Cancer Treatment Reviews 76 (2019) 33–40

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Controversy

Improving attribution of adverse events in oncology clinical trials

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ARTICLE INFO

Keywords:
Attribution
Adverse event
Clinical trial
Cancer treatment
Toxicity
Symptom

ABSTRACT

Attribution of adverse events (AEs) is critical to oncology drug development and the regulatory process. However, processes for determining the causality of AEs are often sub-optimal, unreliable, and inefficient. Thus, we conducted a toxicity-attribution workshop in Silver Springs MD to develop guidance for improving attribution of AEs in oncology clinical trials. Attribution stakeholder experts from regulatory agencies, sponsors and contract research organizations, clinical trial principal investigators, pre-clinical translational scientists, and research staff involved in capturing attribution information participated. We also included patients treated in oncology clinical trials and academic researchers with expertise in attribution. We identified numerous challenges with AE attribution, including the non-informative nature of and burdens associated with the 5-tier system of attribution, increased complexity of trial logistics, costs and time associated with AE attribution data collection, lack of training in attribution for early-career investigators, insufficient baseline assessments, and lack of consistency in the reporting of treatment-related and treatment-emergent AEs in publications and clinical scientific reports. We developed recommendations to improve attribution: we propose transitioning from the present 5-tier system to a 2–3 tier system for attribution, more complete baseline information on patients' clinical status at trial entry, and mechanisms for more rapid sharing of AE information during trials. Oncology societies should develop recommendations and training in attribution of toxicities. We call for further

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https://doi.org/10.1016/j.ctrv.2019.04.004
Received 23 April 2019; Accepted 24 April 2019

harmonization and synchronization of recommendations regarding causality safety reporting between FDA, EMA and other regulatory agencies. Finally, we suggest that journals maintain or develop standardized requirements for reporting attribution in oncology clinical trials.

Introduction

The reporting of adverse events (AEs) is an essential aspect of oncology drug development and the regulatory process. AE reporting is key to determining a new drug's toxicity profile [1], which will ultimately contribute to the benefit–risk assessment and will be included in the label [2]. However, the process for determining the origin of the AE is challenging [3–5], sub-optimal and inefficient and produces information that may be of limited or uncertain value for regulatory decision-making and for informing clinical practice and future research steps. These inefficiencies can result in added burden upon resources (eg, cost, time, and effort) for investigators, industry, ethics committees, and regulatory bodies. Ultimately, inefficient processes affect patients by limiting the number of new medicines that can advance through the clinical trial trajectory and reducing the collection of actionable information that could guide optimal care delivery and support.

The American Society of Clinical Oncology (ASCO) and other groups have recognized these concerns and made recommendations for streamlining the reporting of serious adverse events [3]. Although the published ASCO guidelines address the issue of attribution of the AE (initial assessment of whether or not the event is caused by the agent being tested), they focus primarily on other parts of the process, such as expedited Investigational New Drug safety reporting. The ASCO panel

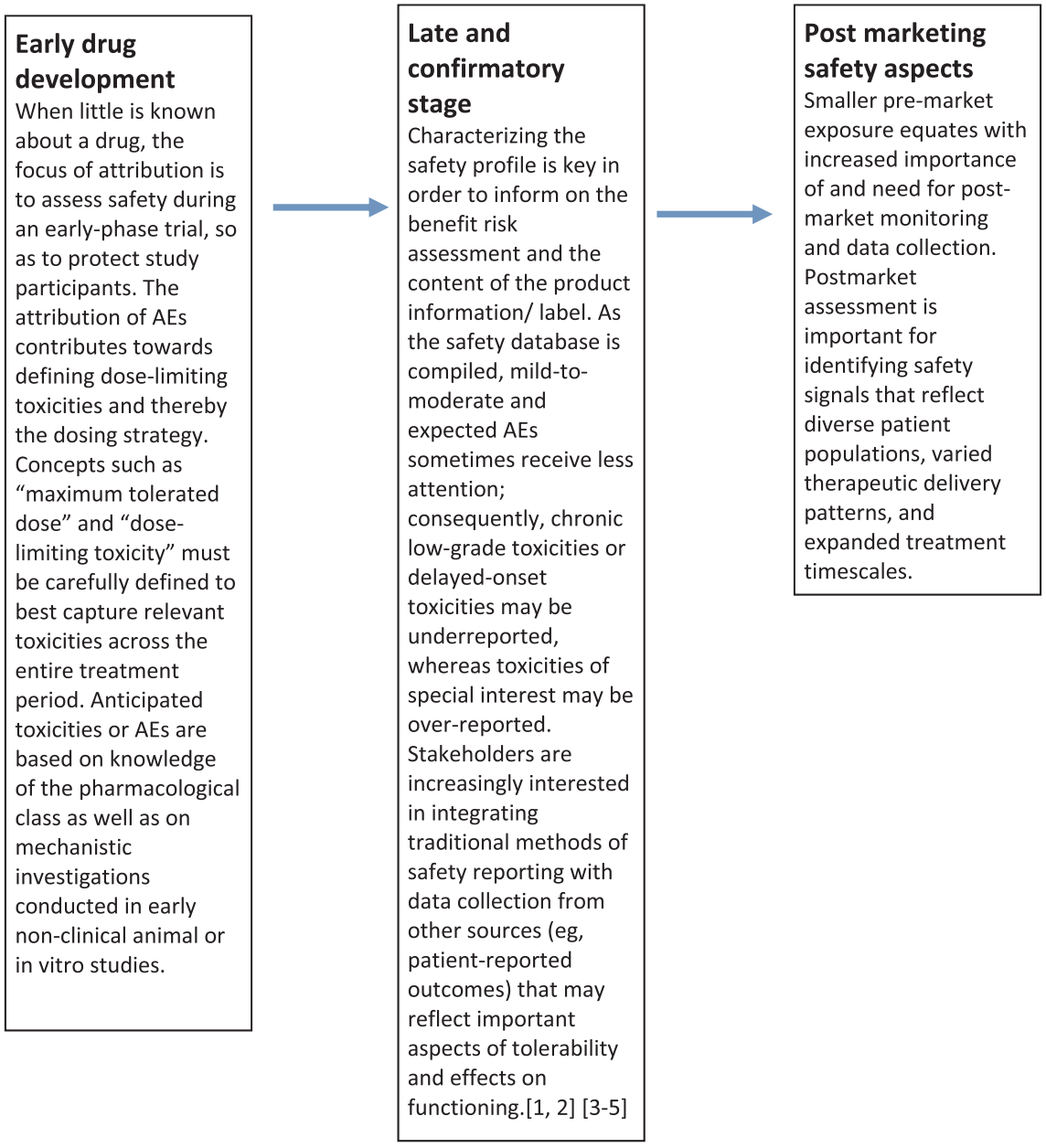

Fig. 1. The Focus of Attribution through the Drug Development Program.

acknowledged that it was often difficult to distinguish AEs that result from an intervention from those with other causes.

In order to review the challenges with attribution and develop recommendations for improving attribution, a consensus-building workshop on toxicity attribution was convened in Silver Springs, Maryland in September 2017. Discussions were held with multiple stakeholders, including representatives from regulatory agencies from both the United States and Europe, the US National Cancer Institute (NCI), pharmaceutical sponsors and contract research organizations, academic clinical trial principal investigators, non-clinical translational safety scientists, and research staff involved in capturing AE attribution information. The working group also included patients who had been treated in early-phase clinical trials and academic researchers with expertise in attribution. The working group attribution stakeholder experts were selected based on nominations from regulatory agencies, experienced clinical trialists, and the NCI. The working group focused on reviewing current practice, including the rigor and utility of AE attribution, identifying major concerns with the current process of attribution, and developing consensus on how AEs might be more precisely attributed to treatment-related versus non–treatment-related causes.

Preparation for the toxicity-attribution workshop included a series of teleconferences with multiple expert stakeholders and a pre-workshop in Houston, Texas in February 2017 to review the current state of AE attribution, identify key issues for further work, and create the agenda topics and key issues and questions for the September workshop. The workshops were co-sponsored by the Friends of Cancer Research, The University of Texas MD Anderson Cancer Center, and The Health and Environmental Sciences Institute®.

Defining attribution and its importance

Attribution is defined as “the act of saying or thinking that something is the result or work of a particular person or thing.”[6] In cancer research, attribution is the determination of whether or not an untoward clinical event that occurred during (or after) the administration of a treatment is related to the treatment. The term is primarily used in relation to the study drug or intervention in a clinical trial. In certain regulatory contexts (eg, the European Union), the terms “causality” or “relatedness to study treatment” are used when referring to attribution. Attribution is referred to as “relatedness to study treatment” in the scientific literature [7]. The purpose of attribution varies during the different phases of the development program for a new medicine (Fig. 1). For the purposes of this paper, we will focus on attribution in the context of its relation to oncology clinical trials.

Implications of misattribution

Accurate attribution of AEs to an experimental drug versus other potential causes, such as other concomitant therapies, symptoms of the underlying disease, or comorbidities, is not always straightforward. An event may be incorrectly attributed to other causes when it is in fact related to the experimental therapy (Type A error), or it may be attributed to the experimental therapy when in fact it is associated with other causes (Type B error) [7,8]. Type A errors can result in more patients being exposed to potentially toxic levels of the drug, with a negative impact on safety, whereas Type B errors may lead to premature study termination [8]. These errors are known to negatively affect estimates of the “true” maximum tolerated dose (MTD) and, consequently, the accuracy, safety, sample size, and/or treatment dose or duration of a future confirmatory trial [8].

The magnitude of impact of these errors is related to the trial design used. Data suggest that the standard “3 + 3” dose-escalation schema (wherein patients are enrolled at increasing dose levels based on the presence or absence of dose-limiting toxicities in a pre-specified proportion of patients until the MTD is determined) [9] is particularly sensitive to Type B errors [8,10]. Misattribution of dose-limiting toxicities also has the potential to lead to underestimation of the MTD. Even with biologic agents (for which a minimally effective dose, rather than an MTD, is frequently preferred), proper understanding of the expected toxicities and therapeutic window of a given agent has important implications for further development and clinical use.

Downstream consequences of misattribution include the potential for evaluating sub-therapeutic doses of the drug and inaccurate safety profiling of the drug in the label. As a worst-case scenario, poor attribution can lead to a faulty final causality assessment, affecting the

Table 1
Principles for Assessing Causality of an Adverse Event.

Broad Factor/Category	Principle	Explanatory wording
Patient-level factors	Timing of the adverse event (AE) relative to drug exposure; plausible temporal relationship	Is the timing of the AE compatible with its being caused by the drug? Did it occur, or increase in severity, during or after exposure to the drug?
	Relation of AE to baseline symptoms, including severity	Is the AE an existing comorbidity, disease symptom, or residual toxicity from previous therapy, as illustrated by existence at baseline? Did it increase in severity after administration of the drug?
	Response to interruption of administration (“de-challenge”) or to readministration of the agent after recovery from the AE (“re-challenge”)	Did the AE resolve with drug interruption? Did it recur if or when the drug was restarted?
	Dose-response patterns in the individual patient that indicate a causal relationship	Is the event increasing and decreasing with dose reductions and increases? Note: Not relevant at first occurrence
	Likelihood of alternative causes, such as disease symptoms, other medication, other disease	Does the patient have comorbidities or concomitant medication likely to cause the AE, or is the AE expected in the patient population (eg, due to age)?
Agent-level factors	Preclinical and clinical knowledge of the drug, its pharmacology and toxicology; AE identified as a drug reaction in the reference safety information (“expectedness”)	Is the AE something that the drug is expected to cause? It the AE biologically plausible if related to the drug?
Trial or program level/ aggregate data level factors	Dose-response patterns across patients that indicate a causal relationship	Is the event increasing and decreasing with dose/exposure?
	Incidence of the AE in the intervention group versus placebo or active comparator groups	Is there a relevantly higher frequency in the experimental arm (which usually indicates that the event has a causal relationship with the drug)? Note: Lower frequencies in the experimental arm versus an active comparator arm still may be compatible with a causal relationship and must undergo further biological-pharmacological plausibility assessment.

benefit–risk assessment. Patients may be taken off active therapy unnecessarily, and the product label may incorrectly identify an event as being causally linked to the drug.

Current status of attribution

Framework for AE reporting

The lexicon for AE identification and grading in the context of oncology clinical trial reporting is the Common Terminology Criteria for Adverse Events (CTCAE), first developed in 1983 by the NCI's Cancer Therapy Evaluation Program (CTEP) [11]. The newest CTCAE version, v5.0, was released in 2018 and includes new AE terms, clarified definitions, and updated grading [12]. In 2016, the NCI released its patient-reported outcomes version of the CTCAE, a new standardized method for assessing symptomatic AEs from the patient's perspective. In 1998, the CTEP introduced the idea of collecting and reporting AE attribution data in clinical trials, based on a set of 5 nominal categories of attribution to study drug: "definitely related," "probably related," "possibly related," "unlikely related," and "unrelated" [13].

Attribution is assigned at the patient level and then summarized at the trial level. However, even in those instances in which attribution appears to be well defined, the selection of an AE term and its grading are highly user dependent and are a potential source of variation in the reporting of trial data [14].

Methods for making attribution

Sponsors are charged with identifying all AEs that are attributable to an agent being tested in a clinical trial, especially in early-phase studies that evaluate the safety of new medicines. This information is collected in a standardized format by site investigators and summarized by the sponsor, who is ultimately responsible for reporting serious and unexpected suspected adverse reactions to the FDA and other regulatory authorities that have jurisdiction over the study locale. A product of these efforts in the United States was a guideline for streamlining AE reporting produced by the Clinical Trials Transformation Initiative, a publicprivate partnership to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials [3,15]. To further this process, the present working group discussed and summarized the main principles for assessing causality in order to provide a hands-on tool to guide study investigators (Table 1).

Challenges in the current state of attribution

The current system for attribution is not optimal. In a retrospective

Table 2
Challenges Associated with Attribution.

Issue	Description
Trial logistics, costs, and time	• Site investigator time to gather sufficient clinical data to review and determine adverse event attribution Extensive amounts of AE attribution data are collected and reported, and this represents a burden for researchers, research site personnel, and regulators [31,32]. Cancer patients may have multiple different AEs over the course of a trial. AE attribution reporting may be particularly burdensome for patients with diseases associated with multiple events as part of the nature of the disease, such as patients with hematologic disease.
Lack of education about assigning attribution	• Specific training and concrete guidelines on how to reliably attribute AEs in clinical research either are often insufficient or lacking altogether [33,33].
Advanced disease, multiple previous therapies, and multiple comorbidities	• Attribution of AEs is particularly challenging in patients with advanced disease who may have undergone multiple treatments (including chemotherapy, radiation, hormonal therapy, targeted agents, and/or hospitalizations) [3]. Some patients with advanced disease may also be older, with higher levels of disease-related symptoms, multiple comorbidities, and concomitant medications [3]. With the broadening of clinical trial eligibility criteria [34], there will likely be more patients with pre-existing conditions and, subsequently, a greater potential for drugdrug interactions and comorbidities as possible causes of AEs.
Insufficient baseline information about health status at trial entry	• Baseline data are often inadequate. There is great variability across institutions in the symptoms or clinical abnormalities assessed at baseline and the degree of comprehensiveness with which baseline assessments are performed. Inadequate baseline examination and documentation and insufficient washout periods can increase the potential for confounding toxicities that are actually late effects of a previous drug. This may cause AEs to be incorrectly attributed to the new therapy being tested in a clinical trial. Also, patients may underreport the use of over-the-counter medications and supplements that could have potential drugdrug interactions, which could affect expected adverse events.
Multiagent studies	• Combinations of cancer drugs are often tested in early-phase clinical trials, yet the safety profile for each of the novel drugs being tested, as well as their combination, may not be fully known. Although some of the individual drugs being tested may not have direct pharmacokinetic or pharmacodynamic interactions, they may have overlapping toxicities, making it very difficult to determine whether the different oncology compounds are synergistic or additive with each other in terms of AEs.
Inconsistencies in reporting of treatment-related AEs	• A lack of consistency in how treatment-related and treatment-emergent AEs are reported in publications and clinical scientific reports can add to confusion around the attribution of AEs [14]. Moreover, results from an individual trial are now being reported in multiple forms, including publications, regulatory documents, clinical study reports, registries, medical meetings and presentations, and patient-level data portals and other databases [35], creating the possibility of greater variation and heterogeneity in AE reporting due to these differing formats [35]. It is also common to default to reporting only serious adverse events (SAEs). This may be confusing, as the trial definition of an SAE may differ from what a reader may understand as "serious" as it relates to an AE. Thus, despite somewhat uniform definitions of what defines an SAE, there is wide heterogeneity on what is reported as an SAE, at least in hematological malignancies.
Attribution process	• Classification that has insufficient sensitivity and reliability Reluctance of investigators to rule out possibility of causal relationship based on the wording of the present 5-tier scale for attribution (i.e., unrelated, unlikely to be related, possibly related, probably related, definitely related)
Utility of attribution	• Lack of clarity to trial sponsors and regulators on the utility of attribution of non-serious AEs. (Expedited reporting of serious AEs and suspected unexpected serious adverse reactions (SUSARs) does require attribution, however, to promote safety of patients on clinical trials.)

analysis of data from Phase III, randomized, double-blind, placebo-controlled trials, Hillman et al. [16]. found a relatively high frequency (up to 50%) of AE reports in placebo arms being reported as at least possibly related to treatment. It was also found that attribution of repeated AEs within the same patient (defined as a second or subsequent occurrence of the same event) changed over time. A subsequent pooled analysis now using data from nine randomized, multicenter, placebo-controlled trials, found that 7585% of all AEs that were deemed related to treatment were classified as only possibly related [7]. They concluded that AE causality determinations were often complex, unreliable, and subjective, suggesting that attribution should be eliminated in randomized double-blind placebo-controlled trials [7]. The working group recognizes that many of the challenges that contribute to the burden of attribution are inherent to the field and cannot easily be overcome, such as frequent overlap of drug toxicity and disease symptoms [5]. The major challenges identified by the working group are summarized in Table 2.

Recommendations for improving attribution

The working group identified actionable issues and proposes the following recommendations, summarized in Table 3.

Recommendation 1: improve attribution efficiencies

Recommendation 1A: collapse the current 5-tier AE attribution categories into a 2-tier or 3-tier system

There was strong consensus that the 5-tier system needs to be changed. In a study based on early-phase trials, Eaton et al. [17] found that toxicities rated as "possibly," "probably," or "definitely" related were associated with dose of study drug, whereas "unlikely" or "unrelated" toxicities were not. Based on this study, Eaton et al. [17]. recommended collapsing attribution categories. Also, multiple attribution stakeholders at the workshop indicated that the differences between "possibly related" and "probably related" categories are difficult to delineate, and that many investigators tend to avoid specifying an AE as unrelated, given that only rarely can one completely rule out the possibility that the drug contributed to the event.

We propose migrating from the 5-tier system to a 2-tier (related or unrelated) or 3-tier (related, unrelated, or unknown) system of attribution. This would simplify the attribution process without losing valuable information. Arguments in favor of a 2-tier system are that it forces investigators to commit to whether or not an AE is related to study treatment and that it may be consistent with what some investigators do on an instinctive basis. Arguments in favor of 3-tier system are that sometimes there may be insufficient information to guide the attribution and that an option to reflect this may be needed, particularly in early-phase development, when the knowledge of the agent's safety profile is limited. Thus, a 3-tier system may provide greater transparency. Also, any uncertainty that may be related to an individual physician or center, i.e., "center effects," will become more transparent and can then be documented and further analyzed. A 3-tier system may allow study designs to prescribe different trial consequences for AEs that are attributed to the unknown middle tier versus AEs that are likely related to study drug. It may further facilitate the principal investigator's assessment of sub-investigator attributions by allowing him or her to focus on the difficult ones, which would not be identified in a 2-tier system. For a 2-tiered system, more time and investigative effort may be needed to identify the true cause. On the other hand, a potential shortfall of the 3-tiered system is that the middle option could become a default, non-committal selection in some instances (for example, for interventions testing less-known drugs).

Regardless of whether a 3-tiered or 2-tiered system is selected, we propose the use of likelihood-based wording that clearly communicates that the attribution to be made is a probability assessment based on the investigator's current knowledge, and not the ultimate "true" attribution. This approach would likely increase the quality of attribution by reducing the proportion of attributions that lean toward the "safe side." Wording for the 2-tier system could be: "more likely related to study drug (than other causes)" or "more likely related to other causes (than study drug)." Wording for the 3-tier system could be: "more likely related to study drug (than other causes)," "equally likely related to study drug and other causes," or "more likely related to other causes (than study drug)." The choice of the middle tier, "equally likely," could be made when there is insufficient information to make the call toward either side; it could be used when it is impossible to differentiate between drug toxicity that overlaps with symptoms of the disease under treatment (eg, fatigue, nausea, or myelosuppression).

Studies would be needed to compare the two- vs. three-tier system of toxicity attribution, and to also test different phrasings of the likelihood-based wording used to describe each tier.

Recommendation 1B: remove attribution of non-SAEs from randomized placebo-controlled trials

Attribution of AEs may be of less value for the regulatory benefitrisk evaluation of randomized placebo-controlled trials. For the protection of trial participants, SAEs still need to be attributed for potential expedited reporting. The working group proposes that AE attribution for non-SAEs should be eliminated in randomized double-blind placebo-controlled trials where objective data are available to determine the relatedness of AEs [7].

Recommendation 1C: for combination regimens, consider attribution in terms of the entire regimen

It is frequently not possible to attribute AEs to individual drugs in combination regimens, but it should always be possible to attribute toxicity to the combination regimen as a whole. This is in line with guidance in the EMA's revision 5 of the "Guideline on the evaluation of anti-cancer medicinal products in man," which encourages defining causality of AEs in relation to the overall combination treatment regimen being evaluated when definition of causality in relation to individual drugs may not be possible [18].

Recommendation 1D: define a process for removing an AE from the list of expected events

In early-phase trials, the inclination is to assume that all toxicities are from the agent under investigation, as it is difficult to rule out its lack of contribution. Conversely, in later-phase trials, AE causality should be reviewed and refined. A standard operating procedure for refining AE causality could be envisaged. An example is provided by the

Table 3
Recommendations for Improving Attribution.

1. Improving attribution efficiencies
   - 1. a Collapse the current 5-tier AE attribution categories into a 2-tier or 3-tier system and use likelihood-based wording to increase the sensitivity of attribution
   - 1. b Remove attribution of non-SAEs from randomized placebo-controlled trials
   - 1. c For combination regimens, consider attribution in terms of the entire regimen
   - 1. d Define a process for removing an AE from the list of expected events
2. Improve processes and tools for attribution
   - 2. a Require more clinically actionable information about expected toxicities
   - 2. b Establish online access to updated safety profile information
   - 2. c Establish standard operating procedures to facilitate and improve the quality of clinical research, especially baseline assessments
   - 2. d Promote the importance of experienced clinical trial investigators and trial sites
   - 2. e Explore the utility of patient-reported outcomes for capturing AEs at baseline and longitudinally
3. Improving the consistency of attribution
   - 3. a Educate those who conduct clinical trials on best practices for attribution
   - 3. b Standardize reporting of attribution in publications
   - 3. c Pursue harmonization of AE reporting recommendations among regulatory agencies

NCI's Cancer Therapy Evaluation Program (CTEP)'s Comprehensive Adverse Events and Potential Risks (CAEPR) source documents [19]. CAEPRs list expected toxicities for each drug as a guide to help the investigator with AE reporting; they are developed on the basis of the number of patients treated and allow for a more realistic assessment of AEs from an agent [19].

CTEP examines various items to develop a CAEPR, including the investigator's brochure, available animal data, safety communications, its own sponsored trial database, and publications [19]. Defining a process for when to remove an AE from the list of expected events would make attribution a fluid process as knowledge accumulates. This should be continued from first-in-human through Phase IV trials and incorporate prescribing data of drugs once approved, to avoid unfairly tagging drugs in perpetuity with events of dubious significance or association.

Additional considerations on improving attribution efficiencies

In addition, the working groups discussed the possibility to limit the reporting of lower grade AEs in order to facilitate the attribution process. However, although lower-grade AEs have often been regarded as clinically less important in the past, and therefore of less interest to collect, this may not hold true for newer agents, such as targeted and immunotherapies and oral agents that are meant for long-term chronic administration, when low-grade adverse drug reactions (such as fatigue and diarrhea) can have a major impact on overall tolerability and the possibility to maintain an efficacious dose-intensity.

Recommendation 2: Improve processes and tools for attribution

Recommendation 2A: require more clinically actionable information about expected toxicities

As part of best practices, investigators need either more clinically relevant information or greater understanding of how to interpret the available pre-clinical data in order to make robust calls on attribution. Although the protocol and the investigator's brochure are required to have preclinical data and information on anticipated AEs, toxicities, and symptoms based on drugs of a similar action, the working group suggests that these resources could be augmented with enhanced discussion on the interpretation of such data in the context of the anticipated presentation of symptoms/toxicities in the patient. Easier access to such information could be provided by sponsors to investigators by digitizing the investigator's brochure to make it searchable. Additionally, the provision in a standardized format of comprehensive lists of reported and potential AEs associated with an investigational agentsimilar to the CAEPR list required by the NCI for CTEP-sponsored clinical trialscould be of value [19]. Better and more standardized, digitalized databases of drugs with potential drugdrug interactions (such as strong inhibitors and inducers of CYP3 and others) also could be included.

Recommendation 2B: establish online access to updated safety profile information

The use of integrated electronic systems with possibilities for a bidirectional flow of safety information could be very useful. For example, investigators and clinical staff in early-phase trials could use a software system to collect and record, as appropriate, patient characteristics, safety and accrual data, patient-reported outcomes (PROs), and laboratory data essential for AE determination, and to report to sponsors safety and accrual data in a more efficient and accurate manner [20]. At the same time, sponsors should be able to give investigators real-time access to cumulative summary data for AEs associated with an experimental therapy from all sites and/or all clinical trials using that therapy. The availability of an online, searchable drug-safety database with expected AEs and observed toxicities that is continuously updated and always accessible may improve the quality of attribution decisions and enhance patient safety during a trial.

Recommendation 2C: establish standard operating procedures to facilitate and improve the quality of clinical research, especially baseline assessments

Stakeholders expressed a clear need for a more standardized collection of baseline data and measurements across institutions to improve attribution, to accurately establish whether a patient's clinical status is stable, worsening, or improving. The standardized baseline assessment and documentation of clinical data can include PROs, clinical laboratory values (such as hepatic enzymes, hemoglobin, fasting blood sugar, blood lipid levels, and blood cell counts), comorbidities, AEs, previous cancer treatments, and current medications, and may use tools such as CAEPRs to help with attribution assessments. A mechanism would ideally include collecting both solicited and unsolicited AEs. Factors to be measured at baseline could be based on preclinical animal toxicity data, expected AEs for the drug class (for example, rash, diarrhea, and pulmonary symptoms may be expected for immune checkpoint inhibitors), and symptoms and AEs that are most commonly seen in early-phase clinical trials. Baseline standardization could include a core set of factors that are measured at baseline in all early-phase trials, the number of baseline assessments, definition of baseline days, and the grading criteria to be used.

Recommendation 2D: promote the importance of experienced clinical trial investigators and trial sites

The quality and experience of a clinical research center and its investigators are recognized as important components of successful AE reporting, including high-quality attribution, particularly in early-phase trials. Changes in the goals, populations, and conduct of early-phase trials have resulted in a shift towards multi-institutional trials and centralized study management by contract research organizations instead of research centers. A disadvantage of this shift is that if too many sites are involved in a single clinical trial, each participating site may contribute only a limited number of patients, thus resulting in investigators at each site having limited experience with the experimental agent and consequently little sense of the toxicities that may be associated with it.

It has been shown that the ability of Phase I trials to predict clinically relevant toxicities in later-phase trials increases as the number of patients on the initial Phase I trial increases (up to 60 patients) [21]. Phase I trials would therefore need sufficient numbers of patients and clear expansion numbers to accurately define and attribute toxicities before Phase II trials were commenced. Limiting the number of sites and ensuring sufficient numbers of patients at each site, whenever feasible, would increase site investigators' experience with the agent and with observing toxicities. When this is not possible, a study management committee can serve as an advisory group to help with attributions and discussion of options.

Recommendation 2E: explore the utility of PROs for capturing AEs at baseline and longitudinally

Scheduled systematic assessment of symptomatic AEs by PROsfor example, at baseline and over time (longitudinal symptom trajectories) - may aid investigators in assigning attribution and grading severity [22,23]. PROs would be very helpful for identifying important symptomatic toxicities that are best reported by the patient (such as fatigue, pain, nausea, and neuropathy). The feasibility of real-time PRO data collection in trial settings has been demonstrated [24,25]. Nonetheless, although PRO data can enhance the detection of AEs, the working group was quite clear that the attribution of symptomatic toxicities should remain the responsibility of the investigator. Patients can report symptoms, but the group agreed that patients should not normally make an attribution for these symptoms. The subjective attribution of AEs by patients themselves might be a topic of interest for academic research, but patient attribution of AEs should not be required for drug development.

Recommendation 3: improve the consistency of attribution

Recommendation 3A: educate those who conduct clinical trials on best practices for attribution

Educating investigators, sponsors, and other professionals involved in clinical trials on best practices and regulations related to attribution will improve the consistency of this process. Including attribution in educational activities, such as the American Association for Cancer Research (AACR)/ASCO Methods in Clinical Cancer Research workshop, and developing content (for example, by using case studies from previous trials) that will better prepare physician-researchers to make accurate and consistent attribution. Mandatory periodic courses that focus on the regulatory framework and Good Clinical Practice guidelines could also be included to ensure that investigators and sponsors comply with relevant regulatory requirements and are up-to-date with changes in best practices [26].

This could be supported by developing an attribution webinar by the FDA, NCI, and possibly even ASCO or AACR, that could be updated periodically. The webinar would include information on how to assess for attribution, how to conduct attribution assessments, and how to report to regulatory agencies. Physician investigators could be required to attend the webinar and to repeat it on a reasonable basis as part of 1572 certification or Good Clinical Practice requirements. For research conducted in other parts of the world (e.g., as in multicenter international trials), sponsors could play the role of ensuring that investigators are educated by making this information a condition for participation in conducting the trial.

For investigators involved in clinical research, engagement with sponsors by participating in safety conference calls is highly recommended, as knowledge and expertise accumulate over the course of a clinical trial. Moreover, a minimum requirement to join safety calls should be employed, as the information shared during these calls can have major implications for the attribution process and MTD definition and can improve patients' safety and experience during the clinical trial.

Recommendation 3B: standardize reporting of attribution in publications

Understanding of the relatedness (attribution) of an AE to a drug will be greatly enhanced by an insistence on standardized reporting of AEs in publications and clinical scientific reports. Reporting of all-cause and treatment-emergent AEs above a certain threshold (for example, for Phase I trials, treatment-emergent AEs exceeding 10% incidence), in addition to AEs of special interest, should be required in publications and clinical scientific reports to help build consistency and standardization in AE reporting. Reporting of all-cause AE frequencies (rather than, or in addition to, treatment-related frequencies) are suggested as all-cause AE frequencies are the measure least likely to be biased by pre-existing understanding [18]. The type and frequency of AEs leading to dose reduction, dose interruption, or permanent treatment discontinuation should also be reported in papers and clinical scientific reports, as should SAEs and deaths. Also, for phase I trials, AEs > 10% should be reported not only for first cycle but for all cycles. Others have also called for more transparent reporting of the seriousness of adverse events in oncology clinical trials [27]. Some have suggested that it would be a great benefit if trialists could provide evidence users with some level of certainty about whether an AE was caused by the intervention. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria have been used in certain settings to provide stakeholders and decision makers (for example, patients, physicians and policy makers) with levels of certainty regarding evidence presented [28,29]. However, early-phase clinical trials may represent too early a setting to gauge certainty of evidence for whether or not an AE was caused by a drug, as the number of patients involved in an early-phase trial are typically relatively small. The rating of certainty of evidence may be more feasible and practical at the regulatory level when larger amounts of data are available, for example, by combining data from early-phase and later-phase clinical trials, as well as post-marketing safety reports. On a related note, there have been recent calls in the literature that the FDA require reports of SAEs associated with black-box warnings to include descriptions of certainty of evidence as a guide to support decision making and implementation [30].

Recommendation 3C: pursue harmonization of AE reporting recommendations among regulatory agencies

Increased harmonization and synchronization of attribution/causality-based safety reporting requirements between international regulatory agencies, such as the FDA, EMA, and others, will greatly facilitate consistent reporting of causality to these various agencies and will increase efficiency, improve compliance [3], and lower costs related to different reporting requirements.

Summary and conclusions

The working group has identified a number of challenges with current safety attribution processes and present 3 broad recommendations (summarized in Table 3) that may streamline and facilitate the attribution process and increase its value. We propose a move from the present 5-tier system of AE reporting to a 2–3-tier system. We also recommend that oncologic societies such as ASCO and AACR move toward developing recommendations and training to improve attribution in clinical trials, baseline assessments, and the logistical ways in which protocols are designed. Finally, we suggest that journals incorporate consistent, standardized requirements for reporting attribution in oncology clinical trials.

Funding

The toxicity attribution workshop was co-sponsored by Friends of Cancer Research, The University of Texas MD Anderson Cancer Center, and The Health and Environmental Sciences Institute. Dr. George received support from the Hawn Foundation.

Conflicts of interest (COI)

Alicyn Campbell: Employee of Genentech, a member of the Roche group while conducting this work. **Jorge E. Cortes:** Grants (Institution): BMS, Novartis, Pfizer, Astellas, Daiichi, Takeda, Immunogen, Arog, Amphivena, BergenBio, Merus. Consulting (Personal): BMS, Novartis, Pfizer, Astellas, Daiichi, Takeda. **David M. Hyman:** Consulting/Advisory Role: Chugai Pharma, CytomX Therapeutics, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer Pharmaceuticals, Genentech / Roche; Research Funding: Loxo Oncology, PUMA Biotechnology, AstraZeneca, Bayer Pharmaceuticals (does not include industry-sponsored clinical trials). **Thomas Karagiannis:** Employee and Stock Ownership in Genentech. **Patricia LoRusso:** Data Safety Monitoring Board/Committee: Agios, FivePrime; Advisory Board Member: Alexion, Ariad, GenMab, Glenmark, Halozyme: Menarini, Novartis, Genentech, CytomX, Omniox, Ignyta, Takeda; Consultant: SOTIO, Cybrexa, Agenus. **Gilbert Y. Wong:** Employee and stock shareholder of Pfizer, Inc. **Chris H. Takimoto:** Stock holder and current employee of Forty Seven, Inc; Stock holder and former employee of Johnson & Johnson. **Timothy A. Yap:** Employment: Medical Director of the Institute for Applied Cancer Science and Associate Director for Translational Research of the Institute for Personalized Cancer Therapy at the University of Texas MD Anderson Cancer Center; Previous employee of the Institute of Cancer Research, London, England; Research support: AstraZeneca, Bayer, Pfizer, Tesaro, Jounce, Eli Lilly, Seattle Genetics, Kyowa, Constellation, and Vertex Pharmaceuticals Consultancies: Aduro, Almac, AstraZeneca, Atrin, Bayer, Bristol-Myers Squibb, Calithera, Clovis, Cybrexa, EMD Serono, Ignyta, Jansen, Merck, Pfizer, Roche, Seattle Genetics, and Vertex Pharmaceuticals; Speaker bureau: AstraZeneca, Merck, Pfizer,

and Tesaro. **David S. Hong:** Research/Grant Funding: AbbVie, Adaptimmune, Amgen, Astra-Zeneca, Bayer, BMS, Daiichi-Sankyo, Eisai, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, MedImmune, Mirati, MiRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Pfizer, Seattle Genetics, Takeda; Travel, Accommodations, Expenses: LOXO, MiRNA; Consulting or Advisory Role: Alpha Insights, Axiom, Adaptimmune, Baxter, Bayer (Ad Board and Speakers Bureau), Genentech, GLG, Group H, Guidepoint Global, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer, Seattle Genetics, Takeda, Trieza Therapeutics; Other ownership interests: Molecular Match (Advisor), OncoResponse (founder), Presagia Inc (Advisor). The other authors have declared no conflicts.

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