Ascertainment of Cause-Specific Mortality in COPD -- Operations of the TORCH Clinical Endpoint Committee

Lorcan P. McGarvey, Matthias John, Julie A. Anderson, Michael Zvarich, Robert A. Wise
The Queen's University of Belfast, Ireland (L.McG.), Respiratory Medicine, Barmer Ostseeklinik, Prerow, Germany (M.J.), GlaxoSmithKline, Greenford, United Kingdom (J.A.) and Research Triangle Park, N.C., U.S.A. (M.Z.), and Johns Hopkins, Baltimore, MD, USA (R.W.)

Lorcan McGarvey and Matthias John were equal contributors on this study and are considered as joint first authors

Running Title: COPD Clinical Endpoint Committee

Key Words: Lung diseases, obstructive; Mortality; adjudication; clinical events committee; clinical trials

Word Count: 3612
Tables: 2
Appendices / Online Data Supplement: 1

Abbreviations: CEC = Clinical Endpoint Committee, CI = Confidence Interval, COPD = Chronic Obstructive Pulmonary Disease, FEV1 = Forced Expiratory Volume in one Second, GSK = GlaxoSmithKline, IDMC = Independent Data Monitoring Committee, TORCH = Towards a Revolution in COPD Health.

Please address correspondence to:
Lorcan P. McGarvey
The Queen's University of Belfast
Grosvenor Road
Belfast, BT12 6BJ, N. Ireland
Tel: 00 44 28 90263 178
Fax: 00 44 28 90329 899
Email: l.mcgarvey@qub.ac.uk
Copyright Assignment:
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its licensees, to permit this article (if accepted) to be published in Thorax and any other BMJPG products and to exploit all subsidiary rights, as set out in the BMJ Publishing Group Ltd licence (http://thorax.bmjjournals.com/ifora/licence.pdf)
ABSTRACT

Background: TORCH (Towards a Revolution in COPD Health) is an international multicentre randomised placebo-controlled clinical trial of inhaled fluticasone propionate/salmeterol combination therapy and its monotherapy components for maintenance therapy of moderately to severely impaired patients with chronic obstructive pulmonary disease (COPD). The primary outcome is all-cause mortality. Cause-specific mortality and deaths related to COPD are additional outcome measures, but systematic methods for ascertainment of these outcomes have not been previously described.

Methods: A clinical end-point committee (CEC) was tasked with categorization of cause of death and relationship of deaths to COPD in a systematic, unbiased, and independent manner. The key elements of the operation of the committee were the use of pre-defined principles of operation and definitions of cause of death and COPD-relatedness; the independent review of cases by all members with development of a consensus opinion; and a substantial infrastructure to collect medical information.

Results: 911 deaths were reviewed and consensus was reached in all. Cause-specific mortality was: Cardiovascular 27%, Respiratory 35%, Cancer 21%, Other 10% and Unknown 8%. 40% of deaths were definitely or probably related to COPD. Adjudications were identical in 83% of blindly re-adjudicated cases (Kappa=0.80) COPD-relatedness was reproduced 84% of the time. (Kappa = 0.73). The CEC adjudication was equivalent to the primary cause of death recorded by the site investigator in 52% of cases.

Conclusion: A CEC can provide standardized, reliable, and informative adjudication of COPD mortality that provides information that frequently differs from data collected from site investigators assessment.

[Word Count – 247]
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. Globally, COPD is projected to rise from the sixth leading cause of death in 1990 to third most common cause of death in 2020. Clinical trials of COPD maintenance treatment have typically used lung function as a primary outcome measure, with secondary outcomes of exacerbation frequency, symptoms, and quality of life. Mortality and cause-specific mortality have infrequently been used as a primary outcome measure because of the requirements for long duration of follow-up and large numbers of participants. Since the domiciliary oxygen trials done in the 1970s, the TORCH (Towards a Revolution in COPD Health) trial was the first international trial of COPD maintenance therapy that used all-cause mortality as a primary outcome measure and cause-specific mortality as a secondary outcome measure. Moreover, because COPD may substantially contribute to mortality in the presence of other primary illnesses, COPD-related mortality was also used as an outcome measure.

Previous COPD clinical trials have used independent review committees to assign cause of death, but the methods, operations, and performance of these committees have not been published. Attribution of cause of death is particularly difficult for COPD patients because they often have other co-morbidities, or the contribution of COPD is not taken into account. TORCH provided an opportunity to develop and evaluate methods for adjudicating causes of mortality in COPD patients. In TORCH, the cause of death was adjudicated by a three-member Clinical Endpoint Committee (CEC), independent of the main Steering Committee. The purpose of this manuscript is to describe the operations and experience of this committee in adjudication of 911 deaths. We present results about the reliability of CEC adjudications and compare CEC cause-specific mortality with causes of death determined by local site investigators.
METHODS

TORCH Study Design

The TORCH trial design has been published previously. Briefly, the trial was a randomized, double-blind, parallel-group, controlled clinical trial comparing inhaled salmeterol $50 \mu g$ bid, inhaled fluticasone propionate $500 \mu g$ bid, combined salmeterol $50 \mu g$ and fluticasone propionate $500 \mu g$ inhaled bid, and placebo. The enrolled participants had moderate to severe COPD (pre-bronchodilator FEV$_1$ < 60% predicted). Each participant was followed for three years. The primary outcome measure is all-cause mortality. Secondary outcomes include exacerbations and quality of life. Other outcome measures include lung function, cause-specific mortality and deaths related to COPD. The study enrolled 6184 participants who were assigned to treatment at 444 centres in 42 countries. Overall, 911 deaths that occurred in randomized participants were reviewed by the CEC. Of these, 875 occurred within 3 years of randomization from non-excluded sites and were used for analysis of the primary trial outcome. Of the 36 deaths not included in the primary efficacy analysis, 7 occurred at sites that were administratively excluded from the analysis prior to unmasking the data and 29 occurred more than 1092 days after randomization. This report analyses the experience from all 911 adjudicated deaths.

Acquisition of Medical Information

When one of the participants died, the study site completed a serious adverse event (SAE) report that was forwarded to the regional study-coordinating centre within 24 hours. The site coordinator and investigator provided whatever information was known about the cause of death at that time. Subsequently, each site conducted an investigation into the cause of the death obtaining the death certificate, medical records including emergency department and hospital records, x-ray reports, laboratory reports, operative and procedure reports, histologic reports from biopsy specimens, and autopsy reports. In deaths that occurred in a non-medical facility, the site attempted to obtain witness interviews to describe the circumstances of the death, when the participant was last known to be alive, and whether symptoms were known to precede the death. In some circumstances, the sites provided additional information such as newspaper accounts, emergency services reports, or medical examiner determinations. These records were reviewed for completeness at the local, regional, and central study offices, and additional information was sought and acquired if possible. The site investigator was asked to provide a primary cause of death as well as secondary causes. If needed, the medical records were translated into English. The medical information was collated into files with information from the Case Report Form including demographic and anthropometric data, serial lung function tests, and medication lists.
Operation of the Clinical Endpoint Committee

The Clinical Endpoint Committee was composed of three physicians who each had clinical and research expertise in Internal Medicine and Pulmonary and Critical Care Medicine (LMcG, MJ, RW). The committee members represented three of the participating countries, but were not site investigators: United Kingdom, Germany, and The United States. The committee members and chairman were appointed by the sponsor, and the composition of the committee was approved by the TORCH Steering Committee. The sponsor drafted a charter for the committee that was approved by the CEC and the TORCH Steering Committee.

The CEC had an initial organizational meeting with representatives of the study sponsor to review, modify and approve the charter, and to design relevant data collection forms. The committee developed a series of hypothetical clinical scenarios representing complex or problematic cases such as might be reviewed by the committee. These cases were reviewed and discussed in order to develop a consensus how such cases might be categorized with respect to cause of death and COPD-relatedness. From these discussions, the committee developed a series of principles of operation that could be applied to categorize the cause of death. (See online data supplement Appendix A.) During subsequent meetings of the committee, principles were added or expanded for cases that did not seem to be otherwise addressed.

The Committee had an in-person meeting three to four times per year. During each meeting, lasting 2 to 3 days, approximately 75 to 150 cases were reviewed. The study sponsor (GlaxoSmithKline, Greenford, United Kingdom and Research Triangle Park, NC, USA) organized the meetings and provided staff support, but did not have a discussant or voting member at the meetings. The three CEC physicians, blinded to treatment assignment and interim study outcomes, independently reviewed each case to assign a cause of death and complete and sign an Endpoint Adjudication Form. At the meeting, the three independent opinions were reconciled and a final form was filled in and signed. If the cause of death was not unanimous, the case was further reviewed and discussed with the aim of developing a consensus. The committee charter provided that in the event of a non-unanimous decision, the cause of death would be established by the study chair. In practice, however, a unanimous consensus was reached in all cases reviewed.

If the committee concluded that additional medical information might be obtained to assist the committee in assigning a more accurate cause of death, the case was referred back to the study site to obtain the additional information. If additional information was provided the case was re-reviewed at a subsequent meeting. If the study site affirmed that the additional requested information could not be obtained, the case was referred back to the committee for a second review. In this circumstance, the committee attempted to assign a cause of death based on the best available evidence; if this was not possible, the CEC classified the cause of death as unknown.

Categorization of Cause of Death and Attribution to COPD
Cause specific mortality was first attributed to specific cause of death, and was then grouped by a general pathophyslogic category, either cardiovascular, respiratory, cancer, or other. If the cause of death could not be determined from the available evidence, it was classified as unknown.

In each case, a second determination was made whether the death was considered related to COPD using a hierarchical scale (No, Unlikely, Possibly, Probably, Yes). If the evidence was not sufficient to make this determination, the relationship to COPD was classified as unknown.

**Principles Used in Attributing Cause of Death to COPD**

A major aim of the committee was to determine which deaths were caused by COPD, or, if not specifically caused by COPD, were related to COPD. There have been no previously published definitions of causation of death from COPD, or whether a death from another primary cause could be considered related to COPD. Therefore, the CEC used systematic definitions that were prepared from a series of hypothetical scenarios prior to the adjudication of cases. The general principle used was that a death was attributed to COPD if the final illness was precipitated by a COPD exacerbation, regardless of subsequent fatal events such as pneumonia, sepsis, or multi-organ system failure. In practice, this meant that the patient demonstrated increasing cough, sputum, or dyspnea for which they received treatment at the onset of the terminal illness. If pneumonia was present, as evidenced by an infiltrate on the chest radiograph at the time of presentation, the cause of death was attributed to pneumonia. If pneumonia occurred after the onset of a terminal COPD exacerbation the case was categorized as a COPD death. In some cases, the medical record indicated that patients with advanced COPD, evidenced by debilitation, poor nutrition, and hypoxemia, were placed into palliative care prior to death. These cases were also categorized as COPD deaths.

The committee considered a death to be related to COPD if, in the judgment of the committee, the terminal illness would likely be non-fatal if COPD were not present. For example, most patients dying of pneumonia and respiratory failure were considered to have COPD-related deaths. In contrast, patients dying of myocardial infarction or incurable cancer were not considered COPD-related even if the incidence of those disorders is elevated in COPD patients.

**Reliability of Procedures**

In order to ascertain the reliability of the mortality attributions by the committee, an analysis was conducted in a sample of 100 cases which had been adjudicated twice. The committee members were aware that cases were being submitted for second review, but were not aware which cases were being submitted a second time.
Comparability of determining cause of death to other methods.

In order to determine whether the CEC adjudication process provided different information compared to other methods of ascertaining cause of death, the CEC adjudication was compared to the attribution of the site investigator in all 911 cases.

**Statistical Methods**

The process for sampling cases for a second masked review was ongoing throughout the course of the trial. A random sample of 25 cases was drawn from the first 252 deaths; then a random sample of an additional 50 cases was drawn from the 540 deaths which had been adjudicated by March 2005, and a final sample of 25 cases from the total 911 deaths. Re-sampled cases were mixed into the cases for each subsequent meeting in a masked fashion.

To assess the extent to which a given adjudication is reliable the Kappa statistic was calculated.\(^\text{10}\) This is a measure of the agreement in excess of the amount of agreement that we would expect by chance. It has a maximum of 1.00 when agreement is perfect, a value of zero indicates no agreement better than chance. All analyses were performed using version 8.02 of the SAS software package (Carey, NC).
RESULTS

A total of 911 deaths were reviewed during 10 meetings each lasting 2-3 days. After independent review and discussion, a consensus was reached on cause of death and relatedness to COPD in all cases. Twenty percent of cases that were reviewed were sent back for additional information. Among the cases where an adjudication was made, the cause of death was considered unknown in only 8 percent, and the relationship to COPD could not be determined in 9 percent.

The committee commonly ascertained causes of death that were different from the free-text entered by the site investigator on the case report form. Among the 911 cases, the committee adjudication was equivalent to the primary cause of death listed by the site investigator in 52% of cases. The committee adjudication for cause of death was listed in either the primary or secondary cause of death provided by the site investigator in 67% of cases.

Of the 100 cases that were submitted for a second blinded review, an identical adjudication of cause-specific mortality was reached in 83 percent (95% CI 76% to 90%). The Kappa statistic for cause of death was 0.80 (95% CI 0.71 to 0.89). The discrepant adjudications in the first and second review are listed in the online data supplement (Appendix B and C). Whether the death was related to COPD was also adjudicated on two separate occasions in the same cases. Among these cases the COPD-relatedness was consistent in 84 percent (95% CI 77 % to 91%). The Kappa statistic for COPD relatedness was 0.73 (95% CI 0.62 to 0.84). The discrepant adjudications are listed in Appendices B and C of the online data supplement.

The adjudicated causes of death are listed in table 1.

<table>
<thead>
<tr>
<th>System</th>
<th>Percent</th>
<th>Subcategory</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>26%</td>
<td>Congestive heart failure</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroke</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudden death</td>
<td>16%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>35%</td>
<td>COPD</td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cancer</td>
<td>21%</td>
<td>Lung</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>7%</td>
</tr>
<tr>
<td>Other cause</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The most common cause of death was respiratory (35%) with approximately three-quarters occurring following a COPD exacerbation. Cardiovascular deaths occurred in
26% of cases, with the most common cause being sudden death. Cancer caused 21% of deaths, with about 2/3 of these due to lung cancer. Overall, 40% of the deaths were judged to be definitely or probably related to COPD, i.e., it was judged that the patient would likely have survived the terminal illness if COPD were not present (see table 2).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (Definite)</td>
<td>38%</td>
</tr>
<tr>
<td>Probably</td>
<td>2%</td>
</tr>
<tr>
<td>Possibly</td>
<td>1%</td>
</tr>
<tr>
<td>Unlikely</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>No (Not related)</td>
<td>50%</td>
</tr>
<tr>
<td>Unknown</td>
<td>9%</td>
</tr>
</tbody>
</table>

DISCUSSION

In this article we describe the operations of a Clinical Endpoint Committee (CEC) that had the task of attributing cause of death in patients with COPD and adjudicating whether the deaths were related to COPD in a large multinational clinical trial.

Clinical Endpoint Committees are routinely used in cardiovascular clinical trials, and several reports have concluded that they can provide independent, systematic, standardized adjudication of outcome events. Outcomes of clinical trials may differ substantially when events are independently and systematically adjudicated rather than relying upon local site investigators or death certificates. In contrast to endpoints in coronary artery disease, COPD provides a particular challenge because there are no accepted definitions of when death is caused by or related to COPD. Many COPD patients die from other causes, particularly cardiovascular disease, pneumonia, and lung cancer. This is because COPD patients suffer from other smoking-related co-morbidities such as coronary artery disease; because COPD patients are vulnerable to fatal outcomes from other illnesses such as pneumonia, and also because cause of death in COPD may be inaccurately or inconsistently attributed.

All-cause mortality is an objective and unbiased outcome measure for clinical trials. Cause-specific mortality, although limited by reduced power and potential for biased ascertainment, can provide information about subtle beneficial or adverse treatment effects that are not of sufficient magnitude to alter all-cause death rates. Moreover, the systematic review and attribution of cause of death in well-characterized cohorts of COPD patients participating in a clinical trial can extend our understanding of the health impact, epidemiology, and natural history of COPD. Because there are no generally agreed upon definitions of what constitutes death from COPD or death related to COPD, the CEC had to develop a set of definitions and working principles to guide their deliberations. We emphasize that these definitions were developed in the context of a clinical trial evaluating
maintenance treatment of COPD and would not necessarily be appropriate for investigations that were targeting other diseases or treatment approaches.

We also evaluated whether the CEC could provide reproducible adjudications by blindly reviewing a sample of cases on two separate occasions. We found that the reliability of the CEC adjudications which were reasonably good with identical adjudications in 85% of cases. We are not aware of similar measures of reproducibility of adjudication by mortality review committees in clinical trials, but our results are comparable to the reproducibility of adjudication of causes of perinatal mortality. Two issues were often problematic for the committee. First, it was often difficult to distinguish between pneumonia and COPD exacerbation as the presenting terminal illness. Second, it was difficult to decide when an unattended death should be called sudden death vs. unknown cause.

We also evaluated whether the CEC, using an independent review and consensus approach could provide information that was different from using site investigator specification of cause of death. The CEC ascertained different causes of death from the site investigator’s primary or secondary cause of death in about one-third of cases. Although some of the site investigators also served as treating physicians for trial participants, the attribution of cause of death was not likely as consistently applied as the CEC adjudications. In many cases, the site investigators specified the cause of death based on the primary cause listed on the death certificate or from the terminal event, e.g. “cardiac arrest or cardiorespiratory arrest.” Many of the cases that the CEC classified as sudden death were attributed to myocardial infarction. Thus, different conclusions regarding cause-specific mortality and the effect of treatment on cause-specific mortality would be reached using CEC adjudication versus site-investigator adjudication. In general, dependence upon site-investigator diagnoses would tend to increase the attribution of death to cardiovascular causes and diminish the attribution to respiratory causes.

The TORCH trial is the first large international clinical trial focusing on COPD mortality. Besides the lack of well-established precedence for operation of a CEC for COPD trials, the large number of independent study sites, and the multiplicity of countries added challenges to attribution of cause of death to COPD. Linguistic, cultural, and legal barriers may have affected the ways that deaths are reported and documented. In several jurisdictions, death certificates were not legally available to investigators, or the cause of death was withheld from the public record. The planning for such studies needs to take into account the substantial effort and infrastructure required to obtain, review for completeness, collate, translate, and distribute the medical information required for central review.

As expected, the causes of death in this COPD population had a larger proportion attributable to respiratory illness than found in the general population of industrialized countries, where cardiovascular and neoplastic causes of death far exceed respiratory illnesses. Several studies have examined causes of death specifically in COPD and have found a lower proportion of deaths from respiratory conditions. The Lung Health Study mortality review panel adjudicated causes of death in 149 patients with mild to moderate
COPD. Lung cancer was the most common cause of death, occurring in 33 percent of patients. Cardiovascular disease, comprising both cerebrovascular accidents and coronary artery disease occurred in 25% of decedents. Respiratory causes of death were uncommon in this group. In Lung Health Study 2, among 34 deaths adjudicated by a mortality review panel, the most commonly reported cause of death was lung cancer. Both Lung Health Studies had patients with milder lung disease than TORCH, so it would be expected that fewer patients would have succumbed to respiratory diseases. Hansell and colleagues examined death-certificate causes of mortality in decedents in England and Wales who had COPD or a related condition listed as primary or a contributing condition on their certificate. They found that cardiovascular disease accounted for 25% of deaths, neoplasm 7% of deaths and respiratory conditions in only 4% of deaths. They suggested that deaths due to COPD were vastly under-reported on death certificates. In a study of 215 patients using chronic oxygen, Zielinski found that 38% died of respiratory failure, 13% with cor pulmonale, 11% pneumonia, 10% pulmonary embolism, cardiac arrhythmia 8% and lung cancer 7%. Thus in this group of more severely impaired COPD patients, respiratory deaths were more common than in the TORCH study.

One of the interesting findings of this study was the large proportion of patients who had sudden death (16%) and the low proportion of patients with documented acute myocardial infarction (3%). Sudden deaths are usually classified as cardiovascular deaths and are attributed to arrhythmias in the setting of coronary artery disease. It was surprising, therefore, that so few patients had documented myocardial infarctions. This finding raises the speculation that many of these deaths might have been attributable to acute respiratory failure as a precipitating cause, a phenomenon that has been well-described in asthma, but not in COPD. It has been previously found that 47% of patients dying after recovering from an episode of acute respiratory failure ultimately die of sudden death – suggesting that this may have accounted for this finding. Thus, we would suggest that future studies of COPD mortality should consider sudden death as a separate entity rather than one necessarily linked to cardiovascular cause.

One of the most difficult decisions made by the committee, and the cause of several of the disparate classifications on re-adjudication was the distinction between COPD exacerbations and pneumonia. Although we had clear definitions to separate the two, based on whether an infiltrate was present on the initial presenting chest radiograph, we had some circumstances where the clinical and official reading of the initial chest radiograph were different or where an infiltrate was noted very shortly after the onset of symptoms but not on the initial radiograph. Moreover, in all but one case, deaths due to pneumonia were judged to be COPD related, and the symptoms of cough, sputum, and dyspnea were virtually always present in the setting of pneumonia. Thus, the distinction between death from COPD exacerbation complicated by pneumonia and pneumonia leading to a COPD exacerbation was sometimes unclear. Therefore, we would suggest that future research that evaluates COPD mortality should subclassify classify such events as “COPD exacerbations accompanied by pneumonia” and “COPD exacerbations without pneumonia”.
CONCLUSION

A Clinical Endpoint Committee can provide systematic and reliable, attributions of death in COPD clinical trials. The key elements of operation of such a committee include preliminary development of principles of operation and working definitions, in-person meetings for discussion of cases, and substantial infrastructure for acquisition of medical information. Based on our experience we would recommend modifications for future COPD clinical trials, in particular the classification of COPD exacerbations that occur in the setting of pneumonia, the classification of sudden death as a cardiovascular event, and attention to training of investigators and site personnel about the operational requirements of such a committee and the substantial effort required to obtain, review, translate and collate relevant medical records.
Funding Source: Funding for the study described in this article was provided by Glaxosmithkline.

Competing Interests:

LMcG is a paid consultant to Glaxosmithkline. MJ is a paid consultant to Glaxosmithkline. JAA is an employee of Glaxosmithkline. MZ is an employee of Glaxosmithkline. RAW is a paid consultant to GlaxoSmithKline. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.
REFERENCES


25 Zielinski J; MacNee W; Wedzicha J; Ambrosino N; Braghiroli A; Dolensky J; Howard P; Gorzelak K; Lahdensuo A; Strom K; Tobiasz M; Weitzenblum E. Causes of death in patients with COPD and chronic respiratory failure. Monaldi Arch Chest Dis. 1997; 52: 43-7.


Ascertainment of Cause-Specific Mortality in COPD -- Operations of the TORCH Clinical Endpoint Committee

Lorcan P McGarvey, Matthias John, Julie A Anderson, Michael T Zvarich and Robert A Wise

Thorax  published online February 20, 2007

Updated information and services can be found at:
http://thorax.bmj.com/content/early/2007/02/20/thx.2006.072348

These include:

Supplementary Material
Supplementary material can be found at:
http://thorax.bmj.com/content/suppl/2015/08/11/thx.2006.072348.DC2

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Epidemiologic studies (1829)
Open access (261)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/