead, the workgroup recommended that registries consider collecting information on symptoms, cognitive and physical functioning, ability to participate in social roles, and toxicity using validated, publicly available tools (or a single tool that captures multiple domains) with strong psychometric properties. Noting the heterogeneous nature of lung cancer, the workgroup recommended that selection of appropriate PRO domains and instruments be guided by the purpose of the registry as well as the specific characteristics of the patient population, particularly stage of disease and treatment modality.

In this area, the workgroup diverged from the recommendations of the International Consortium for Health Outcomes Measurement (ICHOM). ICHOM, which convenes working groups and develops standard sets of outcomes and risk factors for multiple medical conditions, produced a standard set of outcome measures for use in lung cancer in 2016.[4] ICHOM recommended capture of global health status/quality of life, pain, fatigue, dyspnea, cough and physical, social, emotional and cognitive function. In contrast, the workgroup grouped pain, fatigue, dyspnea, and cough under 'symptoms' and recommended capture of physical, social, and cognitive function. The workgroup also did not recommend capture of emotional function or global health status/quality of life as part of the minimum measure set, although the group noted the potential importance of these domains as supplemental measures. In addition, ICHOM recommended use of specific instruments – the European Organization for the Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30)[5] and the corresponding lung cancer-specific module (QLQ-LC13).[6] These validated instruments were considered by the workgroup but were not recommended for three reasons. First, the workgroup did not find evidence of wide use of these instruments in clinical practice or in registry-based research. In fact, only one of the participating registries reported use of these instruments. Second, the workgroup expressed concerns about burden, as completion of both questionnaires requires a patient to answer 43 items. Finally, while these instruments may be used for free in healthcare organizations, a fee is required for use in any study wholly or partially sponsored by industry; therefore, these instruments did not meet the workgroup's requirement that recommended instruments be publicly available for all purposes.

The attempt to produce a consensus-based recommendation for capture of PROs in lung cancer pointed to the need for further research in several areas. Additional research is needed to guide the selection of appropriate PROs, particularly research into which domains are important

[4] Mak KS, van Bommel AC, Stowell C, et al. Defining a standard set of patient-centered outcomes for lung cancer. The European respiratory journal. 2016;48(3):852-60.

[5] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993; 85:365–376.

[6] Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994; 30A: 635–642.

to patients and whether these domains differ depending on disease stage and treatment modality and intent. Next, information is needed about what level of respondent burden, both in terms of number of questions and frequency of completion, is acceptable to patients at various stages of the disease. And lastly, research is needed to explore how information from PROs can be used to inform clinical decision-making.

In addition to the issues related to PROs, some challenges were encountered in translating the text definitions produced by the workgroup into standardized definitions and value sets. Of note, it is unlikely that EHRs have the ability to capture the RECIST definition for progression and recurrence using structured observations. The general case is an imaging report that asserts a change in lesion size, possibly with a measurement, but without specific reference to a specific set of lesions that have been measured.

Regarding toxicity, over 750 Grade 3 or Grade 4 complications are listed in CTCAE v5 for radiation therapy and systemic therapy. Rather than model each complication, observations were created for “CTCAE grade 3” and “CTCAE grade 4” findings. This approach also allows the definition to capture Grade 3 or Grade 4 complications, regardless of the version of CTCAE used. In addition, the concept of complications related to a procedure or treatment may be challenging to capture when using retrospective data, such as data collected from an EHR or billing system. It is often not feasible to attribute causality; events may or may not be recorded as procedure or treatment-related complications, and it can be difficult to verify. In defining toxicity, the relationship between the complication and the presumed inciting procedure/therapy is inferred by date/time stamps (as opposed to a directly asserted causal relationship).

The project team will apply these lessons learned in subsequent workgroups.

Appendix A. Harmonized Definitions for Lung Cancer Outcome Measures

OMF CATEGORY	OUTCOME MEASURE	DEFINITION	MEASUREMENT NOTES
Survival	Overall survival	Overall survival (collect cause of death, if available)	
Survival	30-day mortality	All deaths within 30 days of treatment	
Survival	Progression-free/ disease-free survival	Progression-free/disease-free survival, where feasible (see definition of progression and recurrence under 'Clinical Response')	

OMF CATEGORY	OUTCOME MEASURE	DEFINITION	MEASUREMENT NOTES
Clinical Response	Progression and Recurrence	Progression and recurrence should be measured using RECIST (see below) OR clinician documentation of progression/recurrence OR change in therapy due to progression/recurrence. RECIST (Response Evaluation and Criteria in Solid Tumors) Guideline[1] definition of Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression. Notes: RECIST cannot be used to measure radiated lesions. The sites and numbers of metastases must be captured. The date of progression, defined as the date of the source documentation recording progression or change in lesion, must be captured. [1] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer Oxf Engl 1990. 2009 Jan;45(2):228–47. The above is a brief summary of RECIST 1.1. The actual cited document governs the actual decisions regarding radiologic response or progression, including special considerations for lymph nodes as target lesions. In addition, RECIST 1.1 does not consider symptomatic deterioration or other aspects of clinical progression.	Further work is needed to recommend a consistent approach to evaluation of radiated lesions. Future efforts may also consider use of iRECIST in the context of immunotherapies, although pseudo-progression is sufficiently rare that a separate measure is not recommended for the minimum measure set.

OMF CATEGORY	OUTCOME MEASURE	DEFINITION	MEASUREMENT NOTES
Clinical Response	Change in Performance Status	Change in performance status, as measured using the Eastern Cooperative Oncology Group (ECOG) Performance Status or the Karnofsky Performance Scale Index.	
Events of Interest	Toxicity: Major Complications Other Complications	<u>Major complications</u> Surgical complications, defined as one or more of the following: Pneumonia Acute respiratory distress syndrome Bronchopleural fistula Pulmonary embolus Initial ventilator support greater than 48 hours Reintubation/respiratory failure Tracheotomy Myocardial infarction Unexpected return to operating room (any cause) Radiation therapy complications CTCAE grade 3 or 4 complications due to radiotherapy Systemic therapy complications CTCAE grade 3 or 4 complications due to radiotherapy <u>Other complications</u> Complications that do not meet the definition of major complications that resulted in change in treatment, change in dose, or schedule delay	Registries should record the version of CTCAE that was used.

OMF CATEGORY	OUTCOME MEASURE	DEFINITION	MEASUREMENT NOTES
Patient Reported	Collection of PROs that capture at least some of the important domains using one or more validated instruments is recommended.	Important domains to consider in collecting PROs are: Symptoms Functioning (cognitive, physical) Role (ability to participate) Toxicity These domains should be captured, if feasible. However, patient and clinician burden is an important consideration, and registries may elect to collect a subset of these domains. Validated, publicly available PROs with strong psychometric properties should be used to capture these domains. To minimize burden, use of a tool that captures multiple domains is recommended. Frequency of PRO collection should depend on the stage of disease, treatment modality, and frequency of office visits/patient contact.	
Resource Utilization	Healthcare utilization	All resource utilization related to treatment for lung cancer.	
Experience of Care	No specific measure	Collection of information on 1) availability of resources to manage side effects and symptoms; 2) financial burden of illness; 3) timeliness of care; and 4) goals of care / understanding of illness should be considered.	