Reducing Uninformative IND Safety Reports: A List of Serious Adverse Events anticipated *to Occur in Patients with Lung Cancer*

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Reducing Uninformative IND Safety Reports: A List of Serious Adverse Events *anticipated* to Occur in Patients with Lung Cancer

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Abstract

Expedited reporting of unexpected serious adverse reactions that occur during clinical trials conducted under an IND is a critical component of the clinical trial process designed to protect patients by identifying potential safety issues with new agents. However, in recent years, the US FDA has presented extensive data about the problem of uninformative IND safety reporting. Despite published guidance documents aimed at clarifying requirements for submission of IND safety reports for individual events, there continues to be significant over-reporting of these events by many sponsors. This leads to excessive burden for the sponsors, the investigators who conduct clinical trials, and the FDA reviewers, who must evaluate each individual report submitted by the sponsor. This trend has the potential to endanger patients by obscuring true safety signals. To address this problem, LUNGevity Foundation empaneled a multi-sector working group of its Scientific and Clinical Research Roundtable (SCRT) charged with identifying ways to reduce unnecessary distribution of serious adverse events (SAEs) reports. This paper outlines the working group's activities, including a brief list of serious adverse events "anticipated" to occur within the lung cancer population that are either related to the underlying disease or condition being studied, concomitant or background therapy, or events associated with a demographic parameter such as age. These "anticipated" events, while required to be reported by investigators to sponsors, in general, should not then be individually reported by sponsors to FDA and to individual investigators in an IND safety report because these events require aggregate analysis across the development program to determine if they occur more frequently in treated versus untreated patients. This paper also includes discussion of how the use of background threshold values, generated from real-world data, could serve as one potential tool to guide sponsors in making causality assessments. If sponsors and other key stakeholders within the clinical research ecosystem embrace this type of approach and refrain from reporting "anticipated" events as single IND safety reports to the FDA staff and to each participating investigator, it could significantly reduce the amount of unnecessary reporting and serve as a model for other disease areas.

Introduction

Sponsors of clinical trials conducted under an IND are required to submit IND safety reports to FDA and all participating investigators for suspected adverse reactions that are both serious and unexpected. This reporting is a critical component of the clinical trial process designed to protect patients by identifying potential safety issues with therapies under clinical development. The FDA has published regulatory guidance documents in 2012 and 2015 on IND safety reporting aimed at providing clear instructions for sponsors [1, 2]. Several terms are used throughout FDA guidance, including "expectedness" for the purpose of expedited reporting (referring to serious adverse events that have

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been included in the Investigator Brochure (IB) for the study drug) and "anticipated" (referring to events that, although not "expected" (listed in the IB) are anticipated to occur as a result of the underlying disease or common within the study population) (Table 1).

As stated in FDA guidance, *Safety Reporting Requirements for INDs and BA/BE Studies* [1], sponsors should have a systematic approach to safety surveillance to comply with the IND safety reporting requirements. This includes, as possible, identifying serious adverse events that are anticipated to occur in the population under study, either due to the underlying disease, concomitant therapy, or demographic characteristic (21 CFR 312.32(c)(1)(i)(C)) [3]. These events that are anticipated for the population do not warrant IND safety reporting as individual cases because it is not possible, based on a single case, to conclude that there is a reasonable possibility that the investigational drug caused the event. At the time of protocol development, the sponsor should identify, in the safety surveillance plan, the anticipated serious adverse events that it does not plan to report individually in an IND safety report under Sect. 312.32(c)(1) [1].

An analysis conducted by FDA of a selection of IND safety reports received in 2015, found that 86% were uninformative [4]. In recent years, excessive reporting of individual events has created an excessive workload for clinician investigators who enroll patients on trials and FDA reviewers, potentially reducing the opportunity to identify a true safety signal.

LUNGevity Foundation's Scientific and Clinical Research Roundtable (SCRT) has been focused on understanding and alleviating this problem. Since its inception in 2016, the LUNGevity Scientific and Clinical Roundtable (SCRT) initiative has explored key topics and worked to develop actionable steps to make lung cancer clinical trials accessible to more patients. To date, eight SCRT meetings have provided opportunities to engage leaders from the US FDA and the European Medicines Agency (EMA), and other stakeholders of the clinical trial ecosystem including patients, clinicians, and industry leaders. In 2018, an SCRT working group launched an effort to (1) evaluate how clinicians who enroll patients in lung cancer clinical trials understand and perceive adverse event reporting and (2) develop resources to assist sponsors in assessing events "anticipated" for the population of patients with lung cancer. This paper summarizes the activities of the SCRT working group, including a proposed list of events that are anticipated to occur in lung cancer patients, and an example of how one could generate background rates to use as one tool in assessing a potential causal association between these "anticipated" events and drugs under investigation.

Methods

Clinician Query

LUNGevity Foundation used an online survey to query a small group ($N = 18$) of lung cancer clinicians who serve on the organization's Scientific Advisory Board. The participant pool consisted of thoracic oncologists and pulmonologists who enroll a high number of patients on trials (an average of 100 per year, or more) and are involved in both sponsored and investigator-initiated research. This purposive sampling was meant to gather directional information about the extent of the problem in an engaged sample of seasoned lung cancer clinical trialists. The purpose of the brief survey was to determine the extent of active lung cancer clinical trial investigators' knowledge about the different types of adverse events and the associated reporting requirements (as specified in FDA Regulations and Guidance). The survey was constructed with feedback from the FDA, industry partners, and clinicians.

Analysis of Clinical Trial Data to Identify Types and Numbers of Serious Adverse Events

To inform the development of a list of events "anticipated" to occur in patient with lung cancer, the working group evaluated the types and numbers of serious adverse events

Table 1. Definition of "Expected" and "Anticipated" Events.

Term	Definition[a]
Expected	An adverse event or suspected adverse reaction is considered Expected if it is listed in the investigator brochure or is listed at the specificity or severity that has been observed
Anticipated	Certain serious adverse events can be Anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population)

[a]FDA. Safety reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies. In: Administration USFaD, (ed.) 2012.

(SAEs) in clinical trials in patients with lung cancer that have been submitted to the FDA in the previous 2 years.

Estimating and Developing Threshold Values

The use of background threshold values, generated from real-world data, could serve as one potential tool to guide sponsors in making causality assessments, although this would not replace clinical judgment, nor would its use be mandated. We used the US Surveillance, Epidemiology and End Results (SEER)-Medicare database to examine 5 of the pre-specified anticipated events [pneumonia, chronic obstructive pulmonary disease (COPD) exacerbation, and venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) separately] occurring among the adult non-small-cell lung cancer (NSCLC) population in the inpatient setting between 2007 and 2014. The SEER-Medicare database includes patients aged 65 years and older (Medicare eligible) who are diagnosed with cancer and reside in one of the geographic areas contained in the SEER registries; as of 2013, the SEER Program encompassed about 28% of the US population. The linkage to SEER data allows for the identification of patients with lung cancer by histology and stage, details that are typically missing in administrative health claims databases.

Patients were included in the study if NSCLC was recorded as a first primary diagnosis between January 1, 2007, and December 31, 2014; they were greater than or equal to 65 years of age on this diagnosis index date; and they were continuously enrolled in Medicare Part A and B coverage during the 6-month baseline period and the month of the diagnosis index date. Patients were excluded if multiple primary cancers were recorded in the SEER cancer registry during the patient identification period, if the cancer diagnosis was reported exclusively by death certificate or autopsy, or if the event of interest occurred during the 6-month baseline period prior to the NSCLC diagnosis.

Previously published ICD-9-CM codes and algorithms were employed to define the anticipated events of interest [5–7]. Incidence rates for pre-specified anticipated events, recorded as the principal diagnosis in the inpatient setting (as a surrogate for severity), were determined overall and by several relevant strata as available. Unlike proportions, rates account for variability in patient follow-up time, in this case the observation window following a NSCLC diagnosis.

For each anticipated event separately, incidence rates were calculated using person time. The numerator represents the number of persons with a new anticipated event of interest during the follow-up period. The denominator is the sum of all patient person-years from time of NSCLC diagnosis date until death, disenrollment from Medicare Part A and B coverage, end of the study period, or the first anticipated event occurrence, whichever comes first. The 95% confidence intervals (CIs) were calculated based on the binomial (Clopper–Pearson) exact method. All statistical analyses were conducted using SAS version 9.4

Results

Clinician Query

Six clinicians (representing leading lung cancer specialists and clinical trial investigators) responded to a query via online survey. While the investigators were clear about the distinction between "anticipated" and "expected" events, they were unclear about the sponsor requirements for evaluating and reporting such events as either single case reports or in the aggregate. Unanimously, those investigators reported that the number of individual IND safety reports that they must review is too high and that this excessive amount of reporting does not serve the primary objective of protecting patient safety.

Serious Adverse Events in Recent Lung Cancer Trials

An analysis of nine recent trials in patients with lung cancer submitted to FDA covering more than 3000 patients yielded more than 550 serious adverse events (using MedDRA preferred terms) that were included in the datasets submitted to FDA by trial sponsors (Fig. 1).

This list was used as a starting point to identify serious adverse events that were commonly reported from investigators to sponsors during the conduct of recent clinical trials in patients with lung cancer regardless of drug treatment or causality assessment. Clinicians in the LUNGevity working group reviewed this list and added other serious adverse events that they commonly observed in patients with lung cancer.

"Anticipated" Events List: Proposed Tool for Sponsors of Lung Cancer Trials

Using the clinical trial data as a starting point, the SCRT working group developed a proposed list of events "anticipated" in lung cancer categorized by body systems considering both medical concepts familiar to investigators and MedDRA preferred terms used by sponsors and FDA in safety reporting.

The working group relied on the extensive clinical experience of a small team of lung cancer experts in academic ($N=3$) and community settings ($N=3$), as well as the expertise among industry ($N=2$) and FDA colleagues. The list was compiled and refined through a consensus-driven,

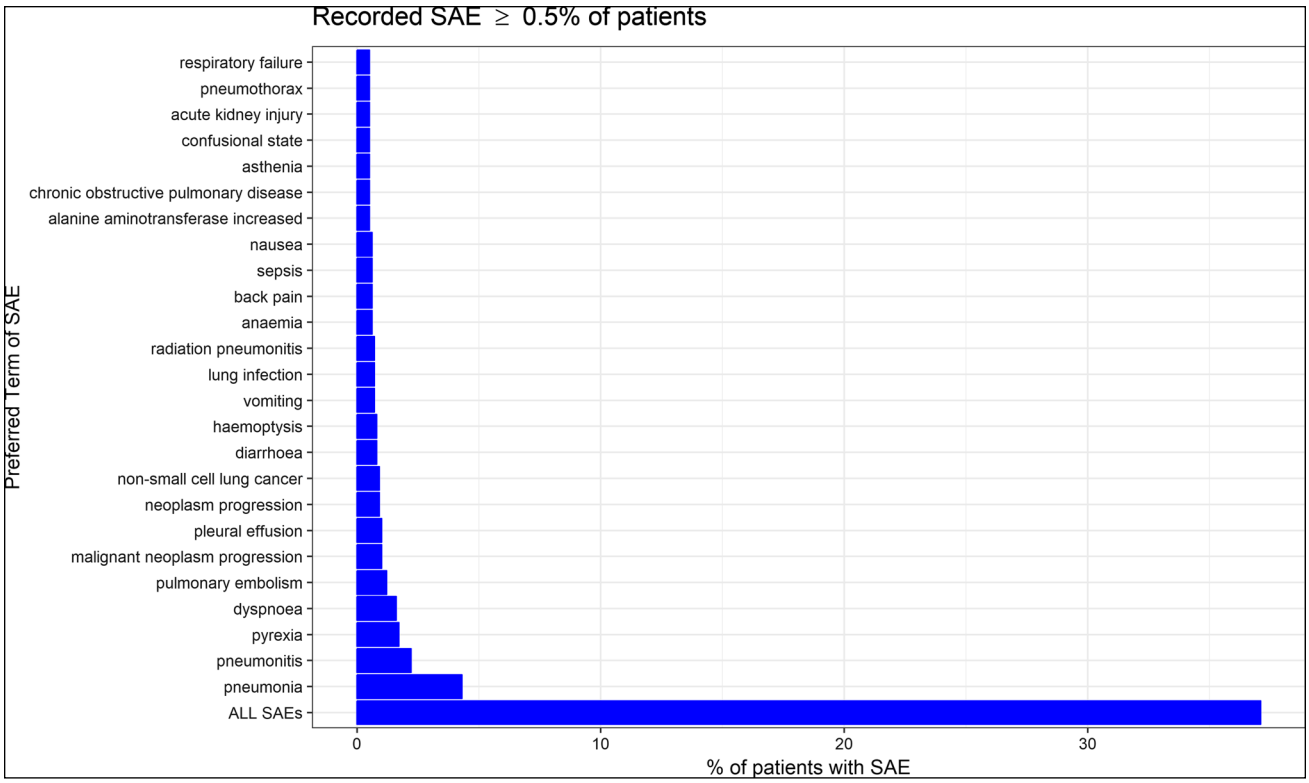

Figure 1. List of MedDRA Terms Used in AE Reporting.

iterative process among working group members, before being presented to the entire SCRT for review and comment. The list of reported terms (Table 2) was reviewed during the November 2018 LUNGevity SCRT meeting and was the focus of discussion with safety representatives from nine biopharmaceutical companies during an interactive webinar (January 23, 2019).

The list is presented here as a resource for sponsors of clinical trials to refer to while developing their pre-specified list of serious adverse events that are anticipated to occur in patients with lung cancer. For example, these patients frequently experience weight loss, decreased appetite and hypoxia that are conditions associated with lung cancer, and are not likely to be causally associated with the investigational medication. Because these events often require hospitalization, they must be reported to the sponsor as serious adverse events. However, absent a compelling reason to assess these events individually, these events should be analyzed periodically during the development program by the sponsor in aggregate analyses to determine whether the events occur more frequently in the drug treatment group than in a concurrent control group or the population under study and therefore meet the criteria for IND safety reporting.

An Approach for Estimating and Utilizing Thresholds

The SEER-Medicare NSCLC cohort consisted of 62,123 patients. Slightly more than half were male (52.4%) and the median age at diagnosis was 75 years (range: 65–105). Most (85.4%) patients were white, 9.0% were Black, and 5.2% were Asian. The majority (68.1%) were from Southern (30.4%) or Western (37.7%) geographic regions. At baseline, roughly one-third (35.3%) had a Charlson comorbidity index (CCI) [8] score of 1 or 2 while 11.3% had a CCI score of 3 or greater. Almost half (45.7%) were diagnosed with stage IV disease; 63.0% had advanced stage disease (stages IIIb and IV) at diagnosis.

The incidence rates of pre-specified anticipated events are shown in Table 3. Incidence rates overall were lowest for DVT and highest for pneumonia. Those with CCI scores greater than or equal to 1 appeared to have higher rates of COPD exacerbation and pneumonia than those with a CCI score of 0, while those with advanced stage disease had higher rates of all pre-specified anticipated events compared to those with early-stage disease.

These data should be viewed primarily as illustrative rather than as benchmark event thresholds. There was no replication of the findings in other databases, no confirmation of the events of interest of their severity through chart

Table 2. Proposed List of Serious "Anticipated" Adverse Events in Lung Cancer.

Condition	Event
Constitutional	Dehydration Sepsis Weakness/asthenia Fatigue Fever/pyrexia Weight loss Failure to thrive Decreased appetite/ anorexia General physical health deterioration (Decline in ECOG performance status)
Respiratory	Pneumonia Upper respiratory infection Lower lung infection Hypoxia Dyspnea Bronchitis (chronic) Emphysema COPD exacerbation Malignant pleural effusion Empyema Pulmonary emboli Pulmonary edema Respiratory failure Pneumothorax Hemoptysis Radiation pneumonitis
Cardiovascular	Heart failure Atrial fibrillation /flutter with rapid ventricular response Superior vena cava syndrome Pericardial effusion Cardiac tamponade (associated with pericardial metastasis) Myocardial infarction Stroke
Gastrointestinal	Dysphagia Esophageal obstruction Intestinal obstruction Bleeding ulcers Diverticulitis
Musculoskeletal (associated with metastatic or advanced disease)	Pain Fractur
Hematologic	Thromboembolic events—deep vein thrombosis, pulmonary emboli Anemia
Neurologic (associated with metastatic or advanced disease)	Cranial nerve palsies Weakness of upper, lower extremities Confusion Mental status changes Seizures Unstable gait
Malignant neoplasm progression	Malignant disease progression

review or independent adjudication), and no consideration of drug exposure or other factors (e.g., smoking status and ECOG performance score (PS)). Therefore, rates in Table 3 reflect a "general" elderly NSCLC population. Ideally, one would define the patient population so that patient characteristics (e.g., disease stage, age, ECOG PS, biomarker status, prior drug exposure) are aligned with the trial population of interest. One would select a database in which both the patient population of interest and the anticipated event of interest could be identified. Therefore,

Table 3. Incidence rates (per 1000 person-years) of Inpatient Anticipated Events in the Non-Small-Cell Lung Cancer (NSCLC) population (SEER-Medicare 2007–2014), Overall and Within Key Strata.

	VTE [8]	PE [8]	DVT [8]	COPD exacerbation [8]	Pneumonia [8]
Overall	33.9 (32.7–35.2)	22.4 (21.4–23.5)	11.9 (11.2–12.6)	52.3 (50.7–53.9)	106.6 (104.4–108.9)
Male	35.5 (33.7–37.4)	23.8 (22.4–25.4)	12.0 (11.0–13.1)	54.4 (52.1–56.8)	128.9 (125.3–132.7)
Female	32.5 (30.8–34.2)	21.1 (19.8–22.5)	11.8 (10.8–12.8)	50.4 (48.3–52.6)	86.9 (84.1–89.8)
Age < 75 (median)	35.6 (33.9–37.5)	23.9 (22.5–25.4)	12.4 (11.4–13.5)	53.2 (51.0–55.5)	103.5 (100.4–106.8)
Age ≥ 75	32.1 (30.4–33.9)	20.9 (19.5–22.3)	11.4 (10.4–12.4)	51.4 (49.2–53.6)	109.8 (106.5–113.2)
CCI [1] = 0	35.3 (33.7–37.1)	24.3 (22.9–25.7)	11.5 (10.6–12.5)	33.3 (31.7–35.0)	89.1 (86.4–91.9)
CCI = 1–2	31.7 (29.8–33.8)	20.1 (18.5–21.7)	12.2 (11.0–13.5)	73.9 (70.7–77.1)	121.3 (117.2–125.6)
CCI = 3 +	33.5 (29.5–38.0)	20.2 (17.1–23.8)	13.0 (10.5–15.8)	96.3 (88.9–104.3)	169.6 (159.5–180.3)
Stages I–IIIa	17.8 (16.7–19.0)	12.2 (11.2–13.1)	5.6 (5.0–6.3)	48.7 (46.8–50.7)	73.8 (71.4–76.3)
Stages IIIb/IV	59.0 (56.4–61.7)	38.3 (36.2–40.5)	21.6 (20.1–23.2)	57.6 (55.0–60.3)	157.4 (153.0–161.9)

Rates are per 1000 person-years and include 95% confidence intervals.

VTE venous thromboembolism (415.×, 451.×, 453.×); *PE* pulmonary emboli (415.×); DVT: deep vein thrombosis (453.x); COPD: chronic obstructive pulmonary disease (491.×, 492.×496); pneumonia (480.××to 486.××); *CCI* Charlson comorbidity index [8].

SEER-Medicare would not be a suitable choice for cancers typically diagnosed below the age of 65. If one wishes to identify an anticipated event requiring hospitalization, one would need to select a database that links to the inpatient experience of patients.

To utilize a background threshold for PE, as an example of a serious, unexpected, but anticipated adverse event, biostatisticians, at the request of safety personnel, would calculate the incidence rate of PE occurring across trials of interest. If the observed rate of PE exceeded the background threshold for PE, a qualitative assessment would be performed to determine if there is a reasonable possibility of a causal association that would meet the criteria for submission as an IND safety report.

Discussion of Global Regulatory Distinctions

Due to divergent global regulatory requirements, it is challenging for many sponsors to develop processes and technologic capabilities to ensure differential safety reporting in accordance with regulatory agency requirements in each region in which a trial is conducted. Although FDA safety reporting guidance [1, 2] states that sponsors should have a systematic approach to safety surveillance, including a process to prospectively develop a list of anticipated serious adverse events to comply with the IND safety reporting requirements, to date such guidance has not been adopted by regulatory agencies outside of the United States.

Therefore, sponsors may be unable to apply processes described in FDA guidance to trials they conduct globally. It would be very beneficial for sponsors and regulatory agencies to collaborate to develop harmonized safety reporting regulations and guidance concerning anticipated events that would enable optimized safety reporting to agencies while assuring patient safety.

Conclusions

The problem of uninformative IND safety reporting is of significant concern to clinicians, regulators, patients, and sponsors. It drains resources, creates unnecessary workload, and, most importantly, has the potential to obscure the identification of true safety signals.

LUNGevity Foundation and its SCRT working group hope the development of a proposed list of events "anticipated" for patients with lung cancer will be embraced by trial sponsors and will help to reduce the numbers of uninformative individual IND safety reports. If this effort proves successful in mitigating a portion of the problem, we hope the "anticipated" events list might serve as a

model for use in clinical trials investigating novel therapies for other diseases.

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