Discordance in investigator-reported and adjudicated sudden death in TIOSPIR®

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SUPPLEMENTAL MATERIAL

MAC documentation and adjudication processes

All deaths were adjudicated to assign one primary cause, coded to preferred-term level using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA terminology is the international medical terminology developed under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [1]. For each death, required documentation included an investigator site (event) narrative, emergency room or admission reports, hospital discharge summary, autopsy report, electrocardiograms and image reports in addition to laboratory reports, if available. Each case was assigned to be voted on by one pulmonologist and one cardiologist from the MAC. If the two MAC adjudicators assigned to the case did not agree with the investigator-reported cause of death or did not agree with each other, the case was referred to a third, randomly selected, adjudicator and subsequently to a full MAC panel discussion, if necessary. If there was disagreement with the investigator-reported cause of death, the adjudicators provided a comment outlining their reasoning.

Cases with more than one cause of death and/or an “unknown” cause of death reported by the site investigator were referred directly to the full panel for review and adjudication to determine the primary cause of death. In cases where consensus could not be achieved, all members attending the panel meeting were required to vote, with the chair having the deciding opinion in case of a tie.

The MAC adjudicated deaths to “sudden cardiac death” when death occurred within 1 h of an abrupt change of a person’s clinical state without other obvious non-cardiac cause (see

Principles of Operation). A death was adjudicated to “sudden death” when it occurred more than 1 h and less than 24 h of the patient last being observed alive and without evidence of a deteriorating medical condition. The MAC was aware that the US Food and Drug Administration (FDA) draft cardiovascular end-point definition document defines sudden cardiac death as a death within 24 h, and that sudden death is used as a component of a major adverse cardiovascular event (MACE), which is included in analyses. Due to the fact that the study population was at high risk for rapid death from pulmonary causes, the MAC did not feel that it would be appropriate to classify all deaths within 24 h as cardiac. Stroke and MI were identified through electrocardiogram and enzyme levels.

In case of disagreement with the principal investigator’s assessment of the primary cause of death, the MAC designated the probable primary cause of death. If a case arose in which multiple primary causes of death remained at the database lock meeting, a blinded physician from Boehringer Ingelheim made the final determination of the single investigator-reported cause of death. This was to enable a 1:1 output from investigator-reported to adjudicated cause of death (SOC shift), and it did not replace the adjudicated terms for end-point reporting.

Quality control

A quality control ((QC) *i.e*. re-read) process was used to ensure the consistency of adjudication. The purpose of the QC process was to obtain a dichotomous response for the agreement on whether a cause of death was cardiovascular (including sudden death) or non-cardiovascular. The estimation was based on a direct inter-rater agreement between the original adjudication and that in the QC sample (the original decision was used in the analysis). Per the QC process, 130 cases were randomly selected, stratified by both adjudicated event type (cardiovascular/sudden death and cardiovascular) and time, to be re-adjudicated in an indistinguishable way for evaluation of quality and reliability (QC sample). Agreement between the original and the quality-check adjudication exceeded the target level (proportion agreement of 94%, inter-rater reliability score κ of 0.83 (CI 0.72–0.95)). Acceptance, warning and action limits for the QC batch were pre-defined, as detailed in the "Statistical analysis" section. In brief, these were: 1) Where the information was incomplete, consideration was given to the circumstances of death and the specificity and source of the available information; 2) The primary cause of death was attributed to the disorder that caused the patient to present for medical treatment, and this was distinguished from terminal events that were the immediate cause of death; and 3) In circumstances in which a patient presented in his or her final medical illness with progressive respiratory symptoms and signs, the primary cause of death was attributed to chronic obstructive pulmonary disease (COPD).

A decision table was compiled on what is probably the most critical decision, that is, whether the death is due to cardiovascular/sudden death or non-cardiovascular causes. From this table, three statistics were obtained: proportion agreement, bias, and the kappa (κ) statistic. The value for the proportion agreement (percentage of QC decision that agreed with the original adjudication decision) was between 0 and 1 (where 1 = 100% agreement). The value for the κ statistic was between 0 and 1 and reflected the "strength of agreement" [2] as

follows: 0, poor; 0 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.0, almost perfect.

For QC testing purposes, the following levels were assigned: 1) Acceptance of process – if the level of agreement was within "substantial" or "almost perfect"', *e.g*. a κ ≥0.61; 2) Warning level – if the level of agreement fell as "moderate", *i.e*. between 0.41 and 0.60; and 3) Action level – if the level of agreement fell below "moderate", *i.e.* ≤0.40. It was predicted that adjudicated cardiovascular/sudden death events would comprise 25% of all agreed adjudicated events and that the proportion agreement would be approximately 0.9; therefore, 130 patients should be sufficient to achieve a κ >0.6.

Principles of operation

TIOSPIR® (Protocol 205.452)

Mortality Adjudication Committee – Principles of Operation

Assignment of Primary Cause of Death

The Mortality Adjudication Committee (MAC) will designate probable primary cause of death when there is disagreement with the principal investigator's assessment of the primary cause of death.

The general principles and methods used in the classification are listed below:

1. In cases where the information is incomplete, consideration will be given to the circumstances of the death and the specificity and source of the available information. A cause of death will be adjudicated as "unknown cause of death" only if the following criteria are met:

- If, after relevant clinical information has been requested and all voting MAC members still feel they are unable to determine the cause of death, the case will be adjudicated as "unknown cause of death" by panel committee determination only.

2. In general, the primary cause of death should be attributed to the disorder that causes the patient to present for medical treatment. This should be distinguished from terminal events that are the immediate cause of death.

- For example, if a patient is admitted to the hospital with a COPD exacerbation from which they do not fully recover, and the patient subsequently develops complications

such as pneumonia, respiratory failure, renal failure, sepsis, or MI, the primary cause of death will be attributed to COPD.

- For example, if a patient undergoes surgery for cancer and dies from complications of the surgery or during the immediate postoperative period, the primary cause of death will be attributed to cancer, even if the cancer was potentially curable by the surgery.
- All diagnoses of cancer should be based on summary information obtained from the primary medical record as noted in the documentation provided to the MAC. If available, documentation should include results from imaging studies, histologic diagnoses, operative or procedure notes, and records of treatment. Patients who die with an uncured cancer (which is likely to result in the patient's death in the short to medium term) will be designated as dying from that cancer.
    - For example, a patient with documented gastric cancer who dies of gastrointestinal haemorrhage will be classified to have died from gastric cancer.
    - A patient who dies from sepsis resulting from profound neutropenia while undergoing chemotherapy for lymphoma will be classified as dying from lymphoma.
- If a patient has multiple predisposing conditions upon presenting for medical treatment that ultimately leads to death, the MAC must select the predisposing condition that is most likely the cause for death.

3. A COPD exacerbation will be defined as typical symptoms and clinical signs coupled with standard treatment measures. Diagnosis of pneumonia in the presence of an exacerbation of COPD should preferably be accompanied by radiological findings. However, the MAC must select the primary cause of death as either COPD or pneumonia in the case where there is diagnosis of pneumonia in the presence of an exacerbation of COPD.

4. In circumstances where a patient presents in their final medical illness with progressive respiratory symptoms and signs (*e.g.* dyspnoea, tachypnoea, hypoxaemia, hypercapnia) and bilateral ankle swelling and in the absence of documentary evidence to support an alternative diagnosis (*e.g*. right and/or left ventricular failure), the primary cause of death will be attributed to COPD. The attribution to COPD should only be considered in those patients with GOLD stage III or IV disease and, if known, coexistent chronic hypoxemia and hypercapnia.

5. Sudden cardiac death will be recorded as follows: Death occurring within 1 h of an abrupt

change of a person’s clinical state without other obvious non-cardiac cause.

6. Sudden death will be recorded as follows: Death occurring more than 1 h and less than 24 h of last being observed alive and without evidence of a deteriorating medical condition.

- The MAC is aware that the FDA draft cardiovascular end-point definition document defines sudden cardiac death as a death within 24 h. Additionally, the MAC is aware that sudden death is used as a component of MACE and will be included in analyses. Due to the fact that this study population is at high risk for rapid death from pulmonary causes, the MAC does not feel that it would be appropriate to classify all deaths within 24 h as cardiac. Therefore, the MAC will continue to classify deaths as sudden cardiac if they occur within 1 h, and as sudden death if after 1 h but within 24 h of witnessed vitality.
- When was the person last known to be alive?
- When was the person found to be deceased?
- What were the events surrounding the death?
- Did the decedent have any symptoms or change in health status that preceded the death? Special mention should be made to symptoms such as dyspnoea, febrile illnesses, chest pain, abdominal pain, syncope, seizures, paralysis and change in mental status.
- Were there recent medical visits or recent changes in medication?
- Was an autopsy performed?

TABLE S1 Shifts in SOC when comparing MAC-adjudicated causes *versus* investigator-reported of death in the TIOSPIR® study

MedDRA SOC	**Causes of death reported by MAC**								
Causes of death reported by investigator	Respiratory, n	Neoplasms, n	General, including sudden (cardiac) death, n			Cardiac, n	Infections, n	Other, n	**Total, N (%)**
			General	*Sudden**	*Sudden cardiac* [a]				
Respiratory, n	**263**	16	31	*12*	*9*	5	6	5	***326 (25.0)***
Neoplasms, n	0	**247**	2	*1*	*0*	0	0	0	***249 (19.1)***
General including sudden (cardiac) death, n	30	5	**172**	*66*	*43*	2	5	12	***226 (17.4)***
Sudden	*5*	*1*	*58*	***38***	*17*	*0*	*0*	*0*	***64 (4.9)***
Sudden cardiac	*1*	*0*	*17*	*4*	***10***	*1*	*3*	*0*	***22 (1.7)***
Cardiac, n	36	11	93	*40*	*34*	**58**	10	6	***214 (16.4)***
Infections, n	33	17	3	*0*	*0*	0	**78**	17	***148 (11.4)***
Other, n	7	9	19	*10*	*2*	1	3	**100**	***139 (10.7)***
Total, N (%)	**369 (28.3)**	**305 (23.4)**	**320 (24.6)**	***129 (9.9)***	***88 (6.8)***	**66 (5.1)**	**102 (7.8)**	**140 (10.8)**	***1302 (100.0)***

*For adjudication, sudden cardiac deaths were those occurring within 1 h of an abrupt change of a person's clinical state without other obvious non-cardiac cause while sudden death refers to those occurring more than 1 h but less than 24 h of the patient last being observed alive and without evidence of a deteriorating medical condition. For clarity, total N are shown in bold, and sudden and sudden cardiac death n are shown

in italic to highlight the fact that they are a subgroup of the general SOC. MAC: mortality adjudication committee; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Medical Dictionary for Regulatory Activities (MedDRA). http://www.meddra.org/. Date last updated: 2016. Date last accessed: February 22 2016.

2. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax 2007; 62: 411-415.