BMJ open

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: cross-sectional study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001963
Article Type:	Research
Date Submitted by the Author:	15-Aug-2012
Complete List of Authors:	Earley, Amy; Tufts Medical Center, Tufts Evidence-based Practice Center Lau, Joseph; Tufts Medical Center, Tufts Evidence-based Practice Center Uhlig, Katrin; Tufts Medical Center,
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Evidence based practice
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, QUALITATIVE RESEARCH

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: cross-sectional study

Amy Earley BS research associate[1], Joseph Lau MD professor of medicine[1, 2], Katrin Uhlig MD MS associate professor of medicine[1, 2, 3]

Author affiliations:

[1] Tufts Evidence-based Practice Center, Tufts Medical Center, Boston, MA 02111, US

[2] Tufts University School of Medicine, Boston, MA 02111, USA

[3] Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA 02111, USA

Corresponding author:

Katrin Uhlig MD, MS

Tufts Medical Center

800 Washington Street, #391

Boston, Massachusetts, 02111, USA

Email: kuhlig@tuftsmedicalcenter.org

Word Count:
Abstract: 261
Manuscript Text: 2796

Abstract

Context: A participant death is a serious event in a clinical trial and needs to be unambiguously and publicly reported.

Objective: To examine: 1) how often and how death counts are reported in ClinicalTrials.gov records; 2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication; 3) how counts may be discordant.

Design: Registry-based study of clinical trial results reporting

Setting: ClinicalTrials.gov results database searched in July 2011 and matched PubMed publications

Selection criteria: A random sample of ClinicalTrials.gov results records. Detailed review of records with a single corresponding publication.

Main outcome measure: ClinicalTrials.gov records reporting a death count under participant flow, primary or secondary outcome, or serious adverse events. Consistency in reporting of death counts between ClinicalTrials.gov records and corresponding publications.

Results: In 500 randomly selected ClinicalTrials.gov records, 123 records (25%) reported some death count. Reporting of deaths across data modules for participant flow, primary or secondary outcomes, and serious adverse events was variable. In a sample of pairs of ClinicalTrials.gov records with death counts and corresponding publications, total deaths per arm could be determined in 56% (15/27 pairs) but were discordant in 19% (5/27). In pairs of ClinicalTrials.gov

records without information on death, 48% (13/27) were discordant since the publications reported absence of deaths in 33% (9/27) and actual deaths in 15% (4/27).

Conclusions: Death counts are variably reported in clinical trials and a reliable total death count per arm cannot always be determined. This highlights a need for unambiguous and complete reporting of death counts in trial registries and publications.

Article Summary

Article focus

- We hypothesized that the discrepant reporting expectations for death give rise to discrepancies in deaths reported across reports of a trial.

Key messages

- There is a lack of clarity, consistency and agreement in reporting of all cause death counts in clinical trials which highlights the need for unambiguous templates to standardize reporting of total death counts per arm in ClinicalTrials.gov records and more stringent reporting guidelines for peer reviewed publications.

Strengths and limitations of this study

- Our findings indicate a need for clarifying expectations in reporting and highlight differences in the legal standards for reporting of serious adverse events after trial completion and expeditious real time reporting of serious adverse events in ongoing trials.
- We suggest amendments to reporting formats such as: number of individuals who started per arm, number of deaths from any cause per arm and the time point of last ascertainment to prompt study investigators to sum up all deaths across participant loss, primary or secondary outcomes, and serious adverse events.
- We examined only a limited number of matched cases. Nevertheless, the discrepant findings even in these small samples demonstrate a clear disconnect between reporting expectations and reporting practices as illustrated by inconsistencies across reports of the same trial.

- We used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous death counts. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications.
- We only gave credit to death counts and not to alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible.
- We followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Introduction

The death of a clinical trial subject is a serious event that needs to be publicly disclosed. Inadequate reporting of deaths may overemphasize health benefits when benefits and harms of medical interventions are summarized[1;2]. For unambiguous reporting, deaths have to be reported for each trial arm and the absence of deaths must be explicitly stated if none were known to have occurred. Trial registries such as ClinicalTrials.gov provide public records of trial results.[3] It is a Web-based trial registration of federally and privately funded trials.

While there is no regulation specifically mandating the reporting of all deaths from any cause in a clinical trial, a death may constitute a serious adverse event and is therefore subject to the regulations on reporting of serious adverse events. However, it appears that there is incongruence between legal reporting expectations for serious adverse events after trial completion versus during trial conduct. The United States Food and Drug Administration (FDA) Amendments Act mandates the reporting of summary results for phase II-IV interventional studies of drugs, biological products, and devices within 1 year of completing data collection for the prespecified primary outcome in ClinicalTrials.gov[3-5]. The Act includes a provision regarding the reporting of aggregate serious adverse events, thus mandating public disclosure. Based on this Act, the results data bank of the ClinicalTrials.gov registry shall include “a table of anticipated and unanticipated serious adverse events grouped by organ system with number and frequency in each arms of the trial”[6]. The ClinicalTrials.gov data element definitions define adverse events as “unfavorable changes in health …, that occur in trial participants during the clinical trial or within a specified period following the trial.” and under serious adverse events include ‘adverse events that result in death’[7].

In contrast to these reporting expectations of all deaths after trial completion, investigators and sponsors of ongoing clinical trials have to report adverse events to respective

drug regulatory authorities. The FDA regulation on drug safety reporting requires sponsors of investigational new drugs to promptly report to the FDA and investigators serious unexpected events if they are suspected adverse reactions, meaning that there is a "reasonable possibility" that the drug caused it[8;9]. Otherwise, adverse events are batched by the sponsor and submitted later. This requires an adjudication of the event as serious or minor; expected or unexpected; and study-related, possibly study-related, or not study-related. Death is by definition a serious event, but it is nonspecific as it may result from natural disease progression, lack of efficacy of an intervention, harm from an intervention or a cause unrelated to a trial. This need for judgment about the possibility of a causal association makes accounting and adjudication of deaths in trials challenging[10].

We hypothesized that the discrepant reporting expectations for death give rise to discrepancies in deaths reported across reports of a trial. We first examined how death counts from any cause were reported in ClinicalTrials.gov records. We then attempted to determine the total deaths per arm in a ClinicalTrials.gov results record and in the corresponding publication. Finally, we conducted a detailed review of cases with discrepancies in crude deaths to identify possible explanations.

Methods

The ClinicalTrials.gov team provided us with a database of results records indexed in ClinicalTrials.gov (search date July 12, 2011). The database contained all records of phase II, III, or IV interventional trials with results entered between September 9, 2009 and June 14, 2011. In 500 randomly selected records, we examined the record for reporting of any death counts. This entailed review of three of the four scientific data modules, i.e. participant flow, primary and secondary outcomes, and serious adverse events, but not baseline characteristics. Appendix 1 shows screenshots for the three pertinent modules from a sample ClinicalTrials.gov record. We considered deaths counts only when a zero or a positive number for death was reported in any module, i.e. we did not derive death counts from information on deaths reported as percentages, rates, risks or survival curves. In 123 records reporting a crude death count, we examined in which module deaths were reported. Deaths from serious adverse events would presumably be a reason for not completing a trial and qualify to be listed as such in the participant flow module. We examined how many records reported death counts only in the serious adverse events module without reporting any deaths as a reason for discontinuation.

Among the 500 records, we also identified studies with an outcome measure description that implied ascertainment of death, including overall survival, time to mortality, all cause deaths, disease specific death, composite outcomes including death and serious adverse events including deaths. In this subset, we examined how often actual death counts were reported as part of the primary or secondary outcome module when the outcome suggested that number of deaths were collected.

We then compared death reporting between ClinicalTrials.gov results records and corresponding publications. To select a sample, we used 2 criteria: 1) ClinicalTrials.gov records had to provide only a single PubMed Identifier (PMID) matching a publication describing trial

results to avoid the need for reconciliation across several publications, and 2) publications had to be electronically accessible through our library. Based on these two criteria, we retrieved 75 matching publications of which 27 corresponded to ClinicalTrials.gov records that reported deaths. We sampled another 27 pairs where the ClinicalTrials.gov record did not report deaths. For each record or publication, we attempted to determine the total deaths per arm and the numbers randomized or analyzed per arm based on the data available in the record and publication, without contacting authors. This required assumptions when reconciling death counts across the three pertinent modules in the ClinicalTrials.gov record. For the publications, we searched the sections of the article corresponding to the modules. We used the following operational rules for decision-making:

- If a report did not provide direct information on death counts, no counts were implied.
- If a death count was reported in only one module in the ClinicalTrials.gov record or the corresponding sections in the publication, i.e., either in participant flow, primary or secondary outcome, or adverse events, this was determined to be the total death count.
- Otherwise, as a default, the highest unambiguous number of deaths in one category was taken as the total death count.

When the death counts could be determined for both the ClinicalTrials.gov record and the corresponding publication following these rules, we compared these death counts between the record and the publication. Discrepant cases were reviewed in more detail. We extracted the denominators for death counts from information on number started, randomized, or analyzed. We further captured information on duration of follow-up and looked for possible reasons for differences in death counts.

Results

Reporting of crude death counts in ClinicalTrials.gov results records

In July 2011, there were 1981 records with results in ClinicalTrials.gov and 500 records were randomly chosen for further analysis (Appendix Figure 1). These included 123 records (25%) which reported a death count in at least one module. Deaths were variably reported across the three modules of participant flow, primary or secondary outcome, and serious adverse events (Figure 1). Sixty-four percent of the records reported crude deaths only in one of the modules, 32% in two modules and 4% in all of them. Approximately one fifth (27/123) of the records reported crude death counts only in the module for the serious adverse events, i.e. there were no deaths reported in the participant flow as a reason for not completing the trial. One fifth (24/123) reported deaths in both of these modules.

Out of the 500 records, we identified 97 with a primary or secondary outcome measure definition that implied ascertainment of deaths. Of the 97, there were 32 (33%) that reported a crude death count in the primary or secondary outcome module, with or without a result for death in another metric. The 65 records that did not report crude death counts in the primary or secondary outcome module nonetheless still reported death counts under participant flow or serious adverse events.

Reporting of information on death, determination of total death counts per arm and congruency in matched pairs

We examined congruence of reporting of deaths across pairs of ClinicalTrials.gov records and corresponding trial publications. Figure 2 tabulates whether there was any information on deaths in a trial report, and if so, whether total death counts could be determined per arm following simple rules, and finally whether the total counts per arm were concordant or discordant across pairs. We examined 27 pairs where the ClinicalTrials.gov record contained

some information on death counts and 27 pairs where the ClinicalTrial.gov record did not contain any information on death.

Of the 27 pairs with information on death counts in the ClinicalTrials.gov record, there were 15 (55%) in which the total death count per arm could be determined in both reports (Figure 2, panel A). The death counts were concordant between the ClinicalTrials.gov record and the publication in 10 pairs (37%), but discordant in five pairs (19%), while in the remaining 12 (44%), concordance could not be assessed. The five discordant pairs are shown in detail in Table 1.

In the 27 pairs where the ClinicalTrials.gov record did not contain information on death, 14 (52%) pairs were concordant regarding the absence of information on deaths, i.e. the trial publications also did not contain any information on deaths (Figure 2, panel B). However 13 (48%) publications contained information on death counts. In 9 studies (33%), the published study affirmatively reported “no deaths” and in four studies, the published report mentioned positive death counts (Figure 2, Panel B). These four cases are shown in Table 2. For example in Case 9, the ClinicalTrials.gov record did not contain information on death; but, the publication reported one death under serious adverse events (Table 2).

Review of cases with discrepant counts

Tables 1 and 2 show the detailed review of the cases with discrepant counts. For each case, the crude death counts for each module or reporting location for the ClinicalTrials.gov record and the corresponding publication are shown, as well as the total number of deaths per arm that was determined following our operational rules. The summary contains comments and interpretation of the discrepancies.

In several cases, information on duration of follow-up or the time point of last assessment was not exact or varied across the reports. Comparison of death counts required reconciliation across reports with discrepant numbers of arms (Cases 5 and 6) or discrepant number of studies (Case 4). For example, in Case 5, the ClinicalTrials.gov record included two arms treated with different drug doses, while the publication reported results only for one of the arms. Ultimately the death counts for this one arm was consistent across the ClinicalTrials.gov record and the publication. In the other cases, however, the inference or certainty about the number of deaths per arm differed. In addition to discrepant counts, problems were lack of provision of crude deaths even when death was an outcome of interest (Cases 1 and 3), imprecision in data entry (Case 4), reporting of deaths under serious adverse events without specification as to whether they were counted as part of the death outcome (Case 4) or the participant flow (Case 7). In most cases, the publication included a slightly higher crude death count. Large discrepancies were noted in cases where the record did not report counts for an outcome that included death, while the report did (Cases 3 and 9).

Discussion

Our study highlights a failure of consistent and clear reporting of death counts in clinical trials. Only 25% of ClinicalTrials.gov results records provided information on death counts, with great variation and overlap in the reporting across the three data modules for participant loss, primary or secondary outcomes, or serious adverse events. While we expected records reporting death as a serious adverse event to also list death as a reason for discontinuation from the trial in participant flow, a fifth of records reported deaths only under serious adverse events. Among trials with a definition for a primary or secondary outcome that implies ascertainment of death, only a third of ClinicalTrials.gov records provided crude death counts in the data module for the primary or secondary outcome. This heterogeneous reporting and the uncertainty of whether deaths are reported in a redundant or exclusive manner across data modules, poses problems for reconciling deaths within a trial report.

Following operational rules, total counts of deaths per arm could not always be determined unambiguously in the ClinicalTrials.gov results records or the corresponding publication. In the small sample where total deaths could be determined in both reports for the same trial, we identified examples where the death counts were discrepant, highlighting lack of coherence and completeness. There were no clear patterns to explain the discrepancies. Finding a slightly higher crude death count in publications than in ClinicalTrial.gov records suggests that death counts in the ClinicalTrials.gov records are not complete. This indicates a violation of the reporting expectations for ClinicalTrials.gov which includes death as a serious adverse event.

Our findings of haphazard reporting of deaths in clinical trials indicate a need for clarifying expectations in reporting and highlight differences in the legal standards for reporting of serious adverse events after trial completion[6] and expeditious real time reporting of serious

adverse events in ongoing trials.[8;9] We suggest that reporting formats for aggregate clinical trial results need to be amended to provide the following information: number of individuals who started per arm, number of deaths from any cause per arm and the time point of last ascertainment. This should prompt study investigators to sum up all deaths across participant loss, primary or secondary outcomes, and serious adverse events. Information on mean duration of follow-up is also needed to allow calculation of rates. Given their prominent role supported by the legal regulations, clinical trials registries can spearhead uniform and consistent reporting of important trial outcomes, such as deaths. Similarly editors and sponsors must educate trialists to better meet the need for uniform reporting of adverse events. [11-13]

Our study has several limitations. We examined only a limited number of matched cases. Nevertheless, the discrepant findings even in these small samples demonstrate a clear disconnect between reporting expectations and reporting practices as illustrated by inconsistencies across reports of the same trial. Also, we used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous death counts. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications. Further, we only gave credit to death counts and not to alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible. Finally, we followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Our findings have to be viewed in context. Only 22% of studies report their results in ClinicalTrials.gov within one year of completion[14] and fewer than half of studies funded by the

National Institutes of Health publish their results in a Medline indexed journal within 30 months of trial completion[15]. Thus our matched pairs are drawn from a minority of trials that have been compliant with both expectations: publication of results in ClinicalTrials.gov and publication in a peer reviewed journal.

Full reporting of all deaths enables more accurate assessment of risks and benefits associated with treatments. Assessment of patient safety relies on capturing signals, even when they are non-specific [16;17]. Thus from an ethical perspective, it is desirable that trials ascertain and report all deaths regardless of whether they appear to be related to study conduct or intervention, are unforeseen or non-specific. Death reporting may never be complete or simple given the challenges in ascertainment and adjudication. Even with a clear instructions and prompts for trials to report deaths, there may be uncertainty depending on the rigor of ascertainment or surveillance and the choice of trial outcomes. Crude numbers are not the only format for reporting deaths in a trial. Time to event reporting may be more meaningful, but may introduce uncertainty about how censoring and deaths are handled. Thus both approaches to presenting information on deaths may be necessary and complementary, but our study suggests that some improvement could be made with simple means of standardized reporting formats.

In summary, our study shows lack of clarity, consistency and agreement in reporting of all cause death counts in clinical trials. This highlights the need for unambiguous templates to standardize reporting of total death counts per arm in ClinicalTrials.gov records and more stringent reporting guidelines for peer reviewed publications.

Data Sharing Statement: There is no additional available.

Contributors: Concept and design: AE, JL, KU; Interpretation of data: AE, JL, KU; Drafting article: AE, KU; Revision of article for important intellectual content: AE, JL, KU

Funding:

This project was funded under Contract No. HHSA 290 2007-10055-I, entitled “Evidence-based Protocol for Reviewing ClinicalTrials.gov Results Database,” from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there are no conflicts of interest.

Tables

Figures

Appendices

Reference List

(1) Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005; 142:1090-1099.

(2) Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001; 285:437-443.

(3) Zarin DA, Tse T, Williams RJ, et al. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med* 2011; 364:852-860.

(4) Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. *Chest* 2009; 136:295-303.

(5) FDAAA. U.S. Public Law 110-85. http://clinicaltrials.gov/ct2/invest . 2012. Accessed: 6-26-2012.
Ref Type: Online Source

(6) Food and Drug Administration Amendments Act of 2007. Public Law 110-95. 2007.
Ref Type: Bill/Resolution

(7) ClinicalTrials.gov. ClinicalTrials.gov "Basic Results" Data Element Definitions. http://prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEvents . 2012. Accessed: 6-26-2012.
Ref Type: Online Source

(8) Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans. Final rule. *Fed Regist* 2010; 75:59935-59963.

(9) Sherman RB, Woodcock J, Norden J, et al. New FDA regulation to improve safety reporting in clinical trials. *N Engl J Med* 2011; 365:3-5.

(10) Lauer MS, Blackstone EH, Young JB, et al. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999; 34:618-620.

(11) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 152:726-732.

(12) Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141:781-788.

(13) Mansi BA, Clark J, David FS, et al. Ten recommendations for closing the credibility gap in reporting industry-sponsored clinical research: a joint journal and pharmaceutical industry perspective. *Mayo Clin Proc* 2012; 87:424-429.

(14) Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012; 344:d7373.

(15) Ross JS, Tse T, Zarin DA, et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012; 344:d7292.

(16) Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. *N Engl J Med* 2005; 352:1131-1132.

(17) Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170:1191-1201.

Table 1: Cases with death counts in ClinicalTrials.gov record that are discrepant with the corresponding publication

Population	Was death a specified outcome?[1], Define	Reporting module or location	ClinicalTrials.gov record Deaths/Randomized		Publication Deaths/Randomized	
			Arm 1	Arm 2	Arm 1	Arm 2
Case 1						
Lung cancer	Yes Survival is a secondary outcome		Follow up: While on study drug + 30 d after last dose (estimated 4 mo)		Follow up: From random assignment until first day of progression or until death	
		Flow	/52	-/51	4/52	2/51
		Outcome	-/52	-/51	--	--
		SAE	1/52	0/51	1/52	2/51
		Total	>1/52	>0/51	>4/52	>2/51
Summary	Both CT.gov record and the publication reported hazards ratios for survival and mean survival in months, but not the number of deaths for the outcome. Both reported deaths under serious adverse events, but counts differed between record and report. In addition the publication reported deaths in the flow diagram, while the record did not. The total number of deaths is discrepant between record and publication; however, neither it likely to represent the total number of deaths that occurred during the study.					
Case 2						
Multiple myeloma	No		Follow up: Up to 18 mo		Follow up: Enrolled 2/06-12/06, analysis through 8/2007	
		Flow	1/53	1/43	1/53	1/43
		Outcome	-/53	-/41	--	--
		SAE	-/53	-/42	4/53	1/42
		Total	1/53	1/43	4/53	1/43
Summary	Both CT.gov record and publication reported 1 death per arm in the participant flow. The total number of deaths is discrepant between record and publication, however, since the publication also reported 5 deaths under SAE.					
Case 3						
Refractory prostate cancer	Yes Survival is the primary outcome		Follow up: Analyzed through 9/2009		Follow up: Analyzed through 9/2009	
		Flow	-/377	-/378	-/377	-/378
		Outcome	-/377	-/378	279/377	234/378
		SAE	0/371 sudden death	1/371 sudden death	275/371	227/371
		Total	>0/377	>1/371	279/377	234/378
Summary	The CT.gov record reported hazards ratios for survival as well as survival in months, but not the total number of deaths per arm for this outcome. The publication reported a large number of deaths per arms for the outcome of survival (as) and also a large number of deaths under SAE. The numerators and denominators differed slightly based on intention to treat analyses or per protocol analyses. The CT.gov record reported only one death under SAE; although based on the survival analysis, it appeared likely that the total number of deaths in the study was higher. The total number of deaths is discrepant between record and report.					
Case 4						
Chronic Obstructive	Yes Death is a secondary		Follow up: 52 wk		Follow up: 52 wk	
		Flow	-/772	-/796	-/772	-/796
		Outcome	-/25	-/25	25/772	25/796

[1] In the ClinicalTrials.gov record

Pulmonary Disease	outcome	SAE	1/778 sudden death; 0/778 death	3/790 sudden death; 2/790 death	-/778	-/790
		Total	25/772	25/796	25/772	25/796
Summary	The CT.gov record reported 25 per arm as number analyzed in the outcome module and defined the number analyzed as the number died. Further, the CT.gov record reports deaths under SAE using two different death definitions ('sudden death' and 'death'), while the publication does not report any. Assuming that the deaths reported under SAE in the record are included in those reported for the outcome of death, the total number of deaths is consistent across record and publication. The publication describes 2 trials of similar design with two separate NCT number, but only the results corresponding to the trial in the index CT.gov record were compared.					
Case 5						
Prostate cancer	Yes Death is a secondary outcome		Follow up: From start of therapy up to 30 d after last dose		Follow up: Duration of therapy + 30 d	
		Flow	-/48	-/47	--	-/47
		Outcome	2/48	2/47	--	-/47
		SAE	-/95		--	2/47
		Total	2/48	2/47	--	2/47
Summary	The CT.gov record reported results for 2 arms. The publication presents only results for Arm 2. The CT.gov report shows 2 deaths in the outcome module, but none under SAE. The publication shows 2 deaths under SAE. The number of deaths reported for this arm was consistent between record and publication.					

Data collection in ClinicalTrials.gov on Feb 14 2012

Abbreviations: CT.gov, ClinicalTrials.gov; D/C, discontinuation; NCT, National Clinical Trial (number); SAE, serious adverse events; -- (dash), not reported;

Table 2. Cases without information on death in ClinicalTrials.gov record but reports of death counts in the corresponding publication

Population	Was death a specified outcome?, Define	Reporting module or location	ClinicalTrials.gov record Deaths/Randomized				Publication Deaths/Randomized	
			Arm 1			Arm 2	Arm 1	Arm 2
Case 6								
Influenza vaccine in elderly	No		Follow up: 6 mo				Follow up: 6 mo	
		Flow	-/857	-/848	-/870	-/1262	-/2575	-/1262
		Outcome	--	--	--	--	--	--
		SAE	-/855	-/848	-/870	-/1260	16/2573	7/1260
		Total	-/2575				-/1262	7/1262
Summary	The CT.gov record did not report deaths counts across 4 arms. The publication described 23 deaths under SAE for 2 arms, collapsing arms 1-3 into one.							
Case 7								
Amyotrophic lateral sclerosis	No		Follow up: 9 mo				Follow up: 10 mo	
		Flow	-/75			-/75	3/75	5/75
		Outcome	-/75			-/75	--	--
		SAE	-/75			-/75	3/75	5/75
		Total	-/75			-/75	3/75	5/75
Summary	The CT.gov record did not report death counts. The publication describes 8 deaths under participant flow as well as under SAE, which are presumably the same.							
Case 8								
Diabetes Mellitus Type 2	No		Follow up: 26 wk				Follow up: 26 wk	
		Flow	-/239			-/241	-/239	-/241
		Outcome	--			--	--	--
		SAE	-/231			-/238	0/231	1/238
		Total	-/239			-/241	0/239	1/241
Summary	The CT.gov record did not report death counts. The publication describes one death under SAE as a 'treatment emergent death'. It also reported 2 deaths during the run-in period that were not included in the participant flow.							
Case 9								
Metastic penile cancer	No (in record); Y (in publication) Overall survival was a reported outcome, unclear whether primary or secondary		Follow up: 'Timeframe 9 y and 6 mo'				Follow up: Duration of enrollment 4/2000 through 9/2008 (max FU up to 7 y 5 mo)	
		Flow	-/30				-/30	
		Outcome	-/30				20/30	
		SAE	-/30				--	
		Total	-/30				20/30	
Summary	The CT.gov record did not include death counts even though "overall survival" was a pre-specified outcome. The publication reported 20 deaths for this outcome.							

Data collection in ClinicalTrials.gov on Feb 14 2012

Abbreviations: CT.gov, ClinicalTrials.gov; D/C, discontinuation; NCT, National Clinical Trial (number); SAE, serious adverse events; – (dash), not reported;

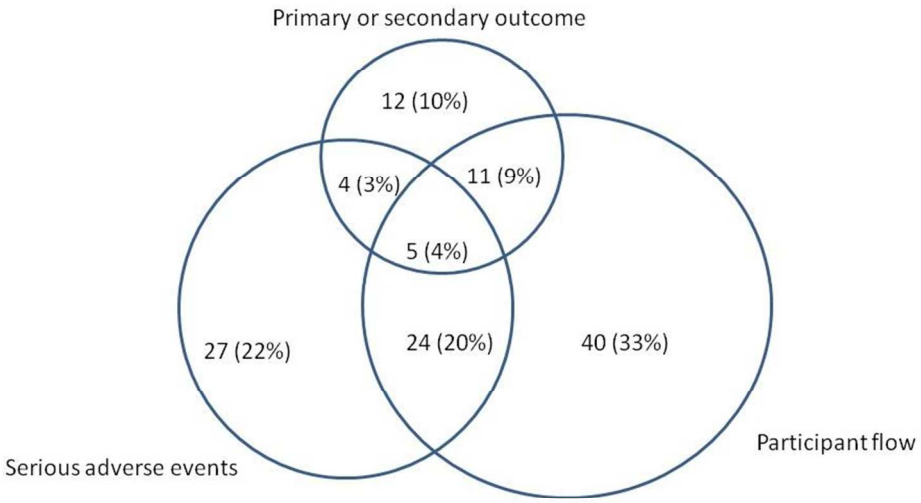


Figure 1. Reporting of death counts by data module in 123 ClinicalTrials.gov records
254x190mm (96 x 96 DPI)

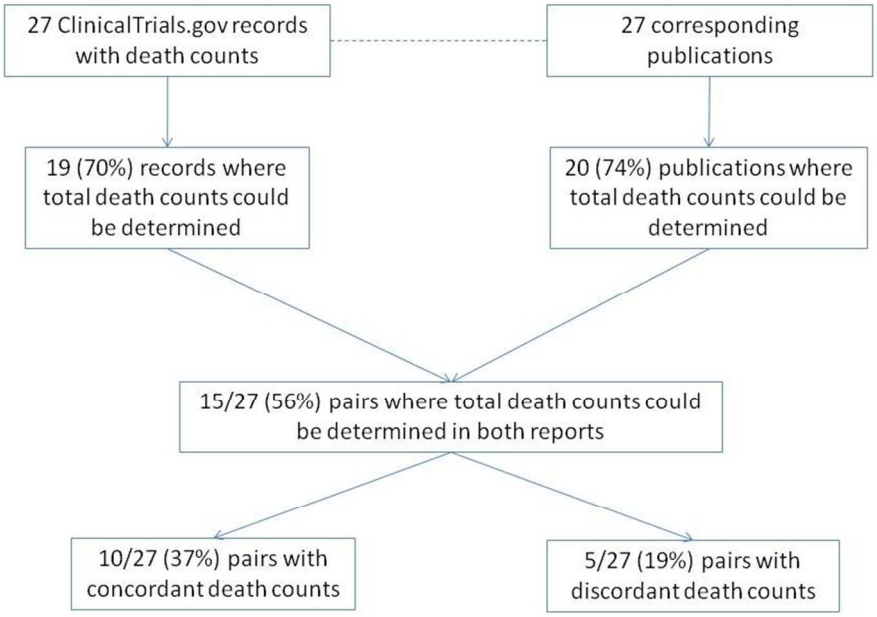
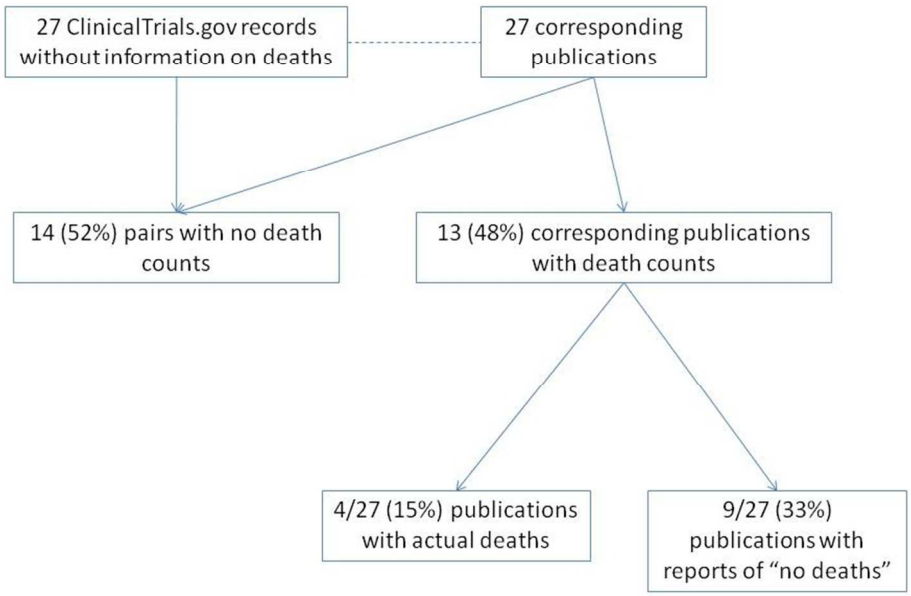
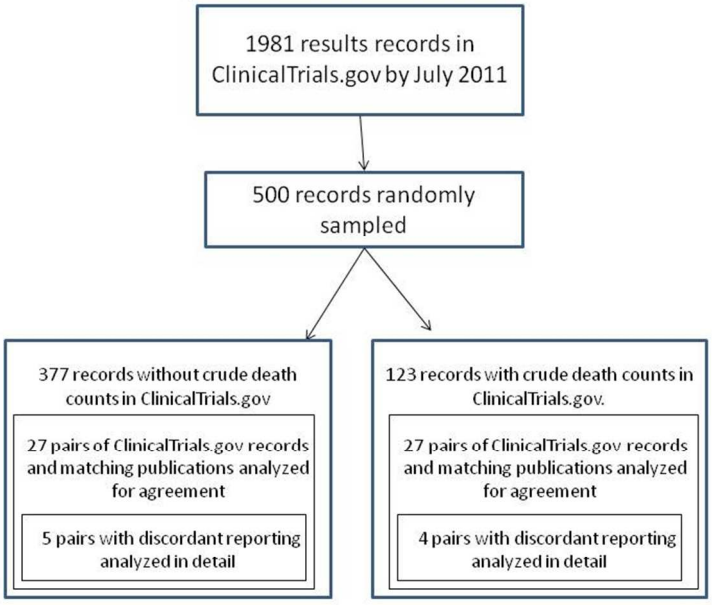


Figure 2. Consistency of death in matched pairs in (A) those with death counts in ClinicalTrials.gov and (B) those without information on death in ClinicalTrials.gov
254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)

Appendix 2. Examples death counts reported in modules in ClinicalTrials.gov records

Primary of secondary outcome

Measured Values

	Evaluable Patients
Number of Participants Analyzed [units: participants]	15
Number of Participants (Patients) Who Died Due to Transplant. [units: Participants]	4

No statistical analysis provided for Number of Participants (Patients) Who Died Due to Transplar

Serious Adverse Events

Serious Adverse Events

	Home Monitoring	Conventional
Total, serious adverse events		
# participants affected / at risk	124/977 (12.69%)	74/473 (15.64%)
Cardiac disorders		
Cardiac related hospitalizations †		
# participants affected / at risk	45/977 (4.61%)	31/473 (6.55%)
# events	64	35
General disorders		
Death †		
# participants affected / at risk	52/977 (5.32%)	26/473 (5.50%)
# events	52	26
Non-cardiac related hospitalizations †		
# participants affected / at risk	16/977 (1.64%)	3/473 (0.63%)
# events	20	4

Participant Flow

Participant Flow: Overall Study

	Docetaxel + Sunitinib	Docetaxel
STARTED	296	297
Treated	295	293
COMPLETED	0	0
NOT COMPLETED	296	297
Study Ongoing	19	31
Protocol Violation	1	1
Lost to Follow-up	2	5
Death	10	4
Objective Progression or Relapse	227	206
Participant refused	3	7
Unspecified	34	43

BMJ open

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: cross-sectional study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001963.R1
Article Type:	Research
Date Submitted by the Author:	16-Oct-2012
Complete List of Authors:	Earley, Amy; Tufts Medical Center, Tufts Evidence-based Practice Center Lau, Joseph; Tufts Medical Center, Tufts Evidence-based Practice Center Uhlig, Katrin; Tufts Medical Center,
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Evidence based practice
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, QUALITATIVE RESEARCH

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: a cross-sectional study

Amy Earley BS research associate[1], Joseph Lau MD professor of medicine[1, 2], Katrin Uhlig MD MS associate professor of medicine[1, 2, 3]

Author affiliations:

[1] Tufts Evidence-based Practice Center, Tufts Medical Center, Boston, MA 02111, US

[2] Tufts University School of Medicine, Boston, MA 02111, US

[3] Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA 02111, US

Corresponding author:

Katrin Uhlig MD, MS

Tufts Medical Center

800 Washington Street, #391

Boston, Massachusetts, 02111, USA

Email: kuhlig@tuftsmedicalcenter.org

Word Count:
Abstract: 287
Manuscript Text: 2917

Abstract

Context: A participant death is a serious event in a clinical trial and needs to be unambiguously and publicly reported.

Objective: To examine: 1) how often and how numbers of deaths are reported in ClinicalTrials.gov records; 2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication; 3) whether counts may be discordant.

Design: Registry-based study of clinical trial results reporting

Setting: ClinicalTrials.gov results database searched in July 2011 and matched PubMed publications

Selection criteria: A random sample of ClinicalTrials.gov results records. Detailed review of records with a single corresponding publication.

Main outcome measure: ClinicalTrials.gov records reporting number of deaths under participant flow, primary or secondary outcome, or serious adverse events. Consistency in reporting of number of deaths between ClinicalTrials.gov records and corresponding publications.

Results: In 500 randomly selected ClinicalTrials.gov records, only 123 records (25%) reported a number for deaths. Reporting of deaths across data modules for participant flow, primary or secondary outcomes, and serious adverse events was variable. In a sample of 27 pairs of ClinicalTrials.gov records with number of deaths and corresponding publications, total deaths

per arm could only be determined in 56% (15/27 pairs) but were discordant in 19% (5/27). In 27 pairs of ClinicalTrials.gov records without any information on number of deaths, 48% (13/27) were discordant since the publications reported absence of deaths in 33% (9/27) and positive death numbers in 15% (4/27).

Conclusions: Deaths are variably reported in ClinicalTrials.gov records. A reliable total number of deaths per arm cannot always be determined with certainty or can be discordant with number reported in corresponding trial publications. This highlights a need for unambiguous and complete reporting of number of deaths in trial registries and publications.

Article Summary

Article focus

- We hypothesized that the lack of clear expectations for reporting all deaths in clinical trials give rise to discrepancies in number of deaths reported across reports of a trial.

Key messages

- There is a lack of clarity, consistency and agreement in reporting of deaths in clinical trials which highlights the need for unambiguous templates to standardize reporting of total number of deaths per arm in ClinicalTrials.gov records and more explicit reporting guidelines for peer reviewed publications.

Strengths and limitations of this study

- Our findings indicate a need for explicit expectations for reporting of all deaths.
- We suggest amendments to reporting formats such as: number of participants who started per arm, total number of deaths from any cause per arm and the time point of last ascertainment to prompt study investigators to sum up all deaths across participant loss, primary or secondary outcomes, and serious adverse events.
- We examined only a limited number of matched cases. Nevertheless, even these small samples demonstrate ambiguity within records and inconsistencies across reports of the same trial.
- We used only data available in the publicly available reports and only counted actual number of deaths and not alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible.

- We followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Introduction

The death of a clinical trial subject is a serious event that needs to be publicly disclosed. Incomplete reporting of deaths may overemphasize health benefits when benefits and harms of medical interventions are summarized.[1;2] For unambiguous reporting, all deaths have to be reported for each trial arm and the absence of deaths must be explicitly stated if none were known to have occurred.

Formal reporting expectations for public disclosure of deaths in clinical trials are complex. During a trial, the United States Food and Drug Administration (FDA) expects a sponsor of an investigational new drug to submit annual reports that include a list of subjects who died during participation in the investigation, with the cause of death for each subject[3]. This means all deaths must be reported to the FDA, regardless of cause.

Sponsors of investigational new drugs also need to promptly report to the FDA and trial investigators serious unexpected events if they are suspected adverse reactions, meaning that there is a "reasonable possibility" that the drug caused it[4;5]. Further, the FDA regulations specify that the sponsor report "an aggregate analysis of specific events observed in a clinical trial …that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group[6]" suggesting that the events may be caused by the drug.[5]

After trial completion, trial registries such as ClinicalTrials.gov provide Web-based public records of trial results of federally and privately funded trials.[7] Results reporting in ClinicalTrials.gov is mandated by the United States Food and Drug Administration (FDA) Amendments Act which requires the reporting of summary results for phase II-IV interventional studies of drugs, biological products, and devices within 1 year of completing data collection for the prespecified primary outcome.[7-9] Based on this Act, the results data bank of the ClinicalTrials.gov registry shall include "a table of anticipated and unanticipated serious adverse events grouped by organ system with number and frequency in each arms of the trial"[10]. The ClinicalTrials.gov data element definitions define adverse events as "unfavorable changes in

health …, that occur in trial participants during the clinical trial or within a specified period following the trial" and under serious adverse events include "adverse events that result in death"[11]. This reporting of deaths as a serious adverse event is currently the only requirement for reporting of deaths in ClinicalTrials.gov and requires a judgment about the possibility of a causal association. However, causality assessment may be a challenge.[12]

The peer reviewed publication of clinical trials is guided by CONSORT.[13] The main reporting CONSORT guideline does not specify a need to report all deaths; however, the extension for reporting of adverse events states that "Authors should always report deaths in each study group during a trial, regardless of whether death is an end point and regardless of whether attribution to a specific cause is possible"[14].

We hypothesized that the complex reporting expectations for death give rise to discordance in deaths documented across reports of a trial. We first examined how number of deaths from any cause was reported in ClinicalTrials.gov records. We then attempted to determine the total deaths per arm in a ClinicalTrials.gov results record and in the corresponding publication. Finally, we conducted a detailed review of cases with discrepancies in death numbers to identify possible explanations.

Methods

The ClinicalTrials.gov team provided us with a database of results records indexed in ClinicalTrials.gov (search date July 12, 2011). The database contained all records of phase II, III, or IV interventional trials with results entered between September 9, 2009 and June 14, 2011. In 500 randomly selected records, we examined the record for reporting of any number of deaths. This entailed review of three of the four scientific data modules, i.e. participant flow, primary and secondary outcomes, and serious adverse events, but not baseline characteristics. Appendix 1 shows screenshots for the three pertinent modules from a sample ClinicalTrials.gov record. We considered deaths only when a zero or a positive number for death was reported in any module, i.e. we did not derive death numbers from information on deaths reported as percentages, rates, risks, or survival curves. In the 123 records that reported some number of death, we examined in which module deaths were reported. Deaths from serious adverse events would presumably be a reason for not completing a trial and qualify to be listed as such in the participant flow module. We examined how many records reported number of deaths only in the serious adverse events module without reporting any deaths as a reason for discontinuation.

Among the 500 records, we also identified studies with an outcome measure description that implied ascertainment of death, including overall survival, time to mortality, all cause deaths, disease-specific death, composite outcomes including death and serious adverse events including deaths. In this subset, we examined how often actual numbers of deaths were reported as part of the primary or secondary outcome module when the outcome suggested that deaths were collected.

We then compared death reporting between ClinicalTrials.gov results records and corresponding publications. To select a sample of pairs, we used 2 criteria: 1) ClinicalTrials.gov records had to provide only a single PubMed Identifier (PMID) matching a publication describing trial results to avoid the need for reconciliation across several publications, and 2) publications

had to be electronically accessible through our library. Based on these two criteria, we retrieved 27 publications matching the ClinicalTrials.gov records that reported death numbers. We sampled another 27 pairs of publications and ClinicalTrials.gov records where the record did not report death numbers.

For each record or publication, we attempted to determine the total deaths per arm and the numbers randomized or analyzed per arm based on the data available in the record and publication, without contacting authors. This required assumptions when reconciling number of deaths across the three pertinent modules in the ClinicalTrials.gov record. For the publications, we searched the sections of the article corresponding to the modules. We used the following operational rules for decision-making:

- If a report did not provide any direct information on number of deaths, no counts were implied.
- If a number of deaths was reported in only one module in the ClinicalTrials.gov record or the corresponding sections in the publication, i.e., either in participant flow, primary or secondary outcome, or adverse events, this was determined to be the total number of deaths.
- Otherwise, as a default, the highest unambiguous number of deaths in one category was taken as the total number of deaths.

Appendix 3 shows an example of a record where the total number of deaths could not be determined with certainty based on these rules. When the number of deaths could be determined for both the ClinicalTrials.gov record and the corresponding publication following the rules, we compared the numbers between the record and the publication. A pair was discordant either when the total number of deaths was not the same, or when the ClinicalTrials.gov record did not include any information on death numbers, yet the publication mentioned a presence or absence of deaths. Discordant cases were reviewed in more detail. We extracted the denominators for number of deaths from information on number started, randomized, or

analyzed. We further captured information on duration of follow-up and looked for possible reasons for differences in number of deaths.

Results

Reporting of crude number of deaths in ClinicalTrials.gov results records

In July 2011, there were 1981 records with results in ClinicalTrials.gov and 500 records were randomly chosen for further analysis (Appendix Figure 1). These included 123 records (25%) which reported a number of deaths in at least one module. Deaths were variably reported across the three modules of participant flow, primary or secondary outcome, and serious adverse events (Figure 1). Sixty-four percent of the records reported death numbers only in one of the modules, 32% in two modules and 4% in all of them. Approximately one fifth (27/123) of the records reported number of deaths only in the module for the serious adverse events, i.e. there were no deaths reported in the participant flow as a reason for not completing the trial. One fifth (24/123) reported deaths in both of these modules.

Out of the 500 records, we identified 97 with a primary or secondary outcome measure definition that implied ascertainment of deaths. Of the 97, there were 32 (33%) that reported a crude number of deaths in the primary or secondary outcome module, with or without a result for death in another metric for death, such as percentage, rate, risk estimate. The 65 records that did not report crude number of deaths in the primary or secondary outcome module nonetheless still reported number of deaths under participant flow or serious adverse events.

Reporting of information on death, determination of total number of deaths per arm and congruency in matched pairs

We examined congruence of reporting of number of deaths across pairs of ClinicalTrials.gov records and corresponding trial publications. Figure 2 tabulates whether there was any information on number of deaths in a trial report, and if so, whether total number of deaths could be determined per arm following simple rules, and finally whether the total numbers per arm were concordant or discordant across pairs. We examined 27 pairs where the

ClinicalTrials.gov record contained some information on number of deaths and 27 pairs where the ClinicalTrial.gov record did not contain any information on death numbers.

Of the 27 pairs with number of deaths reported in the ClinicalTrials.gov record, there were 15 (55%) in which the total number of deaths per arm could be determined in both reports (Figure 2, panel A). The number of deaths were concordant between the ClinicalTrials.gov record and the publication in 10 pairs (37%), but discordant in five (19%). In the remaining 12 (44%), concordance could not be assessed because the total number of deaths per arm could not be determined unambiguously for the record and the publication. The five discordant pairs are shown in detail in Table 1.

In the 27 pairs where the ClinicalTrials.gov record did not contain any information on death numbers, 14 (52%) pairs were concordant regarding the absence of information on deaths, i.e. the trial publications also did not contain any death numbers (Figure 2, panel B). However 13 (48%) publications contained information on number of deaths. In 9 studies (33%), the published study affirmatively reported “no deaths” and in four studies, the published report mentioned positive number of deaths (Figure 2, Panel B). These four cases are shown in Table 2. For example in Case 9, the ClinicalTrials.gov record did not contain any information on number of deaths; but the publication reported one death under serious adverse events (Table 2).

Review of cases with discordant counts

Tables 1 and 2 show the detailed review of the cases with discordant counts. For each case, the crude number of deaths for each module or reporting location for the ClinicalTrials.gov record and the corresponding publication are shown, as well as the total number of deaths per arm that was determined following our operational rules. The summary contains comments and interpretation of the discrepancies.

In several cases, information on duration of follow-up or the time point of last assessment was not exact or varied across the reports. Comparison of number of deaths required reconciliation across reports with discordant numbers of arms (Cases 5 and 6) or discordant number of studies (Case 4). For example, in Case 5, the ClinicalTrials.gov record included two arms treated with different drug doses, while the publication reported results only for one of the arms. The number of deaths for this single arm was consistent across the ClinicalTrials.gov record and the publication. In the other cases with the same number of arms, the inference or certainty about the number of deaths within each arm differed. In addition to discordant counts, problems were lack of provision of crude death numbers even when death was an outcome of interest (Cases 1 and 3), imprecision in data entry (Case 4), reporting of deaths under serious adverse events without specification as to whether they were counted as part of the death outcome (Case 4) or the participant flow (Case 7). In most cases, the publication included a slightly higher crude number of deaths. Large discrepancies were noted in cases where the record did not report counts for an outcome that included death, while the report did (Cases 3 and 9).

Discussion

Our study highlights a failure of consistent and clear reporting of number of deaths in clinical trials. Only 25% of ClinicalTrials.gov results records provided some number of deaths, with great variation and overlap in the reporting across the three data modules for participant flow, primary or secondary outcomes, or serious adverse events. While we expected records reporting death as a serious adverse event to also list death as a reason for discontinuation from the trial in participant flow, a fifth of the records with death numbers reported deaths only under serious adverse events. Among ClinicalTrials.gov records with a definition for a primary or secondary outcome that implies ascertainment of death, only a third provided crude number of deaths in the data module for the primary or secondary outcome. This heterogeneous reporting and the uncertainty of whether deaths are reported in a redundant or exclusive manner across data modules, poses problems for reconciling deaths within a trial report.

Total number of deaths per arm could not always be determined unambiguously in the ClinicalTrials.gov results records or the corresponding publication. In the small sample where total deaths could be determined in both reports for the same trial, we identified examples where the number of deaths was discordant, highlighting lack of coherence and completeness. There were no clear patterns to explain the discrepancies. Finding a slightly higher crude number of deaths in publications than in ClinicalTrial.gov records suggests that number of deaths in the ClinicalTrials.gov records are not complete.

Our findings of haphazard reporting of deaths in clinical trials indicate a need for explicit expectations in reporting of all deaths regardless of whether they are considered to be a serious adverse event or not. We suggest that reporting formats for aggregate clinical trial results need to be amended to provide the following information: number of individuals who started per arm, number of deaths from any cause per arm and the time point of last ascertainment. This should prompt study investigators to sum up all deaths across participant flow, primary or secondary outcomes, and serious adverse events. Information on mean duration of follow-up is also

needed to allow calculation of rates. Given their prominent role supported by the legal regulations, clinical trials registries can spearhead uniform and consistent reporting of important trial outcomes, such as deaths. Similarly editors and sponsors must educate trialists to better meet the need for uniform reporting of all deaths.[13;15]

Our study has several limitations. We examined only a limited number of matched cases. Nevertheless, even these small samples demonstrate ambiguity within records and inconsistencies across reports of the same trial. Also, we used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous number of deaths. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications. Further, we only gave credit to number of deaths and not to alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible. Finally, we followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Our findings have to be viewed in context. Only 22% of studies report their results in ClinicalTrials.gov within one year of completion[16] and fewer than half of studies funded by the National Institutes of Health publish their results in a Medline indexed journal within 30 months of trial completion.[17] Thus, our matched pairs are drawn from a minority of trials that have been compliant with both expectations: publication of results in ClinicalTrials.gov and publication in a peer reviewed journal.

Full reporting of all deaths enables more accurate assessment of risks and benefits associated with treatments. Assessment of patient safety relies on capturing signals, even when they are non-specific.[18;19] Small differences in numbers of death may bias results and distort estimates across studies. From an ethical perspective, it is desirable that trials ascertain and

report all deaths regardless of whether they appear to be related to study conduct or intervention, are unforeseen, or non-specific. Even with a clear instructions and prompts for trials to report deaths; however, there may be remaining uncertainty depending on the rigor of ascertainment or surveillance and the selection of trial outcomes. Further, crude numbers are not the only format for reporting deaths in a trial. Time to event reporting may be more meaningful, but may introduce uncertainty about how censoring and deaths are handled. While both approaches to presenting information on deaths may be necessary and complementary, our study suggests that some improvement could be made with simple means of standardized reporting formats.

In summary, our study shows lack of clarity, consistency and agreement in reporting of deaths in clinical trials. This highlights the need for unambiguous templates to standardize reporting of total number of deaths per arm in ClinicalTrials.gov records and more stringent reporting guidelines for peer reviewed publications.

Data Sharing Statement: There is no additional available.

Contributors: Concept and design: AE, JL, KU; Interpretation of data: AE, JL, KU; Drafting article: AE, KU; Revision of article for important intellectual content: AE, JL, KU

Funding:

This project was funded under Contract No. HHSA 290 2007-10055-I, entitled “Evidence-based Protocol for Reviewing ClinicalTrials.gov Results Database,” from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there are no conflicts of interest.

Tables

Figures

Appendices

Legend: In Module A, the participant flow shows 2 deaths per arm indicating a total of 4 deaths as a reason for non-completion of the trial. In Module B, results are reported for a secondary outcome entitled “Number of Participants With Overall Survival Events”. The Measure Description suggests a survival analysis while the Measure Title and units show actual numbers. Since 188 of 745 participants in the TAC arm and 241 of 746 participants in the FAC arm were counted as alive in the survival analysis, 1062 individuals among 1491 participants were censored (557 vs. 505 per arm respectively). The data module for adverse events (not shown) did not provide additional information on death. Since this is a study of metastatic breast cancer, we assumed that the total number of deaths was greater than 4 as shown in the participant flow, but the actual number could not be determined with certainty.

Reference List

(1) Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005; 142(12 Pt 2):1090-1099.

(2) Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001; 285(4):437-443.

(3) Food and Drug Administration. Code of Federal Regulations Title 21. 21 CFR 312.33(b)(3) - Annual Reports. 2012.
Ref Type: Bill/Resolution

(4) Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans. Final rule. *Fed Regist* 2010; 75(188):59935-59963.

(5) Sherman RB, Woodcock J, Norden J, Grandinetti C, Temple RJ. New FDA regulation to improve safety reporting in clinical trials. *N Engl J Med* 2011; 365(1):3-5.

(6) Food and Drug Administration. Code of Federal Regulations Title 21. 21 CFR 312.32(c)(1)(i)(C)-IND safety reporting. 2012.
Ref Type: Bill/Resolution

(7) Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med* 2011; 364(9):852-860.

(8) Food and Drug Administration Amendments Act. U.S. Public Law 110-85. 2012.
Ref Type: Bill/Resolution

(9) Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. *Chest* 2009; 136(1):295-303.

(10) Food and Drug Administration Amendments Act. U.S. Public Law 110-95. 2007.
Ref Type: Bill/Resolution

(11) ClinicalTrials.gov. ClinicalTrials.gov "Basic Results" Data Element Definitions. http://prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEvents . 2012. 6-26-2012.
Ref Type: Online Source

(12) Cato A. Premarketing adverse drug experiences: data management procedures. Unexpected death occurring early in clinical trials. *Drug Inf J* 1987; 21(1):3-7.

(13) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 152(11):726-732.

(14) Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

(15) Mansi BA, Clark J, David FS, Gesell TM, Glasser S, Gonzalez J et al. Ten recommendations for closing the credibility gap in reporting industry-sponsored clinical

research: a joint journal and pharmaceutical industry perspective. *Mayo Clin Proc* 2012; 87(5):424-429.

(16) Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012; 344:d7373.

(17) Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012; 344:d7292.

(18) Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. *N Engl J Med* 2005; 352(11):1131-1132.

(19) Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170(14):1191-1201.

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: a cross-sectional study

Amy Earley BS research associate[1], Joseph Lau MD professor of medicine[1, 2], Katrin Uhlig MD MS associate professor of medicine[1, 2, 3]

Author affiliations:

[1] Tufts Evidence-based Practice Center, Tufts Medical Center, Boston, MA 02111, US

[2] Tufts University School of Medicine, Boston, MA 02111, USA

[3] Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA 02111, USA

Corresponding author:

Katrin Uhlig MD, MS

Tufts Medical Center

800 Washington Street, #391

Boston, Massachusetts, 02111, USA

Email: kuhlig@tuftsmedicalcenter.org

Word Count:
Abstract: 261287
Manuscript Text: 2935796

Abstract

Context: A participant death is a serious event in a clinical trial and needs to be unambiguously and publicly reported.

Objective: To examine: 1) how often and how numbers of deaths ~~counts~~ are reported in ClinicalTrials.gov records; 2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication; 3) ~~how~~ whether counts may be discordant.

Design: Registry-based study of clinical trial results reporting

Setting: ClinicalTrials.gov results database searched in July 2011 and matched PubMed publications

Selection criteria: A random sample of ClinicalTrials.gov results records. Detailed review of records with a single corresponding publication.

Main outcome measure: ClinicalTrials.gov records reporting number of ~~a~~ deaths ~~count~~ under participant flow, primary or secondary outcome, or serious adverse events. Consistency in reporting of number of death ~~count~~s between ClinicalTrials.gov records and corresponding publications.

Results: In 500 randomly selected ClinicalTrials.gov records, only 123 records (25%) reported ~~some~~ a number ~~of~~ for deaths ~~count~~. Reporting of deaths across data modules for participant flow, primary or secondary outcomes, and serious adverse events was variable. In a sample of 5427 pairs of ClinicalTrials.gov records with number of deaths ~~counts~~ and corresponding

publications, total deaths per arm could only be determined in 56% (15/27 pairs) but were discordant in 19% (5/27). In 27 pairs of ClinicalTrials.gov records without any information on number of deaths, 48% (13/27) were discordant since the publications reported absence of deaths in 33% (9/27) and ~~actual~~ positive death numbers~~s~~ in 15% (4/27).

Conclusions: Deaths ~~counts~~ are variably reported in ~~c~~Clinical ~~t~~Trials.gov records. ~~and a~~A reliable total number of deaths ~~count~~ per arm cannot always be determined with certainty ~~and~~or can be discordant with number reported in corresponding trial publications. This highlights a need for unambiguous and complete reporting of number of death ~~count~~s in trial registries and publications.

Article Summary

Article focus

- We hypothesized that the ~~discordant~~~~repant reporting~~ lack of clear expectations for reporting all deaths in clinical trials give rise to discrepancies in number of deaths reported across reports of a trial.

Key messages

- There is a lack of clarity, consistency and agreement in reporting of ~~all cause~~ death ~~count~~s in clinical trials which highlights the need for unambiguous templates to standardize reporting of total number of deaths ~~counts~~ per arm in ClinicalTrials.gov records and more ~~stringent~~ explicit reporting guidelines for peer reviewed publications.

Strengths and limitations of this study

- Our findings indicate a need for ~~clarifying~~ explicit expectations ~~in~~ for reporting of all deaths. ~~They~~ and highlight differences in the legal standards for reporting of serious adverse events after trial completion in Clinical Trials.gov and for expeditious real time reporting of serious adverse events in ongoing trials by the ~~FDA.~~
- We suggest amendments to reporting formats such as: number of ~~individuals~~ participants who started per arm, total number of deaths from any cause per arm and the time point of last ascertainment to prompt study investigators to sum up all deaths across participant loss, primary or secondary outcomes, and serious adverse events.
- We examined only a limited number of matched cases. Nevertheless, ~~the discrepant findings~~ even ~~in~~ these small samples demonstrate ambiguity within

records and ~~a clear disconnect between reporting expectations and reporting practices as illustrated by~~ inconsistencies across reports of the same trial.

- ~~We used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous death counts. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications.~~
- We used only data available in the publicly available reports and ~~We~~ only ~~gave credit to~~counted actual number of death~~s counts~~ and not ~~to~~ alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible.
- We followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Introduction

The death of a clinical trial subject is a serious event that needs to be publicly disclosed. ~~Inadequate~~ Incomplete reporting of deaths may overemphasize health benefits when benefits and harms of medical interventions are summarized.[1;2] ~~.~~ For unambiguous reporting, all deaths have to be reported for each trial arm and the absence of deaths must be explicitly stated if none were known to have occurred. ~~Trial registries such as ClinicalTrials.gov provide public records of trial results.[3] It is a Web-based trial registration of federally and privately funded trials.~~

Formal reporting expectations for public disclosure of deaths in clinical trials are complex. During a trial, the United States Food and Drug Administration (FDA) ~~FDA~~ expects a sponsor of an investigational new drug to submit annual reports that include a list of subjects who died during participation in the investigation, with the cause of death for each subject (ref IND annual reporting requirements 21 CFR 312.33(b)(3)). This means all deaths must be reported to the FDA, regardless of cause.

~~The FDA regulation on drug safety reporting requires s~~Sponsors of investigational new drugs also need to promptly report to the FDA and trial investigators serious unexpected events if they are suspected adverse reactions, meaning that there is a “reasonable possibility” that the drug caused it[8;9]. ~~.~~Further, the FDA regulations specify that the sponsor report “an aggregate analysis of specific events observed in a clinical trial …that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group(ref IND Safety report 21 CFR 312.32(C)(1)(i)(C))" ~~Further, a sponsor must analyze in the aggregate events that are not interpretable as single cases. However, these must be reported only if there is an observed imbalance between the drug treatment group and a control group~~suggesting that the events may be caused by the drug.[9] ~~Further, FDA regulations specify that the sponsor report "an aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."~~

~~.While there is no regulation specifically mandating the reporting of all deaths from any cause in a clinical trial, a death may constitute a serious adverse event and is therefore subject to the regulations on reporting of serious adverse events. However, it appears that there is incongruence between legal reporting expectations for serious adverse events after trial completion versus during trial conduct.~~

After trial completion, trial registries such as ClinicalTrials.gov provide Web-based public records of trial results~~.~~ of federally and privately funded trials.[3] Results reporting in ClinicalTrials.gov is mandated by~~T~~ the United States Food and Drug Administration (FDA) Amendments Act ~~mandates~~ which requires the reporting of summary results for phase II-IV interventional studies of drugs, biological products, and devices within 1 year of completing data collection for the prespecified primary outcome~~. in ClinicalTrials.gov~~[3-5]~~.~~ ~~The Act includes a provision regarding the reporting of aggregate serious adverse events, thus mandating public disclosure.~~ Based on this Act, the results data bank of the ClinicalTrials.gov registry shall include "a table of anticipated and unanticipated serious adverse events grouped by organ system with number and frequency in each arms of the trial"[6]. The ClinicalTrials.gov data element definitions define adverse events as "unfavorable changes in health …, that occur in trial participants during the clinical trial or within a specified period following the trial~~.~~" and under serious adverse events include ~~:"~~adverse events that result in death~~"~~[7]. This reporting of deaths as a serious adverse event is currently the only requirement for reporting of deaths in ClinicalTrials.gov and requires a judgment about the possibility of a causal ~~association.~~ association. However, causality assessment may be a challenge. (ref Cato)

The peer reviewed publication of clinical trials is guided by CONSORT. (ref Schulz)~~.~~ The main reporting CONSORT guideline~~-~~ does not specify a need to report all deaths; ~~. H~~however, the ~~subsequently published~~ extension for reporting of adverse events states that "Authors

should always report deaths in each study group during a trial, regardless of whether death is an end point and regardless of whether attribution to a specific cause is possible"(ref Ioannidis).

~~In contrast to these reporting expectations sof all deaths after trial completion, investigators and sponsors of ongoing clinical trials have to report adverse events to respective drug regulatory authorities. The FDA regulation on drug safety reporting requires sponsors of investigational new drugs to promptly report to the FDA and investigators serious unexpected events if they are suspected adverse reactions, meaning that there is a "reasonable possibility" that the drug caused it[8;9]. Otherwise, adverse events are batched by the sponsor and submitted later. This requires an adjudication of the event as serious or minor; expected or unexpected; and study-related, possibly study-related, or not study- related. Death is by definition a serious event, but it is nonspecific as it may result from natural disease progression, lack of efficacy of an intervention, harm from an intervention or a cause unrelated to a trial. This need for judgment about the possibility of a causal association makes accounting and adjudication of deaths in trials challenging[10].~~

We hypothesized that the ~~discrepant incongruent~~complex reporting expectations for death give rise to ~~discrepancies~~ discordance in deaths ~~reported~~ documented across reports of a trial. We first examined how number of death ~~count~~s from any cause ~~were~~ was reported in ClinicalTrials.gov records. We then attempted to determine the total deaths per arm in a ClinicalTrials.gov results record and in the corresponding publication. Finally, we conducted a detailed review of cases with discrepancies in ~~crude~~ death numbers to identify possible explanations.

Methods

The ClinicalTrials.gov team provided us with a database of results records indexed in ClinicalTrials.gov (search date July 12, 2011). The database contained all records of phase II, III, or IV interventional trials with results entered between September 9, 2009 and June 14, 2011. In 500 randomly selected records, we examined the record for reporting of any number of death ~~count~~s. This entailed review of three of the four scientific data modules, i.e. participant flow, primary and secondary outcomes, and serious adverse events, but not baseline characteristics. Appendix 1 shows screenshots for the three pertinent modules from a sample ClinicalTrials.gov record. We considered deaths ~~counts~~ only when a zero or a positive number for death was reported in any module, i.e. we did not derive death ~~counts~~numbers from information on deaths reported as percentages, rates, risks, or survival curves. In the 123 records that reported~~ing a crude~~some number of ~~death~~deaths ~~count~~, we examined in which module deaths were reported. Deaths from serious adverse events would presumably be a reason for not completing a trial and qualify to be listed as such in the participant flow module. We examined how many records reported number of death ~~count~~s only in the serious adverse events module without reporting any deaths as a reason for discontinuation.

Among the 500 records, we also identified studies with an outcome measure description that implied ascertainment of death, including overall survival, time to mortality, all cause deaths, disease ~~-~~specific death, composite outcomes including death and serious adverse events including deaths. In this subset, we examined how often actual numbers of death ~~count~~s were reported as part of the primary or secondary outcome module when the outcome suggested that ~~number of~~ deaths were collected.

We then compared death reporting between ClinicalTrials.gov results records and corresponding publications. To select a sample of pairs, we used 2 criteria: 1) ClinicalTrials.gov

records had to provide only a single PubMed Identifier (PMID) matching a publication describing trial results to avoid the need for reconciliation across several publications, and 2) publications had to be electronically accessible through our library. Based on these two criteria, we retrieved ~~75~~ 27 ~~matching~~ publications matching ~~of which 27 corresponded to~~the ~~-~~ClinicalTrials.gov records that reported death numbers. We sampled another 27 pairs of publications and ClinicalTrials.gov records where the ~~ClinicalTrials.gov~~ record did not report death numbers.

For each record or publication, we attempted to determine the total deaths per arm and the numbers randomized or analyzed per arm based on the data available in the record and publication, without contacting authors. This required assumptions when reconciling number of death ~~count~~s across the three pertinent modules in the ClinicalTrials.gov record. For the publications, we searched the sections of the article corresponding to the modules. We used the following operational rules for decision-making:

- If a report did not provide any direct information on number of death ~~count~~s, no counts were implied.
- If a number of death ~~counts~~ was reported in only one module in the ClinicalTrials.gov record or the corresponding sections in the publication, i.e., either in participant flow, primary or secondary outcome, or adverse events, this was determined to be the total number of death~~s count~~.
- Otherwise, as a default, the highest unambiguous number of deaths in one category was taken as the total number of death~~s count~~.

Appendix ~~2~~3 shows an example of a record where the total number of death~~s count~~ could not be determined with certainty based on these rules. When the number of death ~~count~~s could be determined for both the ClinicalTrials.gov record and the corresponding publication following the~~se~~ rules, we compared the~~se death~~ numbers ~~counts~~ between the record and the publication. A pair was discordant either when the total number of deaths was not the same, or when the

ClinicalTrials.gov record did not include any information on death numbers, yet the publication mentioned a presence or absence of deaths. Discordrepant cases were reviewed in more detail. We extracted the denominators for number of death countss from information on number started, randomized, or analyzed. We further captured information on duration of follow-up and looked for possible reasons for differences in number of death counts.

Results

Reporting of crude number of death ~~count~~s in ClinicalTrials.gov results records

In July 2011, there were 1981 records with results in ClinicalTrials.gov and 500 records were randomly chosen for further analysis (Appendix Figure 1). These included 123 records (25%) which reported a number of deaths ~~count~~ in at least one module. Deaths were variably reported across the three modules of participant flow, primary or secondary outcome, and serious adverse events (Figure 1). Sixty-four percent of the records reported ~~crude~~ death numbers only in one of the modules, 32% in two modules and 4% in all of them. Approximately one fifth (27/123) of the records reported ~~crude~~ number of deaths ~~counts~~ only in the module for the serious adverse events, i.e. there were no deaths reported in the participant flow as a reason for not completing the trial. One fifth (24/123) reported deaths in both of these modules.

Out of the 500 records, we identified 97 with a primary or secondary outcome measure definition that implied ascertainment of deaths. Of the 97, there were 32 (33%) that reported a crude number of deaths ~~count~~ in the primary or secondary outcome module, with or without a result for death in another metric for death, such as percentage, rate, risk estimate~~...~~. The 65 records that did not report crude number of death ~~count~~s in the primary or secondary outcome module nonetheless still reported number of death ~~count~~s under participant flow or serious adverse events.

Reporting of information on death, determination of total number of death ~~count~~s per arm and congruency in matched pairs

We examined congruence of reporting of number of deaths across pairs of ClinicalTrials.gov records and corresponding trial publications. Figure 2 tabulates whether there was any information on number of deaths in a trial report, and if so, whether total number of death ~~count~~s could be determined per arm following simple rules, and finally whether the total

~~counts~~ numbers per arm were concordant or discordant across pairs. We examined 27 pairs where the ClinicalTrials.gov record contained some information on number of deaths ~~counts~~ and 27 pairs where the ClinicalTrial.gov record did not contain any information on death numbers.

Of the 27 pairs with ~~information on~~ number of death ~~count~~s reported in the ClinicalTrials.gov record, there were 15 (55%) in which the total number of deaths ~~count~~ per arm could be determined in both reports (Figure 2, panel A). The number of death ~~count~~s were concordant between the ClinicalTrials.gov record and the publication in 10 pairs (37%), but discordant in five ~~pairs~~ (19%). ~~, while i~~In the remaining 12 (44%), concordance could not be assessed because the total number of deaths per arm could not be determined unambiguously for the record and the publication. The five discordant pairs are shown in detail in Table 1.

In the 27 pairs where the ClinicalTrials.gov record did not contain any information on death numbers, 14 (52%) pairs were concordant regarding the absence of information on deaths, i.e. the trial publications also did not contain any ~~information on~~ death numbers (Figure 2, panel B). However 13 (48%) publications contained information on number of death ~~count~~s. In 9 studies (33%), the published study affirmatively reported “no deaths” and in four studies, the published report mentioned positive number of death ~~count~~s (Figure 2, Panel B). These four cases are shown in Table 2. For example in Case 9, the ClinicalTrials.gov record did not contain any information on number of deaths; but~~,~~ the publication reported one death under serious adverse events (Table 2).

Review of cases with ~~discrepant~~ discordant counts

Tables 1 and 2 show the detailed review of the cases with ~~discrepant~~ discordant counts. For each case, the crude number of death ~~count~~s for each module or reporting location for the ClinicalTrials.gov record and the corresponding publication are shown, as well as the total

number of deaths per arm that was determined following our operational rules. The summary contains comments and interpretation of the discrepancies.

In several cases, information on duration of follow-up or the time point of last assessment was not exact or varied across the reports. Comparison of number of death ~~count~~s required reconciliation across reports with ~~discrepant~~ discordant numbers of arms (Cases 5 and 6) or ~~discrepant~~ discordant number of studies (Case 4). For example, in Case 5, the ClinicalTrials.gov record included two arms treated with different drug doses, while the publication reported results only for one of the arms. ~~Ultimately t~~The number of death ~~count~~s for this ~~one~~ single arm was consistent across the ClinicalTrials.gov record and the publication. In the other cases with the same number of arms~~, however~~, the inference or certainty about the number of deaths ~~per~~within each arm differed. In addition to ~~discrepant~~ discordant counts, problems were lack of provision of crude death numbers even when death was an outcome of interest (Cases 1 and 3), imprecision in data entry (Case 4), reporting of deaths under serious adverse events without specification as to whether they were counted as part of the death outcome (Case 4) or the participant flow (Case 7). In most cases, the publication included a slightly higher crude number of death ~~count~~s. Large discrepancies were noted in cases where the record did not report counts for an outcome that included death, while the report did (Cases 3 and 9).

Discussion

Our study highlights a failure of consistent and clear reporting of number of death ~~count~~s in clinical trials. Only 25% of ClinicalTrials.gov results records provided some ~~information on~~ number of death ~~count~~s, with great variation and overlap in the reporting across the three data modules for participant ~~loss~~flow, primary or secondary outcomes, or serious adverse events. While we expected records reporting death as a serious adverse event to also list death as a reason for discontinuation from the trial in participant flow, a fifth of the records with death numbers reported deaths only under serious adverse events. Among ClinicalTrials.gov records ~~trials~~ with a definition for a primary or secondary outcome that implies ascertainment of death, only a third ~~of ClinicalTrials.gov records~~ provided crude number of death ~~count~~s in the data module for the primary or secondary outcome. This heterogeneous reporting and the uncertainty of whether deaths are reported in a redundant or exclusive manner across data modules, poses problems for reconciling deaths within a trial report.

~~Following operational rules, t~~Total ~~counts~~ number of deaths per arm could not always be determined unambiguously in the ClinicalTrials.gov results records or the corresponding publication. In the small sample where total deaths could be determined in both reports for the same trial, we identified examples where the number of death ~~count~~s ~~were~~ was ~~discrepant~~discordant, highlighting lack of coherence and completeness. There were no clear patterns to explain the discrepancies. Finding a slightly higher crude number of death ~~count~~s in publications than in ClinicalTrial.gov records suggests that number of death ~~count~~s in the ClinicalTrials.gov records are not complete. ~~This indicates a violation of the reporting expectations for ClinicalTrials.gov which includes death as a serious adverse event.~~

Our findings of haphazard reporting of deaths in clinical trials indicate a need for ~~clarifying~~ explicit expectations in reporting of all deaths ~~and highlight differences in the legal~~

~~standards for reporting of serious adverse events after trial completion[6] and expeditious real time reporting of serious adverse events in ongoing trials.~~ regardless of whether they are considered to be a serious adverse event or not. We suggest that reporting formats for aggregate clinical trial results need to be amended to provide the following information: number of individuals who started per arm, number of deaths from any cause per arm and the time point of last ascertainment. This should prompt study investigators to sum up all deaths across participant ~~loss~~flow, primary or secondary outcomes, and serious adverse events. Information on mean duration of follow-up is also needed to allow calculation of rates. Given their prominent role supported by the legal regulations, clinical trials registries can spearhead uniform and consistent reporting of important trial outcomes, such as deaths. Similarly editors and sponsors must educate trialists to better meet the need for uniform reporting of all deaths~~adverse events~~. [11-13]

Our study has several limitations. We examined only a limited number of matched cases. Nevertheless, ~~the discrepant findings~~ even ~~in~~ these small samples demonstrate ambiguity within records and ~~clear disconnect between reporting expectations and reporting practices as illustrated by~~ inconsistencies across reports of the same trial. Also, we used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous number of death~~count~~s. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications. Further, we only gave credit to number of death~~count~~s and not to alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible. Finally, we followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Our findings have to be viewed in context. Only 22% of studies report their results in ClinicalTrials.gov within one year of completion[14] and fewer than half of studies funded by the National Institutes of Health publish their results in a Medline indexed journal within 30 months of trial completion.[15] Thus, our matched pairs are drawn from a minority of trials that have been compliant with both expectations: publication of results in ClinicalTrials.gov and publication in a peer reviewed journal.

Full reporting of all deaths enables more accurate assessment of risks and benefits associated with treatments. Assessment of patient safety relies on capturing signals, even when they are non-specific.[16;17] Small differences in numbers of death may bias results and distort estimates across studies. FThus from an ethical perspective, it is desirable that trials ascertain and report all deaths regardless of whether they appear to be related to study conduct or intervention, are unforeseen, or non-specific. Death reporting may never be complete or simple given the challenges in ascertainment and adjudication. However, Even with a clear instructions and prompts for trials to report deaths; however, there may be remaining uncertainty depending on the rigor of ascertainment or surveillance and the choice selection of trial outcomes. Further, Ccrude numbers are not the only format for reporting deaths in a trial. Time to event reporting may be more meaningful, but may introduce uncertainty about how censoring and deaths are handled. Thus While both approaches to presenting information on deaths may be necessary and complementary, but our study suggests that some improvement could be made with simple means of standardized reporting formats.

In summary, our study shows lack of clarity, consistency and agreement in reporting of all cause death counts in clinical trials. This highlights the need for unambiguous templates to

standardize reporting of total number of death ~~count~~s per arm in ClinicalTrials.gov records and more stringent reporting guidelines for peer reviewed publications.

Data Sharing Statement: There is no additional available.

Contributors: Concept and design: AE, JL, KU; Interpretation of data: AE, JL, KU; Drafting article: AE, KU; Revision of article for important intellectual content: AE, JL, KU

Funding:

This project was funded under Contract No. HHSA 290 2007-10055-I, entitled “Evidence-based Protocol for Reviewing ClinicalTrials.gov Results Database,” from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there are no conflicts of interest.

Tables

Figures

Appendices

Legend: In Module A, ~~the number of deaths stated in~~ the participant flow shows ~~as~~ 2 deaths per arm indicating ~~meaning~~a total of 4 deaths as a reason for non-completion of the trial ~~during the trial~~. In Module B, results are reported for a ~~which is the~~ secondary outcome entitled ~~of~~ "~~'~~Number of Participants With Overall Survival Events~~'~~". ~~, the~~ The ~~m~~Measure Description suggests a survival analysis while the Measure Title and units ~~suggest~~show ~~that this outcome reports the~~ actual number~~s of participants who survived~~. ~~Assuming this to be the case, the number of deaths is not consistent with that in the participant flow. If~~ Since 188 of 745 participants in the TAC arm and 241 of 746 participants in the FAC arm were counted as alive in the survival analysis ~~survived~~, ~~that would indicate a total of~~ 1062 individuals ~~deaths in~~among 1491 participants were censored or died (557 vs. 505 ~~deaths~~ per arm respectively). The data module for adverse events (not shown) did not provide additional information on deaths. Since this is a study of metastatic breast cancer, we assumed that the total number of deaths was

greater than 4 as shown in the participant flow, but the actual number could not be determined with certainty. ~~The number of assumptions and unclear reporting for death flag this record as one where we are unable to determine the total number of deaths with certainty.~~

Reference List

(1) Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005; 142:1090-1099.

(2) Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001; 285:437-443.

(3) Zarin DA, Tse T, Williams RJ, et al. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med* 2011; 364:852-860.

(4) Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. *Chest* 2009; 136:295-303.

(5) FDAAA. U.S. Public Law 110-85. http://clinicaltrials.gov/ct2/invest . 2012. Accessed: 6-26-2012.
Ref Type: Online Source

(6) Food and Drug Administration Amendments Act of 2007. Public Law 110-95. 2007.
Ref Type: Bill/Resolution

(7) ClinicalTrials.gov. ClinicalTrials.gov "Basic Results" Data Element Definitions. http://prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEvents . 2012. Accessed: 6-26-2012.
Ref Type: Online Source

(8) Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans. Final rule. *Fed Regist* 2010; 75:59935-59963.

(9) Sherman RB, Woodcock J, Norden J, et al. New FDA regulation to improve safety reporting in clinical trials. *N Engl J Med* 2011; 365:3-5.

(10) Lauer MS, Blackstone EH, Young JB, et al. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999; 34:618-620.

(11) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 152:726-732.

(12) Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141:781-788.

(13) Mansi BA, Clark J, David FS, et al. Ten recommendations for closing the credibility gap in reporting industry-sponsored clinical research: a joint journal and pharmaceutical industry perspective. *Mayo Clin Proc* 2012; 87:424-429.

(14) Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012; 344:d7373.

(15) Ross JS, Tse T, Zarin DA, et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012; 344:d7292.

(16) Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. *N Engl J Med* 2005; 352:1131-1132.

(17) Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170:1191-1201.

Dr. Trish Groves
Editor in Chief
British Medical Journal Open

Mr. Richard Sands
Managing Editor
British Medical Journal Open

October 16, 2012

Dear Dr. Groves and Mr. Sands,

Please see attached our revised manuscript titled: Haphazard Reporting of Deaths in Clinical Trials – a Review of ClinicalTrials.gov Records and corresponding Publications.
We hope you will now find it satisfactory for publication.

We took into consideration all reviewer comments and made a number of edits. The most substantive edits are: 1) We addressed all reviewer comments that requested clarification, in particular to better explain our methods and definitions. 2) In the introduction, we provided more detail on the complex reporting requirements for deaths and serious adverse events from the FDA, ClinicalTrials.gov, and CONSORT statements. 3) In the appendix, we added an example of a ClinicalTrial.gov record where we were not able to determine the total number of deaths per arm. 4) We shortened the article summary. We attach two versions of the article, one with changes tracked and one with edits accepted. Please see our responses to the reviewer comments below.

As previously stated, this work is an empirical methods project, **thus no particular reporting standard or research checklist applies.** Also, we made the PMID and CT.gov identifiers for the pairs with discrepant findings available for the reviewers but **would prefer not to include them in a publication as we wish to highlight a generic problem rather than one related to specific trials.**

Sincerely,

Katrin Uhlig MD MS
Tufts Evidence-based Practice Center
Tufts Medical Center
800 Washington Street, #391
Boston, MA 02111
Email: kuhlig@tuftsmedicalcenter.org

Reviewer(s)' Comments to Author:

Reviewer: Andrew Prayle, Clinical Research Fellow, University of Nottingham.

Competing interests - I have previously published with data from ClinicalTrials.gov.

This study highlights shortcoming on reporting of trial mortality results as shown through discrepancies between the number of deaths reported on the ClinicalTrials.gov website compared to the peer reviewed manuscript. This is an important aspect of clinical trials reporting – one would think it would be possible to report things as simple to define as mortality consistency across data sources about a trial.
The methods used appear appropriate. However, it isn't fully clear to me why the authors did not also search for a publication themselves when one wasn't given on ClinicalTrials.gov. Our group has found that the 'publications' section of the ClinicalTrials.gov record frequently does not give citation details when in fact a paper has been published. This could possibly have increased the sample size, and made the findings more robust.

Response: We asked the ClinicalTrials.gov team to run a search for us using the available information. Also our intention was not to provide estimates of uncertainty. Rather to demonstrate a disconnect between reporting expectations and real-life practices.

Having read and re-read the methods section regarding how the authors determining the total death count, I am still not sure exactly how some records came to have a total death count assigned and some not. Perhaps an example could be given in the appendix of a record where the total death count could not be determined?

Response: Please see new Appendix 3.

Overall, the number of trials in the main analysis (54) is low. Have the authors done everything they can to maximise the number of included trials? I think that as the authors have essentially taken a sample from a population of larger studies, some estimate of certainty should be used in the statistics, such as 95% confidence intervals.

Response: Our study highlights the issues resulting from lack of unequivocal reporting guidelines for reporting of deaths in clinical trial reports. We started out with 500 records but had attrition of records due to the lack of clarity in reporting leaving a smaller number of records eligible for detailed analysis. We, therefore, did not want to provide estimates of certainty for the frequency of the problem. Yet, the discrepant findings even in these small samples demonstrate a clear disconnect between reporting expectations and reporting practices.

Something odd has happened in the denominator of Table 2, Case 6, Arm 1, Publication column – it drops from 2563 to 1262 – is this a typographical error?

Response: We have corrected this error. Thank you.

Are the authors planning to put the dataset into a public repository?

Response: We will leave this to the discretion of the editor considering the pros and cons of an online appendix identifying records by their NCT numbers.

I think that this paper raises an important issue with the reporting of trials. However, the main limitations are the sample size (which may not be able to be increased further), and difficulty in deciding how the authors had decided when they could not determine a total death count.

Reviewer: Peter C Gøtzsche
The Nordic Cochrane Centre
No competing interests

I think there is something interesting in this paper that we can learn from, but it needs to be written much better and in a way that allows us to understand whether the problems are major or minor without consulting the tables. It is really difficult to follow the flow of information in this paper, and the language is also difficult and sometimes inappropriate. I feel the senior author should have contributed more, as he is capable of writing far better than in this manuscript.

Abstract

Line 17: please write "whether" counts may be discordant (not "how" as you don't know whether you will find any and therefore cannot say how).

Response: We have revised the Abstract accordingly.

I have not seen the term "death counts" before and it feels pretty odd, like the US Republications' false allegations of government "death panels", please consider using another term, e.g. number of deaths, which is how we describe this.

Response: Thank you. We have changed "death counts" to "number of deaths" or "death numbers" throughout.

Please describe how many pairs you sampled right from the start.

Response: We have made the suggested edits to the Results section of the Abstract.

I do not understand how there can be pairs in the database, as a pair comes from an entry in the database and a published report, furthermore, if there was no information on deaths, how can then the information be discordant, particularly since some publications reported absence of death just as in the registry. This is too confusingly written.

Response: We specified that 'without information on deaths' means "without any information on number of deaths", i.e. death or mortality were not mentioned in the CT.gov trial record. There was discordance when the publication mentioned that there were no deaths (number of deaths = 0), or that there was some death(s). We included a definition of discordance in the methods. See additional line in the last paragraph on page 9.

Under Conclusion we hear about death count per arm, which was not what we heard about in Results, there must be consistency.

Response: Thank you but we have mentioned "total deaths per arm" in the Results section.

P4, line 8: "the discrepant reporting expectations for death," confusing construct, please revise.

Response: Please see the revisions to the Article focus.

Line 14: we now hear about all cause death, which is commonly called all cause mortality, have not heard about this before, only death counts. You need to be consistent.

Response: we have revised to simply "deaths".

Line 27-34: not clear, use much simpler language so that we can follow your thinking.

Response: Please see revisions to this first bullet.

Line 52: I cannot recall you have defined what you mean by reporting expectations?

Response: The reporting expectations are those by the FDA, ClinicalTrials.gov, and CONSORT.

There is far too much in the Article Summary, page 4, and it continues on p 5, please abbreviate considerably. The first limitation on p 5 is not really a limitation, and not relevant for the Summary; it can be mentioned in the Discussion.

Response: We deleted the first limitation on page 5.

Several places: I do not like calling people or participants for subjects or individuals, seems a bit denigrating to me.

Response: We revised accordingly.

P6 line 14: the idea of explicitly stating even if no deaths occurred is a good one although it may seem over the top in many cases, e.g. in a small migraine trial. But we so often wonder whether no deaths occurred when nothing is mentioned about this that I believe it would be better if all papers involving patients needed to say that no one died if that is the case.

Response: Thank you. We agree.

Line 21: I am highly surprised that there are no regulations mandating the reporting of all deaths in a trial, I would have expected there were, at least for drug trials. Are you absolutely sure about this? In your text below you say that death is a serious adverse event and that it therefore must always be reported in drug trials. This appears inconsistent.

P7: again, I seriously doubt that if a drug company does not consider a death related to their drug they are not required to report all deaths to FDA.

Response (to the 2 comments above): We appreciate your query. We contacted the FDA and obtained additional information on regulations which we have now incorporated into the third paragraph of the introduction.

P7: I was really amused to read that "deaths from serious adverse events would presumably be a reason for not completing a trial." I am pretty sure that dead patients cannot complete a trial! I am not really sure what the idea is that is described in lines 32-34, does it matter that deaths are only reported in the serious adverse events section, and not as a reason for discontinuation?

Response: A death is not always a reason for non-completion, (e.g. when death is an outcome, or in survival analyses where deaths may be censored). Regardless, we believe a death should at minimum be accounted for in the participant flow, if not also in results or adverse events.

P1, line 36: what is "a result for death in another metric?" Metric has to do with measuring, e.g. kg, and a death is a death so I think your use of terms is not optimal.

Response: See additional examples in the second paragraph of the Results.

Line 58: I have forgotten whether the 27 pairs where randomly selected from all the pairs, I therefore went back to the top of P9 where I could see that you selected 75 matching publications of which 27 corresponded to database records of reported deaths. At this point, it is not exactly clear to me how the study was done. It may be my fault, but I am usually able to understand what I read and I am now a bit confused about the methods.

Response: Please see revisions to the third paragraph of the Methods.

P11, lines 10-20: I wonder why concordance could not be assessed in 12 of the 27 pairs when they were carefully selected in order to have number of deaths per arm for both trial database and publication.

Response: The 27 records were selected because they contained some number for deaths in at least one data module. However, in 12 pairs we could not compare the counts, because either the record or the publication did not allow unambiguous determination of the total number of deaths per arm.

I also miss some information about what was different, e.g. was it one or two deaths out of many or what?

Response: Please see table 2.

Lines 25-40: I would not call it discordant when the database does not say anything about deaths and the publication says that were no deaths.

Response: We chose to count this as discordant given the difference in certainty about death counts between absence of any information and confirmation of number of deaths equal to zero.

P12, line 14: so, when treatment arms were missing, did you call this concordant or discordant? I suggest that you focus on the really important issues, e.g. P14, line 31 to 36, it is very serious when it is not possible to judge how many died in a trial in the two treatment arms because of ambiguity.

Response: We agree that this is an important finding. We stated this as the first sentence of the second paragraph in the discussion.

I also suggest the authors write something about that just a couple of deaths may bias the trial considerably and if it happens in several trials, we can get it very wrong.

Response: See addition to the sixth paragraph in the Discussion.

A good case in point is not about death but about the three missing cases of myocardial infarction in the infamous Vigor trial published in NEJM in 2000. These myocardial infarctions were deleted very shortly before final submission of the manuscript and it changed the result from significant harm to no significant difference. That fraud cost the lives of thousands of patients.

Response: Thank you. We cited the editorial by Dr Dazen on this case study. See ref 16.

P15, line 23: please be careful with your choice of words, "death reporting may never be complete or simple given the challenges in ascertainment and adjudication."

Response: We deleted this sentence.

I always favour total number of deaths whatever the cause, which I suggest you also write about here as we know that assessment of cause death can be biased, sometimes to a considerable degree. So do not mix up total number of deaths, which you describe somewhere in your paper and cause specific mortality.

Response: We agree. This is stated in the new sentence added to the sixth paragraph of the Discussion.

P15, line 45: you say here "In summary, our study shows lack of clarity….." Forgive me for saying this, but this is exactly the problem with your study, that the way it has been written up is not sufficiently clear (although this was not what you meant in this sentence of course).

Response: We hope it is clearer now. Thank you for your comments.

One of your references is to the paper about better reporting of harms according to CONSORT. I therefore wonder why you do not quote this paper specifically, as it says under recommendation 6 that authors should always report deaths in each study group during a trial, regardless of whether death is an endpoint and regardless of whether attributions to a specific cause is possible. I believe you should quote this.

Response: Thank you for this comment. We have included this reference in the introduction. see revision.

Table 1: Cases with number of deaths in ClinicalTrials.gov record that are discordant with the corresponding publication

Population	Was death a specified outcome?[1], Define	Reporting module or location	ClinicalTrials.gov record Deaths/Randomized		Publication Deaths/Randomized	
			Arm 1	Arm 2	Arm 1	Arm 2
Case 1						
Lung cancer	Yes Survival is a secondary outcome		Follow up: While on study drug + 30 d after last dose (estimated 4 mo)		Follow up: From random assignment until first day of progression or until death	
		Flow	/52	-/51	4/52	2/51
		Outcome	-/52	-/51	--	--
		SAE	1/52	0/51	1/52	2/51
		Total	>1/52	>0/51	>4/52	>2/51
Summary	Both CT.gov record and the publication reported hazards ratios for survival and mean survival in months, but not the number of deaths for the outcome. Both reported deaths under serious adverse events, but counts differed between record and report. In addition the publication reported deaths in the flow diagram, while the record did not. The total number of deaths is discrepant between record and publication; however, neither it likely to represent the total number of deaths that occurred during the study.					
Case 2						
Multiple myeloma	No		Follow up: Up to 18 mo		Follow up: Enrolled 2/06-12/06, analysis through 8/2007	
		Flow	1/53	1/43	1/53	1/43
		Outcome	-/53	-/41	--	--
		SAE	-/53	-/42	4/53	1/42
		Total	1/53	1/43	4/53	1/43
Summary	Both CT.gov record and publication reported 1 death per arm in the participant flow. The total number of deaths is discrepant between record and publication, however, since the publication also reported 5 deaths under SAE.					
Case 3						
Refractory prostate cancer	Yes Survival is the primary outcome		Follow up: Analyzed through 9/2009		Follow up: Analyzed through 9/2009	
		Flow	-/377	-/378	-/377	-/378
		Outcome	-/377	-/378	279/377	234/378
		SAE	0/371 sudden death	1/371 sudden death	275/371	227/371
		Total	>0/377	>1/371	279/377	234/378
Summary	The CT.gov record reported hazards ratios for survival as well as survival in months, but not the total number of deaths per arm for this outcome. The publication reported a large number of deaths per arms for the outcome of survival (as) and also a large number of deaths under SAE. The numerators and denominators differed slightly based on intention to treat analyses or per protocol analyses. The CT.gov record reported only one death under SAE; although based on the survival analysis, it appeared likely that the total number of deaths in the study was higher. The total number of deaths is discrepant between record and report.					
Case 4						
Chronic Obstructive	Yes Death is a secondary		Follow up: 52 wk		Follow up: 52 wk	
		Flow	-/772	-/796	-/772	-/796
		Outcome	-/25	-/25	25/772	25/796

[1] In the ClinicalTrials.gov record

Pulmonary Disease	outcome	SAE	1/778 sudden death; 0/778 death	3/790 sudden death; 2/790 death	-/778	-/790
		Total	25/772	25/796	25/772	25/796
Summary	The CT.gov record reported 25 per arm as number analyzed in the outcome module and defined the number analyzed as the number died. Further, the CT.gov record reports deaths under SAE using two different death definitions ('sudden death' and 'death'), while the publication does not report any. Assuming that the deaths reported under SAE in the record are included in those reported for the outcome of death, the total number of deaths is consistent across record and publication. The publication describes 2 trials of similar design with two separate NCT number, but only the results corresponding to the trial in the index CT.gov record were compared.					
Case 5						
Prostate cancer	Yes Death is a secondary outcome		Follow up: From start of therapy up to 30 d after last dose		Follow up: Duration of therapy + 30 d	
		Flow	-/48	-/47	--	-/47
		Outcome	2/48	2/47	--	-/47
		SAE	-/95		--	2/47
		Total	2/48	2/47	--	2/47
Summary	The CT.gov record reported results for 2 arms. The publication presents only results for Arm 2. The CT.gov report shows 2 deaths in the outcome module, but none under SAE. The publication shows 2 deaths under SAE. The number of deaths reported for this arm was consistent between record and publication.					

Data collection in ClinicalTrials.gov on Feb 14 2012

Abbreviations: CT.gov, ClinicalTrials.gov; D/C, discontinuation; NCT, National Clinical Trial (number); SAE, serious adverse events; -- (dash), not reported;

Table 2. Cases without any information on death numbers in ClinicalTrials.gov record but reports of number of deaths in the corresponding publication

Population	Was death a specified outcome?, Define	Reporting module or location	ClinicalTrials.gov record Deaths/Randomized				Publication Deaths/Randomized	
			Arm 1			Arm 2	Arm 1	Arm 2
Case 6								
Influenza vaccine in elderly	No		Follow up: 6 mo				Follow up: 6 mo	
		Flow	-/857	-/848	-/870	-/1262	-/2575	-/1262
		Outcome	--	--	--	--	--	--
		SAE	-/855	-/848	-/870	-/1260	16/2573	7/1260
		Total	-/2575				-/2575	7/1262
Summary	The CT.gov record did not report deaths counts across 4 arms. The publication described 23 deaths under SAE for 2 arms, collapsing arms 1-3 into one.							
Case 7								
Amyotrophic lateral sclerosis	No		Follow up: 9 mo				Follow up: 10 mo	
		Flow	-/75			-/75	3/75	5/75
		Outcome	-/75			-/75	--	--
		SAE	-/75			-/75	3/75	5/75
		Total	-/75			-/75	3/75	5/75
Summary	The CT.gov record did not report death counts. The publication describes 8 deaths under participant flow as well as under SAE, which are presumably the same.							
Case 8								
Diabetes Mellitus Type 2	No		Follow up: 26 wk				Follow up: 26 wk	
		Flow	-/239			-/241	-/239	-/241
		Outcome	--			--	--	--
		SAE	-/231			-/238	0/231	1/238
		Total	-/239			-/241	0/239	1/241
Summary	The CT.gov record did not report death counts. The publication describes one death under SAE as a 'treatment emergent death'. It also reported 2 deaths during the run-in period that were not included in the participant flow.							
Case 9								
Metastic penile cancer	No (in record); Y (in publication) Overall survival was a reported outcome, unclear whether primary or secondary		Follow up: 'Timeframe 9 y and 6 mo'				Follow up: Duration of enrollment 4/2000 through 9/2008 (max FU up to 7 y 5 mo)	
		Flow	-/30				-/30	
		Outcome	-/30				20/30	
		SAE	-/30				--	
		Total	-/30				20/30	
Summary	The CT.gov record did not include death counts even though "overall survival" was a pre-specified outcome. The publication reported 20 deaths for this outcome.							

Data collection in ClinicalTrials.gov on Feb 14 2012

Abbreviations: CT.gov, ClinicalTrials.gov; D/C, discontinuation; NCT, National Clinical Trial (number); SAE, serious adverse events; – (dash), not reported;

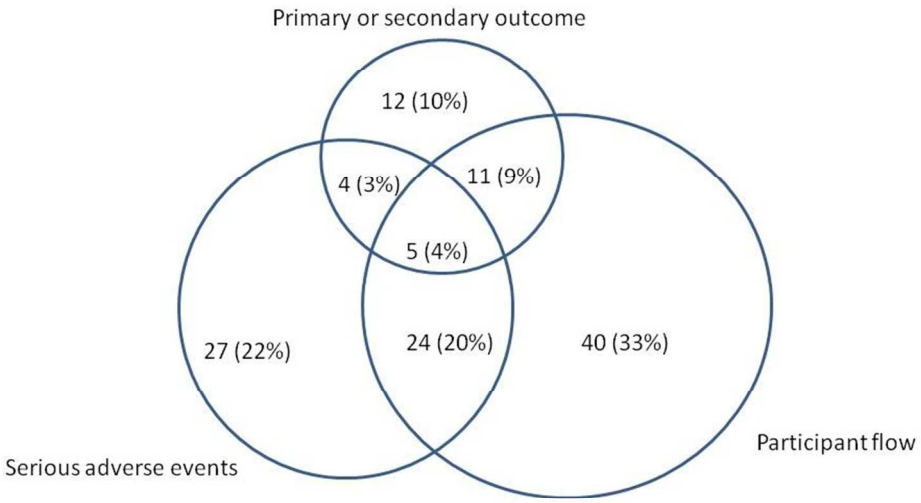


Figure 1. Reporting of death counts by data module in 123 ClinicalTrials.gov records
254x190mm (96 x 96 DPI)

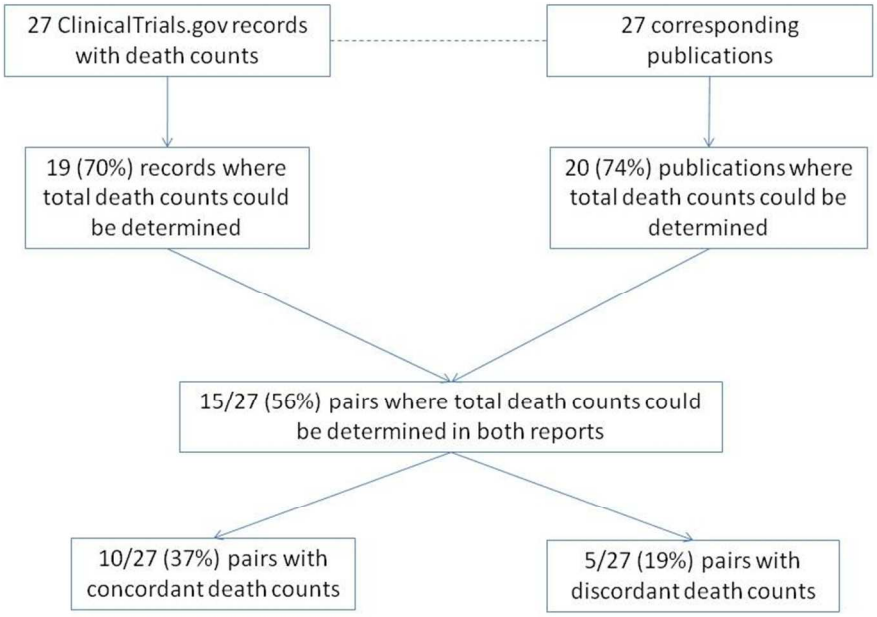
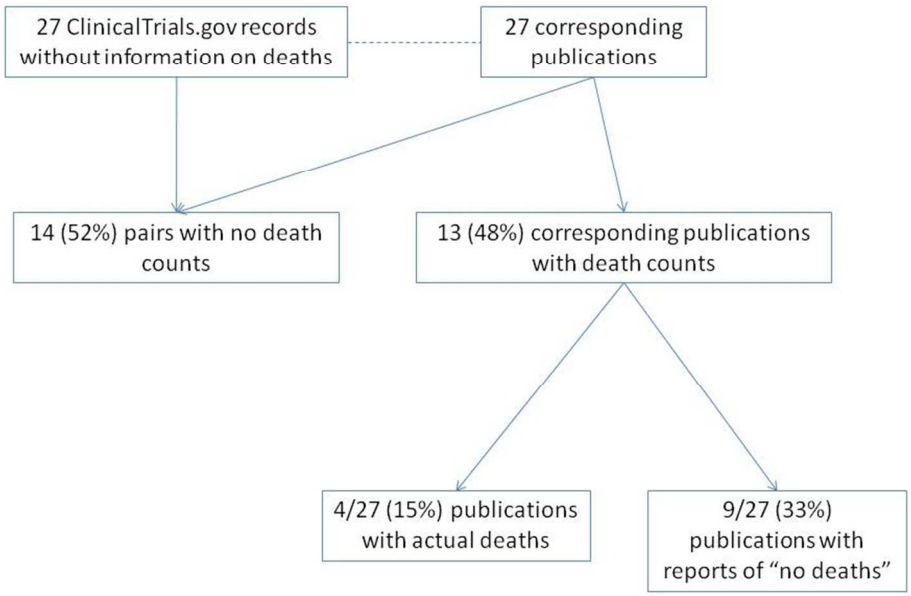
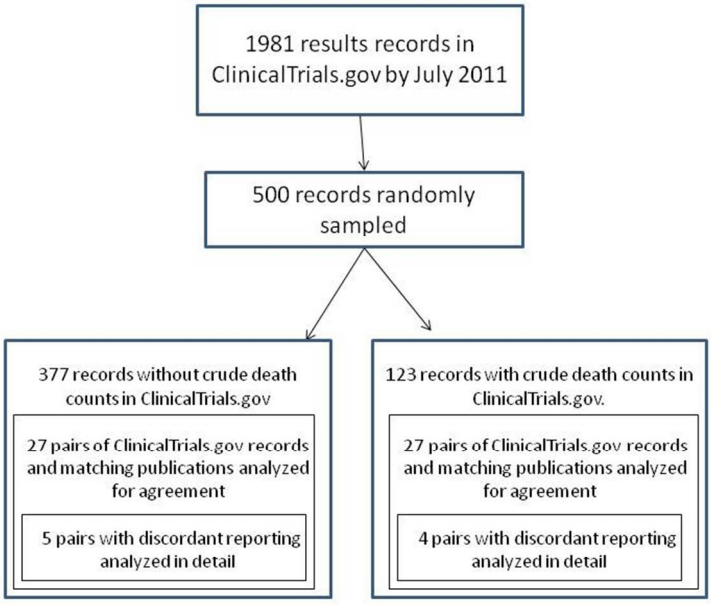


Figure 2. Consistency of death in matched pairs in (A) those with death counts in ClinicalTrials.gov and (B) those without information on death in ClinicalTrials.gov
254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)

Appendix 2. Examples death counts reported in modules in ClinicalTrials.gov records

Primary of secondary outcome

Measured Values

	Evaluable Patients
Number of Participants Analyzed [units: participants]	15
Number of Participants (Patients) Who Died Due to Transplant. [units: Participants]	4

No statistical analysis provided for Number of Participants (Patients) Who Died Due to Transplar

Serious Adverse Events

Serious Adverse Events

	Home Monitoring	Conventional
Total, serious adverse events		
# participants affected / at risk	124/977 (12.69%)	74/473 (15.64%)
Cardiac disorders		
Cardiac related hospitalizations †		
# participants affected / at risk	45/977 (4.61%)	31/473 (6.55%)
# events	64	35
General disorders		
Death †		
# participants affected / at risk	52/977 (5.32%)	26/473 (5.50%)
# events	52	26
Non-cardiac related hospitalizations †		
# participants affected / at risk	16/977 (1.64%)	3/473 (0.63%)
# events	20	4

Participant Flow

Participant Flow: Overall Study

	Docetaxel + Sunitinib	Docetaxel
STARTED	296	297
Treated	295	293
COMPLETED	0	0
NOT COMPLETED	296	297
Study Ongoing	19	31
Protocol Violation	1	1
Lost to Follow-up	2	5
Death	10	4
Objective Progression or Relapse	227	206
Participant refused	3	7
Unspecified	34	43

Appendix 3. Example of a ClinicalTrials.gov record with an indeterminate total number of deaths

Module A

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
Between June 1997 and June 1999, 1491 women from 20 countries were enrolled in the study. The last patient last visit occurred in January 2010.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
Eleven women (1 who had been randomly assigned to receive TAC and 10 assigned to receive FAC) did not receive any treatment for the following reasons: 8 withdrew consent, 1 was lost to follow-up, and 2 did not receive treatment for other reasons. In total 1480 patients (744 in the TAC group and 736 in the FAC group) were treated.

Reporting Groups

	Description
TAC (Docetaxel)	docetaxel in combination with doxorubicin and cyclophosphamide
FAC (5-fluorouracil)	5-fluorouracil in combination with doxorubicin and cyclophosphamide

Participant Flow: Overall Study

	TAC (Docetaxel)	FAC (5-fluorouracil)
STARTED	745	746
COMPLETED	679	711
NOT COMPLETED	66	35
Adverse Event	45	8
Death	2	2
Lost to Follow-up	0	1
Consent Withdrawn	17	17
Breast Cancer Relapse	1	4
Violation of Inclusion Criteria	1	3

Module B

2. Secondary: Number of Participants With Overall Survival Events [Time Frame: up to 10 year follow-up]

Hide Outcome Measure 2

Measure Type	Secondary
Measure Title	Number of Participants With Overall Survival Events
Measure Description	Overall Survival - time from the date of randomization up to the date of death of any cause.
Time Frame	up to 10 year follow-up
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
TAC (Docetaxel)	docetaxel in combination with doxorubicin and cyclophosphamide
FAC (5-fluorouracil)	5-fluorouracil in combination with doxorubicin and cyclophosphamide

Measured Values

	TAC (Docetaxel)	FAC (5-fluorouracil)
Number of Participants Analyzed [units: participants]	745	746
Number of Participants With Overall Survival Events [units: Participants]	188	241

Table 1: Cases with number of death ~~count~~s in ClinicalTrials.gov record that are ~~discrepant~~ discordant with the corresponding publication

Population	Was death a specified outcome?[1], Define	Reporting module or location	ClinicalTrials.gov record Deaths/Randomized		Publication Deaths/Randomized	
			Arm 1	Arm 2	Arm 1	Arm 2
Case 1						
Lung cancer	Yes Survival is a secondary outcome		Follow up: While on study drug + 30 d after last dose (estimated 4 mo)		Follow up: From random assignment until first day of progression or until death	
		Flow	/52	-/51	4/52	2/51
		Outcome	-/52	-/51	--	--
		SAE	1/52	0/51	1/52	2/51
		Total	>1/52	>0/51	>4/52	>2/51
Summary	Both CT.gov record and the publication reported hazards ratios for survival and mean survival in months, but not the number of deaths for the outcome. Both reported deaths under serious adverse events, but counts differed between record and report. In addition the publication reported deaths in the flow diagram, while the record did not. The total number of deaths is discrepant between record and publication; however, neither it likely to represent the total number of deaths that occurred during the study.					
Case 2						
Multiple myeloma	No		Follow up: Up to 18 mo		Follow up: Enrolled 2/06-12/06, analysis through 8/2007	
		Flow	1/53	1/43	1/53	1/43
		Outcome	-/53	-/41	--	--
		SAE	-/53	-/42	4/53	1/42
		Total	1/53	1/43	4/53	1/43
Summary	Both CT.gov record and publication reported 1 death per arm in the participant flow. The total number of deaths is discrepant between record and publication, however, since the publication also reported 5 deaths under SAE.					
Case 3						
Refractory prostate cancer	Yes Survival is the primary outcome		Follow up: Analyzed through 9/2009		Follow up: Analyzed through 9/2009	
		Flow	-/377	-/378	-/377	-/378
		Outcome	-/377	-/378	279/377	234/378
		SAE	0/371 sudden death	1/371 sudden death	275/371	227/371
		Total	>0/377	>1/371	279/377	234/378
Summary	The CT.gov record reported hazards ratios for survival as well as survival in months, but not the total number of deaths per arm for this outcome. The publication reported a large number of deaths per arms for the outcome of survival (as) and also a large number of deaths under SAE. The numerators and denominators differed slightly based on intention to treat analyses or per protocol analyses. The CT.gov record reported only one death under SAE; although based on the survival analysis, it appeared likely that the total number of deaths in the study was higher. The total number of deaths is discrepant between record and report.					
Case 4						
Chronic Obstructive	Yes Death is a secondary		Follow up: 52 wk		Follow up: 52 wk	
		Flow	-/772	-/796	-/772	-/796
		Outcome	-/25	-/25	25/772	25/796

[1] In the ClinicalTrials.gov record

Pulmonary Disease	outcome	SAE	1/778 sudden death; 0/778 death	3/790 sudden death; 2/790 death	-/778	-/790
		Total	25/772	25/796	25/772	25/796
Summary	The CT.gov record reported 25 per arm as number analyzed in the outcome module and defined the number analyzed as the number died. Further, the CT.gov record reports deaths under SAE using two different death definitions ('sudden death' and 'death'), while the publication does not report any. Assuming that the deaths reported under SAE in the record are included in those reported for the outcome of death, the total number of deaths is consistent across record and publication. The publication describes 2 trials of similar design with two separate NCT number, but only the results corresponding to the trial in the index CT.gov record were compared.					
Case 5						
Prostate cancer	Yes Death is a secondary outcome		Follow up: From start of therapy up to 30 d after last dose		Follow up: Duration of therapy + 30 d	
		Flow	-/48	-/47	--	-/47
		Outcome	2/48	2/47	--	-/47
		SAE	-/95		--	2/47
		Total	2/48	2/47	--	2/47
Summary	The CT.gov record reported results for 2 arms. The publication presents only results for Arm 2. The CT.gov report shows 2 deaths in the outcome module, but none under SAE. The publication shows 2 deaths under SAE. The number of deaths reported for this arm was consistent between record and publication.					

Data collection in ClinicalTrials.gov on Feb 14 2012

Abbreviations: CT.gov, ClinicalTrials.gov; D/C, discontinuation; NCT, National Clinical Trial (number); SAE, serious adverse events; -- (dash), not reported;

Table 2 Cases without any information on death numbers in ClinicalTrials.gov record but reports of number of death ~~count~~s in the corresponding publication

Population	Was death a specified outcome?, Define	Reporting module or location	ClinicalTrials.gov record Deaths/Randomized Arm 1			ClinicalTrials.gov record Deaths/Randomized Arm 2	Publication Deaths/Randomized Arm 1	Publication Deaths/Randomized Arm 2
Case 6								
Influenza vaccine in elderly	No		Follow up: 6 mo				Follow up: 6 mo	
		Flow	-/857	-/848	-/870	-/1262	-/2575	-/1262
		Outcome	--	--	--	--	--	--
		SAE	-/855	-/848	-/870	-/1260	16/2573	7/1260
		Total	-/2575				-/~~1262~~2575	7/1262
Summary	The CT.gov record did not report deaths counts across 4 arms. The publication described 23 deaths under SAE for 2 arms, collapsing arms 1-3 into one.							
Case 7								
Amyotrophic lateral sclerosis	No		Follow up: 9 mo				Follow up: 10 mo	
		Flow	-/75			-/75	3/75	5/75
		Outcome	-/75			-/75	--	--
		SAE	-/75			-/75	3/75	5/75
		Total	-/75			-/75	3/75	5/75
Summary	The CT.gov record did not report death counts. The publication describes 8 deaths under participant flow as well as under SAE, which are presumably the same.							
Case 8								
Diabetes Mellitus Type 2	No		Follow up: 26 wk				Follow up: 26 wk	
		Flow	-/239			-/241	-/239	-/241
		Outcome	--			--	--	--
		SAE	-/231			-/238	0/231	1/238
		Total	-/239			-/241	0/239	1/241
Summary	The CT.gov record did not report death counts. The publication describes one death under SAE as a 'treatment emergent death'. It also reported 2 deaths during the run-in period that were not included in the participant flow.							
Case 9								
Metastic penile cancer	No (in record); Y (in publication) Overall survival was a reported outcome, unclear whether primary or secondary		Follow up: 'Timeframe 9 y and 6 mo'				Follow up: Duration of enrollment 4/2000 through 9/2008 (max FU up to 7 y 5 mo)	
		Flow	-/30				-/30	
		Outcome	-/30				20/30	
		SAE	-/30				--	
		Total	-/30				20/30	
Summary	The CT.gov record did not include death counts even though "overall survival" was a pre-specified outcome. The publication reported 20 deaths for this outcome.							

Data collection in ClinicalTrials.gov on Feb 14 2012

Abbreviations: CT.gov, ClinicalTrials.gov; D/C, discontinuation; NCT, National Clinical Trial (number); SAE, serious adverse events; – (dash), not reported;

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: cross-sectional study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001963.R2
Article Type:	Research
Date Submitted by the Author:	04-Dec-2012
Complete List of Authors:	Earley, Amy; Tufts Medical Center, Tufts Evidence-based Practice Center Lau, Joseph; Tufts Medical Center, Tufts Evidence-based Practice Center Uhlig, Katrin; Tufts Medical Center,
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Evidence based practice
Keywords:	EPIDEMIOLOGY, PUBLIC HEALTH, STATISTICS & RESEARCH METHODS, QUALITATIVE RESEARCH

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: a cross-sectional study

Amy Earley BS research associate[1], Joseph Lau MD professor of medicine[1, 2], Katrin Uhlig MD MS associate professor of medicine[1, 2, 3]

Author affiliations:

[1] Tufts Evidence-based Practice Center, Tufts Medical Center, Boston, MA 02111, US

[2] Tufts University School of Medicine, Boston, MA 02111, US

[3] Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA 02111, US

Corresponding author:

Katrin Uhlig MD, MS

Tufts Medical Center

800 Washington Street, #391

Boston, Massachusetts, 02111, USA

Email: kuhlig@tuftsmedicalcenter.org

Word Count:
Abstract: 287
Manuscript Text: 2945

Abstract

Context: A participant death is a serious event in a clinical trial and needs to be unambiguously and publicly reported.

Objective: To examine: 1) how often and how numbers of deaths are reported in ClinicalTrials.gov records; 2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication; 3) whether counts may be discordant.

Design: Registry-based study of clinical trial results reporting

Setting: ClinicalTrials.gov results database searched in July 2011 and matched PubMed publications

Selection criteria: A random sample of ClinicalTrials.gov results records. Detailed review of records with a single corresponding publication.

Main outcome measure: ClinicalTrials.gov records reporting number of deaths under participant flow, primary or secondary outcome, or serious adverse events. Consistency in reporting of number of deaths between ClinicalTrials.gov records and corresponding publications.

Results: In 500 randomly selected ClinicalTrials.gov records, only 123 records (25%) reported a number for deaths. Reporting of deaths across data modules for participant flow, primary or secondary outcomes, and serious adverse events was variable. In a sample of 27 pairs of ClinicalTrials.gov records with number of deaths and corresponding publications, total deaths

per arm could only be determined in 56% (15/27 pairs) but were discordant in 19% (5/27). In 27 pairs of ClinicalTrials.gov records without any information on number of deaths, 48% (13/27) were discordant since the publications reported absence of deaths in 33% (9/27) and positive death numbers in 15% (4/27).

Conclusions: Deaths are variably reported in ClinicalTrials.gov records. A reliable total number of deaths per arm cannot always be determined with certainty or can be discordant with number reported in corresponding trial publications. This highlights a need for unambiguous and complete reporting of number of deaths in trial registries and publications.

Article Summary

Article focus

- We hypothesized that the lack of clear expectations for reporting all deaths in clinical trials give rise to discrepancies in number of deaths reported across reports of a trial.

Key messages

- There is a lack of clarity, consistency and agreement in reporting of deaths in clinical trials which highlights the need for unambiguous templates to standardize reporting of total number of deaths per arm in ClinicalTrials.gov records and more explicit reporting guidelines for peer reviewed publications.

Strengths and limitations of this study

- Our findings indicate a need for explicit expectations for reporting of all deaths.
- We suggest amendments to reporting formats such as: number of participants who started per arm, total number of deaths from any cause per arm and the time point of last ascertainment to prompt study investigators to sum up all deaths across participant loss, primary or secondary outcomes, and serious adverse events.
- We examined only a small number of matched cases which may not be generalisable. Nevertheless, even these small samples illustrate ambiguity within records and inconsistencies across reports of the same trial.
- We used only data available in the publicly available reports and only counted actual number of deaths and not alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible.

- We followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Introduction

The death of a clinical trial subject is a serious event that needs to be publicly disclosed. Incomplete reporting of deaths may overemphasize health benefits when benefits and harms of medical interventions are summarized.[1;2] For unambiguous reporting, all deaths have to be reported for each trial arm and the absence of deaths must be explicitly stated if none were known to have occurred.

Formal reporting expectations for public disclosure of deaths in clinical trials are complex. During a trial, the United States Food and Drug Administration (FDA) expects a sponsor of an investigational new drug to submit annual reports that include a list of subjects who died during participation in the investigation, with the cause of death for each subject[3]. This means all deaths must be reported to the FDA, regardless of cause.

Sponsors of investigational new drugs also need to promptly report to the FDA and trial investigators serious unexpected events if they are suspected adverse reactions, meaning that there is a "reasonable possibility" that the drug caused it[4;5]. Further, the FDA regulations specify that the sponsor report "an aggregate analysis of specific events observed in a clinical trial …that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group[6]" suggesting that the events may be caused by the drug.[5]

After trial completion, trial registries such as ClinicalTrials.gov provide Web-based public records of trial results of federally and privately funded trials.[7] Results reporting in ClinicalTrials.gov is mandated by the United States Food and Drug Administration (FDA) Amendments Act which requires the reporting of summary results for certain studies within 1 year of completing data collection for the prespecified primary outcome.[7-9]. These are phase II-IV interventional studies of FDA approved drugs, biological products, and devices with at last one US site ongoing after 2007[7-9] . Based on this Act, the results data bank of the ClinicalTrials.gov registry shall include "a table of anticipated and unanticipated serious adverse events grouped by organ system with number and frequency in each arms of the trial"[10]. The

ClinicalTrials.gov data element definitions define adverse events as “unfavorable changes in health …, that occur in trial participants during the clinical trial or within a specified period following the trial” and under serious adverse events include ”adverse events that result in death”[11]. This reporting of deaths as a serious adverse event is currently the only requirement for reporting of deaths in ClinicalTrials.gov and requires a judgment about the possibility of a causal association. However, causality assessment for a nonspecific event such as death may be a challenge.[12]

The peer reviewed publication of clinical trials is guided by CONSORT.[13] The main reporting CONSORT guideline does not specify a need to report all deaths; however, the extension for reporting of adverse events states that “Authors should always report deaths in each study group during a trial, regardless of whether death is an end point and regardless of whether attribution to a specific cause is possible”[14].

We hypothesized that the complex reporting expectations for death give rise to discordance in deaths documented across reports of a trial. We first examined how number of deaths from any cause was reported in ClinicalTrials.gov records. We then attempted to determine the total deaths per arm in a ClinicalTrials.gov results record and in the corresponding publication. Finally, we conducted a detailed review of cases with discrepancies in death numbers to identify possible explanations.

Methods

The ClinicalTrials.gov team provided us with a database of results records indexed in ClinicalTrials.gov (search date July 12, 2011). The database contained all records of phase II, III, or IV interventional trials with results entered between September 9, 2009 and June 14, 2011. In 500 randomly selected records, we examined the record for reporting of any number of deaths. This entailed review of three of the four scientific data modules, i.e. participant flow, primary and secondary outcomes, and serious adverse events, but not baseline characteristics. Appendix 1 shows screenshots for the three pertinent modules from a sample ClinicalTrials.gov record. We considered deaths only when a zero or a positive number for death was reported in any module, i.e. we did not derive death numbers from information on deaths reported as percentages, rates, risks, or survival curves. In the 123 records that reported some number of death, we examined in which module deaths were reported. Deaths from serious adverse events would presumably be a reason for not completing a trial and qualify to be listed as such in the participant flow module. We examined how many records reported number of deaths only in the serious adverse events module without reporting any deaths as a reason for discontinuation.

Among the 500 records, we also identified studies with an outcome measure description that implied ascertainment of death, including overall survival, time to mortality, all cause deaths, disease-specific death, composite outcomes including death and serious adverse events including deaths. In this subset, we examined how often actual numbers of deaths were reported as part of the primary or secondary outcome module when the outcome suggested that deaths were collected.

We then compared death reporting between ClinicalTrials.gov results records and corresponding publications. To select a sample of pairs, we used 2 criteria: 1) ClinicalTrials.gov records had to provide only a single PubMed Identifier (PMID) matching a publication describing trial results to avoid the need for reconciliation across several publications, and 2) publications

had to be electronically accessible through our library. Based on these two criteria, we retrieved 27 publications matching the ClinicalTrials.gov records that reported death numbers. We sampled another 27 pairs of publications and ClinicalTrials.gov records where the record did not report death numbers.

For each record or publication, we attempted to determine the total deaths per arm and the numbers randomized or analyzed per arm based on the data available in the record and publication, without contacting authors. This required assumptions when reconciling number of deaths across the three pertinent modules in the ClinicalTrials.gov record. For the publications, we searched the sections of the article corresponding to the modules. We used the following operational rules for decision-making:

- If a report did not provide any direct information on number of deaths, no counts were implied.
- If a number of deaths was reported in only one module in the ClinicalTrials.gov record or the corresponding sections in the publication, i.e., either in participant flow, primary or secondary outcome, or adverse events, this was determined to be the total number of deaths.
- Otherwise, as a default, the highest unambiguous number of deaths in one category was taken as the total number of deaths.

Appendix 3 shows an example of a record where the total number of deaths could not be determined with certainty based on these rules. When the number of deaths could be determined for both the ClinicalTrials.gov record and the corresponding publication following the rules, we compared the numbers between the record and the publication. A pair was discordant either when the total number of deaths was not the same, or when the ClinicalTrials.gov record did not include any information on death numbers, yet the publication mentioned a presence or absence of deaths. Discordant cases were reviewed in more detail. We extracted the denominators for number of deaths from information on number started, randomized, or

analyzed. We further captured information on duration of follow-up and looked for possible reasons for differences in number of deaths.

Results

Reporting of crude number of deaths in ClinicalTrials.gov results records

In July 2011, there were 1981 records with results in ClinicalTrials.gov and 500 records were randomly chosen for further analysis (Appendix Figure 1). These included 123 records (25%) which reported a number of deaths in at least one module. Deaths were variably reported across the three modules of participant flow, primary or secondary outcome, and serious adverse events (Figure 1). Sixty-four percent of the records reported death numbers only in one of the modules, 32% in two modules and 4% in all of them. Approximately one fifth (27/123) of the records reported number of deaths only in the module for the serious adverse events, i.e. there were no deaths reported in the participant flow as a reason for not completing the trial. One fifth (24/123) reported deaths in both of these modules.

Out of the 500 records, we identified 97 with a primary or secondary outcome measure definition that implied ascertainment of deaths. Of the 97, there were 32 (33%) that reported a crude number of deaths in the primary or secondary outcome module, with or without a result for death in another metric for death, such as percentage, rate, risk estimate. The 65 records that did not report crude number of deaths in the primary or secondary outcome module nonetheless still reported number of deaths under participant flow or serious adverse events.

Reporting of information on death, determination of total number of deaths per arm and congruency in matched pairs

We examined congruence of reporting of number of deaths across pairs of ClinicalTrials.gov records and corresponding trial publications. Figure 2 tabulates whether there was any information on number of deaths in a trial report, and if so, whether total number of deaths could be determined per arm following simple rules, and finally whether the total numbers per arm were concordant or discordant across pairs. We examined 27 pairs where the

ClinicalTrials.gov record contained some information on number of deaths and 27 pairs where the ClinicalTrial.gov record did not contain any information on death numbers.

Of the 27 pairs with number of deaths reported in the ClinicalTrials.gov record, there were 15 (55%) in which the total number of deaths per arm could be determined in both reports (Figure 2, panel A). The number of deaths were concordant between the ClinicalTrials.gov record and the publication in 10 pairs (37%), but discordant in five (19%). In the remaining 12 (44%), concordance could not be assessed because the total number of deaths per arm could not be determined unambiguously for the record and the publication. The five discordant pairs are shown in detail in Table 1.

In the 27 pairs where the ClinicalTrials.gov record did not contain any information on death numbers, 14 (52%) pairs were concordant regarding the absence of information on deaths, i.e. the trial publications also did not contain any death numbers (Figure 2, panel B). However 13 (48%) publications contained information on number of deaths. In 9 studies (33%), the published study affirmatively reported “no deaths” and in four studies, the published report mentioned positive number of deaths (Figure 2, Panel B). These four cases are shown in Table 2. For example in Case 9, the ClinicalTrials.gov record did not contain any information on number of deaths; but the publication reported one death under serious adverse events (Table 2).

Review of cases with discordant counts

Tables 1 and 2 show the detailed review of the cases with discordant counts. For each case, the crude number of deaths for each module or reporting location for the ClinicalTrials.gov record and the corresponding publication are shown, as well as the total number of deaths per arm that was determined following our operational rules. The summary contains comments and interpretation of the discrepancies.

In several cases, information on duration of follow-up or the time point of last assessment was not exact or varied across the reports. Comparison of number of deaths required reconciliation across reports with discordant numbers of arms (Cases 5 and 6) or discordant number of studies (Case 4). For example, in Case 5, the ClinicalTrials.gov record included two arms treated with different drug doses, while the publication reported results only for one of the arms. The number of deaths for this single arm was consistent across the ClinicalTrials.gov record and the publication. In the other cases with the same number of arms, the inference or certainty about the number of deaths within each arm differed. In addition to discordant counts, problems were lack of provision of crude death numbers even when death was an outcome of interest (Cases 1 and 3), imprecision in data entry (Case 4), reporting of deaths under serious adverse events without specification as to whether they were counted as part of the death outcome (Case 4) or the participant flow (Case 7). In most cases, the publication included a slightly higher crude number of deaths. Large discrepancies were noted in cases where the record did not report counts for an outcome that included death, while the report did (Cases 3 and 9).

Discussion

Our study highlights a failure of consistent and clear reporting of number of deaths in clinical trials. Only 25% of ClinicalTrials.gov results records provided some number of deaths, with great variation and overlap in the reporting across the three data modules for participant flow, primary or secondary outcomes, or serious adverse events. While we expected records reporting death as a serious adverse event to also list death as a reason for discontinuation from the trial in participant flow, a fifth of the records with death numbers reported deaths only under serious adverse events. Among ClinicalTrials.gov records with a definition for a primary or secondary outcome that implies ascertainment of death, only a third provided crude number of deaths in the data module for the primary or secondary outcome. This heterogeneous reporting and the uncertainty of whether deaths are reported in a redundant or exclusive manner across data modules, poses problems for reconciling deaths within a trial report.

Total number of deaths per arm could not always be determined unambiguously in the ClinicalTrials.gov results records or the corresponding publication. In the small sample where total deaths could be determined in both reports for the same trial, we identified examples where the number of deaths was discordant, highlighting lack of coherence and completeness. There were no clear patterns to explain the discrepancies. Finding a slightly higher crude number of deaths in publications than in ClinicalTrial.gov records suggests that number of deaths in the ClinicalTrials.gov records are not complete.

Our findings of haphazard reporting of deaths in clinical trials indicate a need for explicit expectations in reporting of all deaths regardless of whether they are considered to be a serious adverse event or not. We suggest that reporting formats for aggregate clinical trial results need to be amended to provide the following information: number of individuals who started per arm, number of deaths from any cause per arm and the time point of last ascertainment. This should prompt study investigators to sum up all deaths across participant flow, primary or secondary outcomes, and serious adverse events. Information on mean duration of follow-up is also

needed to allow calculation of rates. Given their prominent role supported by the legal regulations, clinical trials registries can spearhead uniform and consistent reporting of important trial outcomes, such as deaths. Similarly editors and sponsors must educate trialists to better meet the need for uniform reporting of all deaths.[13;15]

Our study has several limitations. We examined only a small number of matched cases which may not be generalisable. Nevertheless, even these small samples illustrate ambiguity within records and inconsistencies across reports of the same trial. Also, we used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous number of deaths. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications. Further, we only gave credit to number of deaths and not to alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible. Finally, we followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Our findings have to be viewed in context. Only 22% of studies report their results in ClinicalTrials.gov within one year of completion[16] and fewer than half of studies funded by the National Institutes of Health publish their results in a Medline indexed journal within 30 months of trial completion.[17] Thus, our matched pairs are drawn from a minority of trials that have been compliant with both expectations: publication of results in ClinicalTrials.gov and publication in a peer reviewed journal.

Full reporting of all deaths enables more accurate assessment of risks and benefits associated with treatments. Assessment of patient safety relies on capturing signals, even when they are non-specific.[18;19] Small differences in numbers of death may bias results and distort estimates across studies. From an ethical perspective, it is desirable that trials ascertain and

report all deaths regardless of whether they appear to be related to study conduct or intervention, are unforeseen, or non-specific. Even with a clear instructions and prompts for trials to report deaths; however, there may be remaining uncertainty depending on the rigor of ascertainment or surveillance and the selection of trial outcomes. Further, crude numbers are not the only format for reporting deaths in a trial. Time to event reporting may be more meaningful, but may introduce uncertainty about how censoring and deaths are handled. While both approaches to presenting information on deaths may be necessary and complementary, our study suggests that some improvement could be made with simple means of standardized reporting formats.

In summary, our study shows lack of clarity, consistency and agreement in reporting of deaths in clinical trials. This highlights the need for unambiguous templates to standardize reporting of total number of deaths per arm in ClinicalTrials.gov records and more stringent reporting guidelines for peer reviewed publications.

Data Sharing Statement: There is no additional available.

Contributors: Concept and design: AE, JL, KU; Interpretation of data: AE, JL, KU; Drafting article: AE, KU; Revision of article for important intellectual content: AE, JL, KU

Funding:

This project was funded under Contract No. HHSA 290 2007-10055-I, entitled “Evidence-based Protocol for Reviewing ClinicalTrials.gov Results Database,” from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there are no conflicts of interest.

Tables

Figures

Appendices

Legend: In Module A, the participant flow shows 2 deaths per arm indicating a total of 4 deaths as a reason for non-completion of the trial. In Module B, results are reported for a secondary outcome entitled “Number of Participants With Overall Survival Events”. The Measure Description suggests a survival analysis while the Measure Title and units show actual numbers. Since 188 of 745 participants in the TAC arm and 241 of 746 participants in the FAC arm were counted as alive in the survival analysis, 1062 individuals among 1491 participants were censored (557 vs. 505 per arm respectively). The data module for adverse events (not shown) did not provide additional information on death. Since this is a study of metastatic breast cancer, we assumed that the total number of deaths was greater than 4 as shown in the participant flow, but the actual number could not be determined with certainty.

Reference List

(1) Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005; 142(12 Pt 2):1090-1099.

(2) Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001; 285(4):437-443.

(3) Food and Drug Administration. Code of Federal Regulations Title 21. 21 CFR 312.33(b)(3) - Annual Reports. 2012.
Ref Type: Bill/Resolution

(4) Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans. Final rule. *Fed Regist* 2010; 75(188):59935-59963.

(5) Sherman RB, Woodcock J, Norden J, Grandinetti C, Temple RJ. New FDA regulation to improve safety reporting in clinical trials. *N Engl J Med* 2011; 365(1):3-5.

(6) Food and Drug Administration. Code of Federal Regulations Title 21. 21 CFR 312.32(c)(1)(i)(C)-IND safety reporting. 2012.
Ref Type: Bill/Resolution

(7) Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med* 2011; 364(9):852-860.

(8) Food and Drug Administration Amendments Act. U.S. Public Law 110-85. 2012.
Ref Type: Bill/Resolution

(9) Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. *Chest* 2009; 136(1):295-303.

(10) Food and Drug Administration Amendments Act. U.S. Public Law 110-95. 2007.
Ref Type: Bill/Resolution

(11) ClinicalTrials.gov. ClinicalTrials.gov "Basic Results" Data Element Definitions. http://prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEvents . 2012. 6-26-2012.
Ref Type: Online Source

(12) Cato A. Premarketing adverse drug experiences: data management procedures. Unexpected death occurring early in clinical trials. *Drug Inf J* 1987; 21(1):3-7.

(13) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 152(11):726-732.

(14) Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

(15) Mansi BA, Clark J, David FS, Gesell TM, Glasser S, Gonzalez J et al. Ten recommendations for closing the credibility gap in reporting industry-sponsored clinical

research: a joint journal and pharmaceutical industry perspective. *Mayo Clin Proc* 2012; 87(5):424-429.

(16) Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012; 344:d7373.

(17) Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012; 344:d7292.

(18) Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. *N Engl J Med* 2005; 352(11):1131-1132.

(19) Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170(14):1191-1201.

Haphazard Reporting of Deaths in Clinical Trials – a Review of Cases of ClinicalTrials.gov Records and Matched Publications: a cross-sectional study

Amy Earley BS research associate[1], Joseph Lau MD professor of medicine[1, 2], Katrin Uhlig MD MS associate professor of medicine[1, 2, 3]

Author affiliations:

[1] Tufts Evidence-based Practice Center, Tufts Medical Center, Boston, MA 02111, US

[2] Tufts University School of Medicine, Boston, MA 02111, US

[3] Division of Nephrology, Department of Medicine, Tufts Medical Center, Boston, MA 02111, US

Corresponding author:

Katrin Uhlig MD, MS

Tufts Medical Center

800 Washington Street, #391

Boston, Massachusetts, 02111, USA

Email: kuhlig@tuftsmedicalcenter.org

Word Count:
Abstract: 287
Manuscript Text: ~~29172~~2945

Abstract

Context: A participant death is a serious event in a clinical trial and needs to be unambiguously and publicly reported.

Objective: To examine: 1) how often and how numbers of deaths are reported in ClinicalTrials.gov records; 2) how often total deaths can be determined per arm within a ClinicalTrials.gov results record and its corresponding publication; 3) whether counts may be discordant.

Design: Registry-based study of clinical trial results reporting

Setting: ClinicalTrials.gov results database searched in July 2011 and matched PubMed publications

Selection criteria: A random sample of ClinicalTrials.gov results records. Detailed review of records with a single corresponding publication.

Main outcome measure: ClinicalTrials.gov records reporting number of deaths under participant flow, primary or secondary outcome, or serious adverse events. Consistency in reporting of number of deaths between ClinicalTrials.gov records and corresponding publications.

Results: In 500 randomly selected ClinicalTrials.gov records, only 123 records (25%) reported a number for deaths. Reporting of deaths across data modules for participant flow, primary or secondary outcomes, and serious adverse events was variable. In a sample of 27 pairs of ClinicalTrials.gov records with number of deaths and corresponding publications, total deaths

per arm could only be determined in 56% (15/27 pairs) but were discordant in 19% (5/27). In 27 pairs of ClinicalTrials.gov records without any information on number of deaths, 48% (13/27) were discordant since the publications reported absence of deaths in 33% (9/27) and positive death numbers in 15% (4/27).

Conclusions: Deaths are variably reported in ClinicalTrials.gov records. A reliable total number of deaths per arm cannot always be determined with certainty or can be discordant with number reported in corresponding trial publications. This highlights a need for unambiguous and complete reporting of number of deaths in trial registries and publications.

Article Summary

Article focus

- We hypothesized that the lack of clear expectations for reporting all deaths in clinical trials give rise to discrepancies in number of deaths reported across reports of a trial.

Key messages

- There is a lack of clarity, consistency and agreement in reporting of deaths in clinical trials which highlights the need for unambiguous templates to standardize reporting of total number of deaths per arm in ClinicalTrials.gov records and more explicit reporting guidelines for peer reviewed publications.

Strengths and limitations of this study

- Our findings indicate a need for explicit expectations for reporting of all deaths.
- We suggest amendments to reporting formats such as: number of participants who started per arm, total number of deaths from any cause per arm and the time point of last ascertainment to prompt study investigators to sum up all deaths across participant loss, primary or secondary outcomes, and serious adverse events.
- We examined only a ~~limited~~ small number of matched cases which may not be generalisable. Nevertheless, even these small samples illustrate ~~demonstrate~~ ambiguity within records and inconsistencies across reports of the same trial.
- We used only data available in the publicly available reports and only counted actual number of deaths and not alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible.

- We followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Introduction

The death of a clinical trial subject is a serious event that needs to be publicly disclosed. Incomplete reporting of deaths may overemphasize health benefits when benefits and harms of medical interventions are summarized.[1;2] For unambiguous reporting, all deaths have to be reported for each trial arm and the absence of deaths must be explicitly stated if none were known to have occurred.

Formal reporting expectations for public disclosure of deaths in clinical trials are complex. During a trial, the United States Food and Drug Administration (FDA) expects a sponsor of an investigational new drug to submit annual reports that include a list of subjects who died during participation in the investigation, with the cause of death for each subject[3]. This means all deaths must be reported to the FDA, regardless of cause.

Sponsors of investigational new drugs also need to promptly report to the FDA and trial investigators serious unexpected events if they are suspected adverse reactions, meaning that there is a "reasonable possibility" that the drug caused it[4;5]. Further, the FDA regulations specify that the sponsor report "an aggregate analysis of specific events observed in a clinical trial …that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group[6]" suggesting that the events may be caused by the drug.[5]

After trial completion, trial registries such as ClinicalTrials.gov provide Web-based public records of trial results of federally and privately funded trials.[7] Results reporting in ClinicalTrials.gov is mandated by the United States Food and Drug Administration (FDA) Amendments Act which requires the reporting of summary results for certain studies within 1 year of completing data collection for the prespecified primary outcome.[7-9]. These are phase II-IV interventional studies of FDA approved drugs, biological products, and devices with at last one US site ongoing after 2007 ~~within 1 year of completing data collection for the prespecified primary outcome.~~[7-9] . Based on this Act, the results data bank of the ClinicalTrials.gov registry shall include "a table of anticipated and unanticipated serious adverse events grouped by organ

system with number and frequency in each arms of the trial"[10]. The ClinicalTrials.gov data element definitions define adverse events as "unfavorable changes in health …, that occur in trial participants during the clinical trial or within a specified period following the trial" and under serious adverse events include "adverse events that result in death"[11]. This reporting of deaths as a serious adverse event is currently the only requirement for reporting of deaths in ClinicalTrials.gov and requires a judgment about the possibility of a causal association. However, causality assessment for a nonspecific event such as death may be a challenge.[12]

The peer reviewed publication of clinical trials is guided by CONSORT.[13] The main reporting CONSORT guideline does not specify a need to report all deaths; however, the extension for reporting of adverse events states that "Authors should always report deaths in each study group during a trial, regardless of whether death is an end point and regardless of whether attribution to a specific cause is possible"[14].

We hypothesized that the complex reporting expectations for death give rise to discordance in deaths documented across reports of a trial. We first examined how number of deaths from any cause was reported in ClinicalTrials.gov records. We then attempted to determine the total deaths per arm in a ClinicalTrials.gov results record and in the corresponding publication. Finally, we conducted a detailed review of cases with discrepancies in death numbers to identify possible explanations.

Methods

The ClinicalTrials.gov team provided us with a database of results records indexed in ClinicalTrials.gov (search date July 12, 2011). The database contained all records of phase II, III, or IV interventional trials with results entered between September 9, 2009 and June 14, 2011. In 500 randomly selected records, we examined the record for reporting of any number of deaths. This entailed review of three of the four scientific data modules, i.e. participant flow, primary and secondary outcomes, and serious adverse events, but not baseline characteristics. Appendix 1 shows screenshots for the three pertinent modules from a sample ClinicalTrials.gov record. We considered deaths only when a zero or a positive number for death was reported in any module, i.e. we did not derive death numbers from information on deaths reported as percentages, rates, risks, or survival curves. In the 123 records that reported some number of death, we examined in which module deaths were reported. Deaths from serious adverse events would presumably be a reason for not completing a trial and qualify to be listed as such in the participant flow module. We examined how many records reported number of deaths only in the serious adverse events module without reporting any deaths as a reason for discontinuation.

Among the 500 records, we also identified studies with an outcome measure description that implied ascertainment of death, including overall survival, time to mortality, all cause deaths, disease-specific death, composite outcomes including death and serious adverse events including deaths. In this subset, we examined how often actual numbers of deaths were reported as part of the primary or secondary outcome module when the outcome suggested that deaths were collected.

We then compared death reporting between ClinicalTrials.gov results records and corresponding publications. To select a sample of pairs, we used 2 criteria: 1) ClinicalTrials.gov records had to provide only a single PubMed Identifier (PMID) matching a publication describing trial results to avoid the need for reconciliation across several publications, and 2) publications

had to be electronically accessible through our library. Based on these two criteria, we retrieved 27 publications matching the ClinicalTrials.gov records that reported death numbers. We sampled another 27 pairs of publications and ClinicalTrials.gov records where the record did not report death numbers.

For each record or publication, we attempted to determine the total deaths per arm and the numbers randomized or analyzed per arm based on the data available in the record and publication, without contacting authors. This required assumptions when reconciling number of deaths across the three pertinent modules in the ClinicalTrials.gov record. For the publications, we searched the sections of the article corresponding to the modules. We used the following operational rules for decision-making:

- If a report did not provide any direct information on number of deaths, no counts were implied.
- If a number of deaths was reported in only one module in the ClinicalTrials.gov record or the corresponding sections in the publication, i.e., either in participant flow, primary or secondary outcome, or adverse events, this was determined to be the total number of deaths.
- Otherwise, as a default, the highest unambiguous number of deaths in one category was taken as the total number of deaths.

Appendix 3 shows an example of a record where the total number of deaths could not be determined with certainty based on these rules. When the number of deaths could be determined for both the ClinicalTrials.gov record and the corresponding publication following the rules, we compared the numbers between the record and the publication. A pair was discordant either when the total number of deaths was not the same, or when the ClinicalTrials.gov record did not include any information on death numbers, yet the publication mentioned a presence or absence of deaths. Discordant cases were reviewed in more detail. We extracted the denominators for number of deaths from information on number started, randomized, or

analyzed. We further captured information on duration of follow-up and looked for possible reasons for differences in number of deaths.

Results

Reporting of crude number of deaths in ClinicalTrials.gov results records

In July 2011, there were 1981 records with results in ClinicalTrials.gov and 500 records were randomly chosen for further analysis (Appendix Figure 1). These included 123 records (25%) which reported a number of deaths in at least one module. Deaths were variably reported across the three modules of participant flow, primary or secondary outcome, and serious adverse events (Figure 1). Sixty-four percent of the records reported death numbers only in one of the modules, 32% in two modules and 4% in all of them. Approximately one fifth (27/123) of the records reported number of deaths only in the module for the serious adverse events, i.e. there were no deaths reported in the participant flow as a reason for not completing the trial. One fifth (24/123) reported deaths in both of these modules.

Out of the 500 records, we identified 97 with a primary or secondary outcome measure definition that implied ascertainment of deaths. Of the 97, there were 32 (33%) that reported a crude number of deaths in the primary or secondary outcome module, with or without a result for death in another metric for death, such as percentage, rate, risk estimate. The 65 records that did not report crude number of deaths in the primary or secondary outcome module nonetheless still reported number of deaths under participant flow or serious adverse events.

Reporting of information on death, determination of total number of deaths per arm and congruency in matched pairs

We examined congruence of reporting of number of deaths across pairs of ClinicalTrials.gov records and corresponding trial publications. Figure 2 tabulates whether there was any information on number of deaths in a trial report, and if so, whether total number of deaths could be determined per arm following simple rules, and finally whether the total numbers per arm were concordant or discordant across pairs. We examined 27 pairs where the

ClinicalTrials.gov record contained some information on number of deaths and 27 pairs where the ClinicalTrial.gov record did not contain any information on death numbers.

Of the 27 pairs with number of deaths reported in the ClinicalTrials.gov record, there were 15 (55%) in which the total number of deaths per arm could be determined in both reports (Figure 2, panel A). The number of deaths were concordant between the ClinicalTrials.gov record and the publication in 10 pairs (37%), but discordant in five (19%). In the remaining 12 (44%), concordance could not be assessed because the total number of deaths per arm could not be determined unambiguously for the record and the publication. The five discordant pairs are shown in detail in Table 1.

In the 27 pairs where the ClinicalTrials.gov record did not contain any information on death numbers, 14 (52%) pairs were concordant regarding the absence of information on deaths, i.e. the trial publications also did not contain any death numbers (Figure 2, panel B). However 13 (48%) publications contained information on number of deaths. In 9 studies (33%), the published study affirmatively reported “no deaths” and in four studies, the published report mentioned positive number of deaths (Figure 2, Panel B). These four cases are shown in Table 2. For example in Case 9, the ClinicalTrials.gov record did not contain any information on number of deaths; but the publication reported one death under serious adverse events (Table 2).

Review of cases with discordant counts

Tables 1 and 2 show the detailed review of the cases with discordant counts. For each case, the crude number of deaths for each module or reporting location for the ClinicalTrials.gov record and the corresponding publication are shown, as well as the total number of deaths per arm that was determined following our operational rules. The summary contains comments and interpretation of the discrepancies.

In several cases, information on duration of follow-up or the time point of last assessment was not exact or varied across the reports. Comparison of number of deaths required reconciliation across reports with discordant numbers of arms (Cases 5 and 6) or discordant number of studies (Case 4). For example, in Case 5, the ClinicalTrials.gov record included two arms treated with different drug doses, while the publication reported results only for one of the arms. The number of deaths for this single arm was consistent across the ClinicalTrials.gov record and the publication. In the other cases with the same number of arms, the inference or certainty about the number of deaths within each arm differed. In addition to discordant counts, problems were lack of provision of crude death numbers even when death was an outcome of interest (Cases 1 and 3), imprecision in data entry (Case 4), reporting of deaths under serious adverse events without specification as to whether they were counted as part of the death outcome (Case 4) or the participant flow (Case 7). In most cases, the publication included a slightly higher crude number of deaths. Large discrepancies were noted in cases where the record did not report counts for an outcome that included death, while the report did (Cases 3 and 9).

Discussion

Our study highlights a failure of consistent and clear reporting of number of deaths in clinical trials. Only 25% of ClinicalTrials.gov results records provided some number of deaths, with great variation and overlap in the reporting across the three data modules for participant flow, primary or secondary outcomes, or serious adverse events. While we expected records reporting death as a serious adverse event to also list death as a reason for discontinuation from the trial in participant flow, a fifth of the records with death numbers reported deaths only under serious adverse events. Among ClinicalTrials.gov records with a definition for a primary or secondary outcome that implies ascertainment of death, only a third provided crude number of deaths in the data module for the primary or secondary outcome. This heterogeneous reporting and the uncertainty of whether deaths are reported in a redundant or exclusive manner across data modules, poses problems for reconciling deaths within a trial report.

Total number of deaths per arm could not always be determined unambiguously in the ClinicalTrials.gov results records or the corresponding publication. In the small sample where total deaths could be determined in both reports for the same trial, we identified examples where the number of deaths was discordant, highlighting lack of coherence and completeness. There were no clear patterns to explain the discrepancies. Finding a slightly higher crude number of deaths in publications than in ClinicalTrial.gov records suggests that number of deaths in the ClinicalTrials.gov records are not complete.

Our findings of haphazard reporting of deaths in clinical trials indicate a need for explicit expectations in reporting of all deaths regardless of whether they are considered to be a serious adverse event or not. We suggest that reporting formats for aggregate clinical trial results need to be amended to provide the following information: number of individuals who started per arm, number of deaths from any cause per arm and the time point of last ascertainment. This should prompt study investigators to sum up all deaths across participant flow, primary or secondary outcomes, and serious adverse events. Information on mean duration of follow-up is also

needed to allow calculation of rates. Given their prominent role supported by the legal regulations, clinical trials registries can spearhead uniform and consistent reporting of important trial outcomes, such as deaths. Similarly editors and sponsors must educate trialists to better meet the need for uniform reporting of all deaths.[13;15]

Our study has several limitations. We examined only a ~~limited~~ small number of matched cases which may not be generalisable. Nevertheless, even these small samples ~~demonstrate~~ illustrate ambiguity within records and inconsistencies across reports of the same trial. Also, we used only data available in these reports to determine the total number of deaths per arm. It is possible that individual patient data available to the trial investigators would allow more studies to provide unambiguous number of deaths. However, this information is not publicly available and clinicians and policy makers rely on publicly accessible trial results reported in ClinicalTrials.gov records and in journal publications. Further, we only gave credit to number of deaths and not to alternate information on death, such as percents or survival analyses, as exact back calculations are not always possible. Finally, we followed operational rules to determine total deaths per arm within a report. These operational rules were not overly stringent and more rigid expectations would have resulted in fewer reports with the data amenable for detailed analysis.

Our findings have to be viewed in context. Only 22% of studies report their results in ClinicalTrials.gov within one year of completion[16] and fewer than half of studies funded by the National Institutes of Health publish their results in a Medline indexed journal within 30 months of trial completion.[17] Thus, our matched pairs are drawn from a minority of trials that have been compliant with both expectations: publication of results in ClinicalTrials.gov and publication in a peer reviewed journal.

Full reporting of all deaths enables more accurate assessment of risks and benefits associated with treatments. Assessment of patient safety relies on capturing signals, even when they are non-specific.[18;19] Small differences in numbers of death may bias results and distort

estimates across studies. From an ethical perspective, it is desirable that trials ascertain and report all deaths regardless of whether they appear to be related to study conduct or intervention, are unforeseen, or non-specific. Even with a clear instructions and prompts for trials to report deaths; however, there may be remaining uncertainty depending on the rigor of ascertainment or surveillance and the selection of trial outcomes. Further, crude numbers are not the only format for reporting deaths in a trial. Time to event reporting may be more meaningful, but may introduce uncertainty about how censoring and deaths are handled. While both approaches to presenting information on deaths may be necessary and complementary, our study suggests that some improvement could be made with simple means of standardized reporting formats.

In summary, our study shows lack of clarity, consistency and agreement in reporting of deaths in clinical trials. This highlights the need for unambiguous templates to standardize reporting of total number of deaths per arm in ClinicalTrials.gov records and more stringent reporting guidelines for peer reviewed publications.

Data Sharing Statement: There is no additional available.

Contributors: Concept and design: AE, JL, KU; Interpretation of data: AE, JL, KU; Drafting article: AE, KU; Revision of article for important intellectual content: AE, JL, KU

Funding:

This project was funded under Contract No. HHSA 290 2007-10055-I, entitled “Evidence-based Protocol for Reviewing ClinicalTrials.gov Results Database,” from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there are no conflicts of interest.

Tables

Figures

Appendices

Legend: In Module A, the participant flow shows 2 deaths per arm indicating a total of 4 deaths as a reason for non-completion of the trial. In Module B, results are reported for a secondary outcome entitled “Number of Participants With Overall Survival Events”. The Measure Description suggests a survival analysis while the Measure Title and units show actual numbers. Since 188 of 745 participants in the TAC arm and 241 of 746 participants in the FAC arm were counted as alive in the survival analysis, 1062 individuals among 1491 participants were censored (557 vs. 505 per arm respectively). The data module for adverse events (not shown) did not provide additional information on death. Since this is a study of metastatic breast cancer, we assumed that the total number of deaths was greater than 4 as shown in the participant flow, but the actual number could not be determined with certainty.

Reference List

(1) Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005; 142(12 Pt 2):1090-1099.

(2) Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001; 285(4):437-443.

(3) Food and Drug Administration. Code of Federal Regulations Title 21. 21 CFR 312.33(b)(3) - Annual Reports. 2012.
Ref Type: Bill/Resolution

(4) Investigational new drug safety reporting requirements for human drug and biological products and safety reporting requirements for bioavailability and bioequivalence studies in humans. Final rule. *Fed Regist* 2010; 75(188):59935-59963.

(5) Sherman RB, Woodcock J, Norden J, Grandinetti C, Temple RJ. New FDA regulation to improve safety reporting in clinical trials. *N Engl J Med* 2011; 365(1):3-5.

(6) Food and Drug Administration. Code of Federal Regulations Title 21. 21 CFR 312.32(c)(1)(i)(C)-IND safety reporting. 2012.
Ref Type: Bill/Resolution

(7) Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database--update and key issues. *N Engl J Med* 2011; 364(9):852-860.

(8) Food and Drug Administration Amendments Act. U.S. Public Law 110-85. 2012.
Ref Type: Bill/Resolution

(9) Tse T, Williams RJ, Zarin DA. Reporting "basic results" in ClinicalTrials.gov. *Chest* 2009; 136(1):295-303.

(10) Food and Drug Administration Amendments Act. U.S. Public Law 110-95. 2007.
Ref Type: Bill/Resolution

(11) ClinicalTrials.gov. ClinicalTrials.gov "Basic Results" Data Element Definitions. http://prsinfo.clinicaltrials.gov/results_definitions.html#AdverseEvents . 2012. 6-26-2012.
Ref Type: Online Source

(12) Cato A. Premarketing adverse drug experiences: data management procedures. Unexpected death occurring early in clinical trials. *Drug Inf J* 1987; 21(1):3-7.

(13) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; 152(11):726-732.

(14) Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

(15) Mansi BA, Clark J, David FS, Gesell TM, Glasser S, Gonzalez J et al. Ten recommendations for closing the credibility gap in reporting industry-sponsored clinical

research: a joint journal and pharmaceutical industry perspective. *Mayo Clin Proc* 2012; 87(5):424-429.

(16) Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2012; 344:d7373.

(17) Ross JS, Tse T, Zarin DA, Xu H, Zhou L, Krumholz HM. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *BMJ* 2012; 344:d7292.

(18) Drazen JM. COX-2 inhibitors--a lesson in unexpected problems. *N Engl J Med* 2005; 352(11):1131-1132.

(19) Nissen SE, Wolski K. Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. *Arch Intern Med* 2010; 170(14):1191-1201.

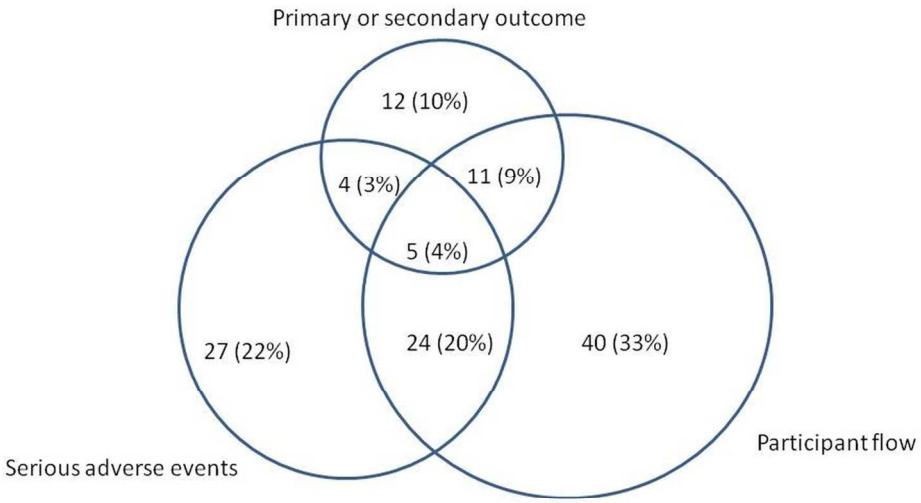


Figure 1. Reporting of death counts by data module in 123 ClinicalTrials.gov records
119x90mm (300 x 300 DPI)

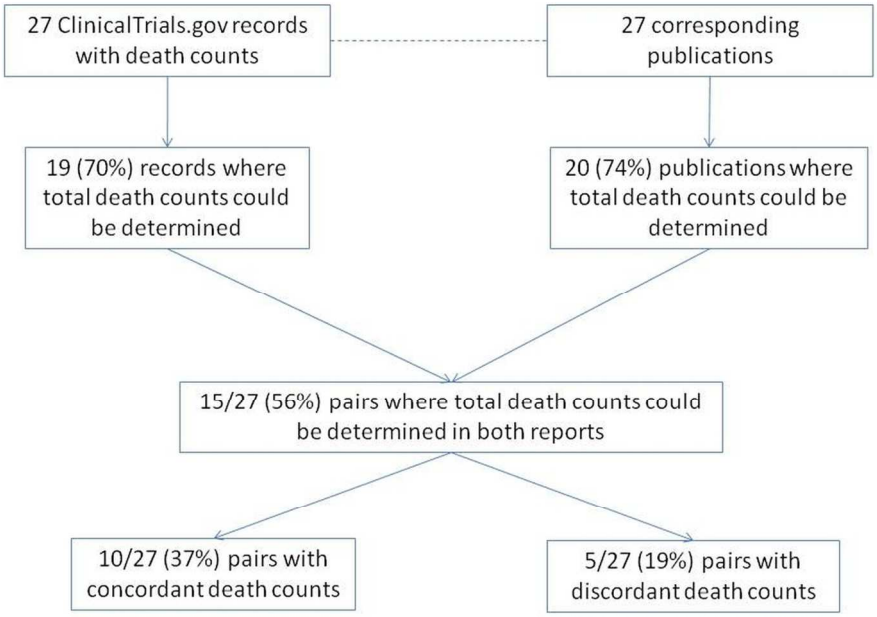
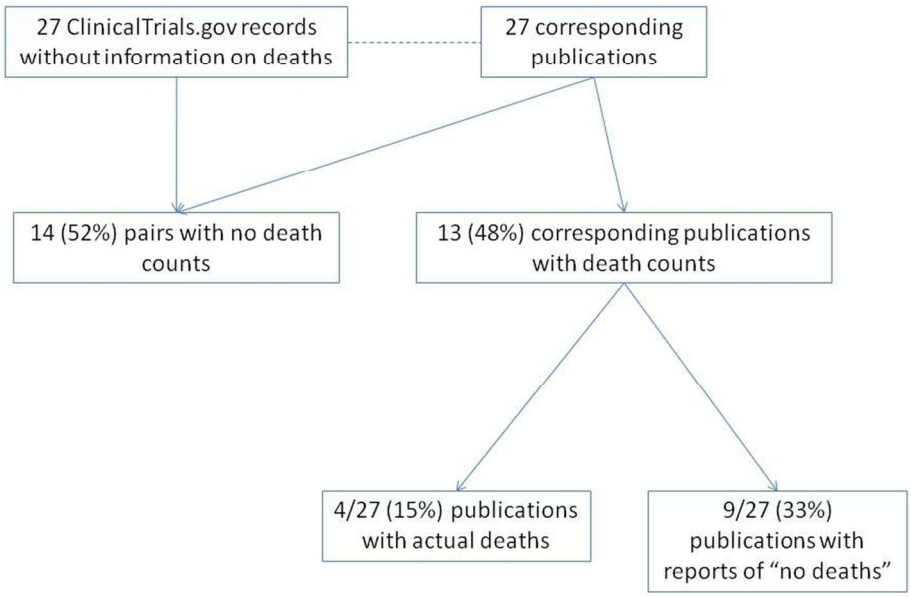
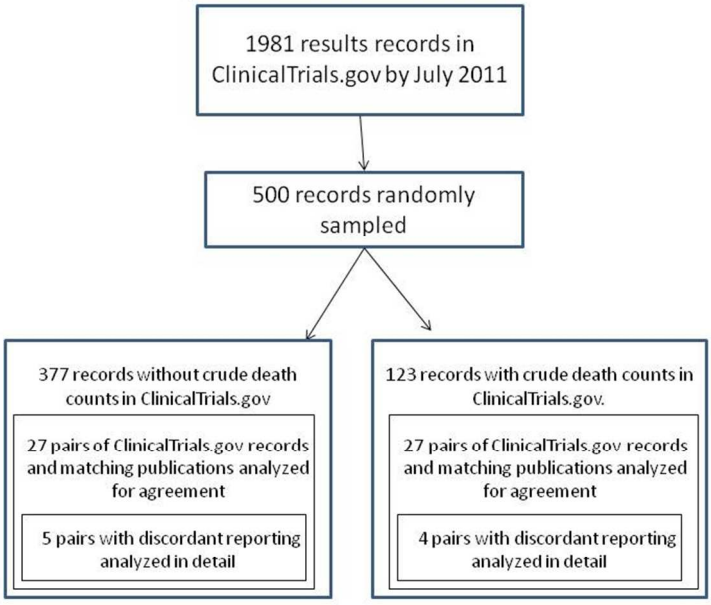


Figure 2. Consistency of death in matched pairs in (A) those with death counts in ClinicalTrials.gov and (B) those without information on death in ClinicalTrials.gov
119x90mm (300 x 300 DPI)



119x90mm (300 x 300 DPI)



254x190mm (96 x 96 DPI)

Appendix 2. Examples death counts reported in modules in ClinicalTrials.gov records

Primary of secondary outcome

Measured Values

	Evaluable Patients
Number of Participants Analyzed [units: participants]	15
Number of Participants (Patients) Who Died Due to Transplant. [units: Participants]	4

No statistical analysis provided for Number of Participants (Patients) Who Died Due to Transplar

Serious Adverse Events

Serious Adverse Events

	Home Monitoring	Conventional
Total, serious adverse events		
# participants affected / at risk	124/977 (12.69%)	74/473 (15.64%)
Cardiac disorders		
Cardiac related hospitalizations †		
# participants affected / at risk	45/977 (4.61%)	31/473 (6.55%)
# events	64	35
General disorders		
Death †		
# participants affected / at risk	52/977 (5.32%)	26/473 (5.50%)
# events	52	26
Non-cardiac related hospitalizations †		
# participants affected / at risk	16/977 (1.64%)	3/473 (0.63%)
# events	20	4

Participant Flow

Participant Flow: Overall Study

	Docetaxel + Sunitinib	Docetaxel
STARTED	296	297
Treated	295	293
COMPLETED	0	0
NOT COMPLETED	296	297
Study Ongoing	19	31
Protocol Violation	1	1
Lost to Follow-up	2	5
Death	10	4
Objective Progression or Relapse	227	206
Participant refused	3	7
Unspecified	34	43

Appendix 3. Example of a ClinicalTrials.gov record with an indeterminate total number of deaths

Module A

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
Between June 1997 and June 1999, 1491 women from 20 countries were enrolled in the study. The last patient last visit occurred in January 2010.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
Eleven women (1 who had been randomly assigned to receive TAC and 10 assigned to receive FAC) did not receive any treatment for the following reasons: 8 withdrew consent, 1 was lost to follow-up, and 2 did not receive treatment for other reasons. In total 1480 patients (744 in the TAC group and 736 in the FAC group) were treated.

Reporting Groups

	Description
TAC (Docetaxel)	docetaxel in combination with doxorubicin and cyclophosphamide
FAC (5-fluorouracil)	5-fluorouracil in combination with doxorubicin and cyclophosphamide

Participant Flow: Overall Study

	TAC (Docetaxel)	FAC (5-fluorouracil)
STARTED	745	746
COMPLETED	679	711
NOT COMPLETED	66	35
Adverse Event	45	8
Death	2	2
Lost to Follow-up	0	1
Consent Withdrawn	17	17
Breast Cancer Relapse	1	4
Violation of Inclusion Criteria	1	3

Module B

2. Secondary: Number of Participants With Overall Survival Events [Time Frame: up to 10 year follow-up]

Hide Outcome Measure 2

Measure Type	Secondary
Measure Title	Number of Participants With Overall Survival Events
Measure Description	Overall Survival - time from the date of randomization up to the date of death of any cause.
Time Frame	up to 10 year follow-up
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
TAC (Docetaxel)	docetaxel in combination with doxorubicin and cyclophosphamide
FAC (5-fluorouracil)	5-fluorouracil in combination with doxorubicin and cyclophosphamide

Measured Values

	TAC (Docetaxel)	FAC (5-fluorouracil)
Number of Participants Analyzed [units: participants]	745	746
Number of Participants With Overall Survival Events [units: Participants]	188	241