Post-Marketing Safety Surveillance Studies Requiring Access to Patients and Charts: Does Persistence Yield Results?

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Abstract

Background: Post-marketing safety surveillance studies are increasingly important and require a variety of study methods. In the case of rare outcomes and outcomes with possible long latency, traditional large databases may not be sufficient. Some studies require collection of data directly from patients. However, gaining access to patients for interview or to their medical records for abstraction is becoming increasingly more difficult in the new post-Health Insurance Portability and Accountability Act (HIPAA) era.

Objectives: Describe logistical challenges encountered in an ongoing 10-year post-marketing safety surveillance study in which patients are identified through cancer registries and possible prior exposure is ascertained by telephone interview.

Methods: We conducted descriptive analyses of site approval requirements and time to approval for a post-marketing safety surveillance study of adult osteosarcoma patients in the United States (US). To identify a cohort of at least 40% of diagnosed cases of this rare tumor each year, oncology referral centers (ORCs) with the greatest volume of adult osteosarcoma cases were targeted for recruitment. ORCs include comprehensive cancer centers and regional SEER or state central cancer registries. We describe time to final approval, time to first data delivery, number of different consent protocols and mean number of submissions for ORCs initiated for this study.

Results: Between December 2002 and December 2004, the IRB application process was initiated at 15 ORCs. As of January 2005, approvals had been granted for 7 ORCs. Of these, 5 required revision of original procedures due to data privacy concerns. Average time from first contact to final approval was 5.2 months (range of 1 to 12 months). Average time from final approval to data delivery ranged from 1 to 8 months, and data delivery is still pending for 2 ORCs. Mean number of formal submissions was 3.1, ranging from 1 to 8. Of 7 ORCs, 6 different protocols were required to obtain patient consent. Mean time to approval and number of submissions will increase once final decisions are made for 8 ORC applications still under review.

Conclusions: The route to final approval requires persistence and the ability to adapt the study procedures to meet individual site requirements due to the following: (1) institutions' lack of understanding of case-finding surveillance study methods (in contrast to clinical trials or case-control studies) and (2) privacy concerns post-HIPAA. Researchers should be aware of and plan for the increased resources and time required to launch post-marketing safety studies.

Conflict of Interest

Eli Lilly and Company and RTI Health Solutions employees contributed significantly to the design and analysis plan for this study. Data collection and analyses are being conducted by employees of RTI Health Solutions, a nonprofit research organization. The safety surveillance study is fully funded by Eli Lilly and Company.

Background

- Post-marketing safety surveillance studies are increasingly important.
- Traditional study methods and data sources may not be sufficient in the case of rare diseases and/or exposures and outcomes with possible long latency.
- Some studies require collection of data directly from patients.
- Gaining access to patients for interview or to their medical records for abstraction is becoming increasingly difficult in the post-HIPAA era.

Osteosarcoma Safety Surveillance Study

In order to monitor for the possibility of a potential signal of an association between a newly approved drug and adult osteosarcoma, a 10-year safety surveillance study was initiated.

STUDY OBJECTIVES

Primary
To identify approximately 40% of newly diagnosed cases of osteosarcoma in men and women aged 40 years and older each year, for a duration of at least 10 years.

To identify incident cases of adult osteosarcoma, if any, who have a history of treatment with a drug of interest.

Secondary
To systematically collect, for descriptive epidemiology purposes, additional patient information, including demographics, other drug treatments, relevant exposures and comorbid conditions.

STUDY PROCEDURES
The study protocol underwent extensive review and was approved by the study sponsor, RTI's research team and RTI's Institutional Review Board (IRB). Following approval of the final protocol, RTI began recruitment of the targeted ORCs. Site initiation began when the site approval process started at each site. After site approval, RTI identifies patients through the cancer registry, obtains consent and conducts telephone interviews with patient or proxy.

Objective

To describe the site recruitment challenges encountered in an ongoing 10-year post-marketing safety surveillance study in which patients are identified through cancer registries and possible prior exposure is ascertained by telephone interview in the US.

Methods

Design

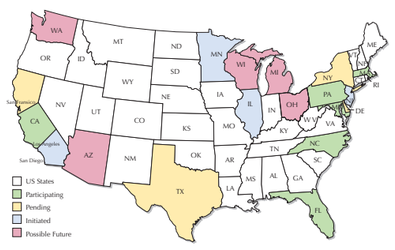
- Ad hoc descriptive analyses were conducted of site approval requirements and time to approval for this post-marketing safety surveillance study.
- To determine the time to approval and number of submissions and revisions, contact logs for each site were manually reviewed.

Setting

US oncology referral centers (ORCs) with a high number of cases of adult osteosarcoma in the US that were participating or for which approval was pending as of January 2005:

- Eight state or regional central cancer registries (population-based)
- Seven comprehensive cancer centers

Figure 1. States or Cancer Centers Targeted for Site Recruitment



Main Measures

The following were the main measures of the study:

- Mean number of IRB submissions to ORCs per site
- Number of different consent protocols
- Mean time to final approval
- Mean time to first data delivery

Results [1]

ORC Approval Status

Figure 2. Approval Status as of July 31, 2005 for 15 ORC Applications Initiated Between December 2002 and December 2004

Approval Status	Total
Approvals granted	8
Not approved by Scientific Review Committee*	2
Application withdrawn **	1
In IRB review	1
Initiated but approval still pending	3

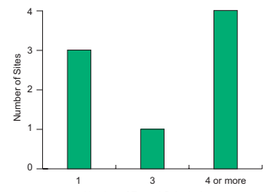
* The Scientific Review Committee had no experience with proposed case-finding surveillance design; alternate site covering same geographic area was identified and initiated in June 2005.
** Application withdrawn more than 1 year after initial submission and multiple revisions to application and protocol; alternate site covering same geographic area was initiated in December 2004.

Results [2]

Number of Submissions for Approved Sites

- Eight approved submissions
  - Three approved based on original study procedures to obtain patient information
  - Five required revision of original study procedures to address local data privacy concerns
- Mean number of formal submissions per site: 3.5
  - Range: 1–8 submissions

Figure 3. Number of IRB Submissions to Eight Approved ORCs

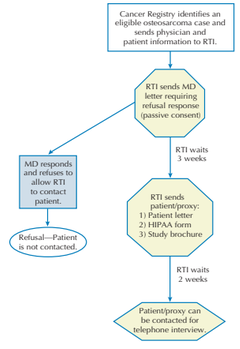


Results [3]

Number of Different Consent Protocols

- Eight participating ORCs.
- Each site required customized adaptations to three basic patient consent procedures (Passive Physician, Active Physician, Direct Patient).
- Of the eight participating ORCs, six unique procedures were required.
- Three examples of these customized procedures to obtain patient consent are shown in Figures 4 through 6.

Figure 4. Passive Physician Consent

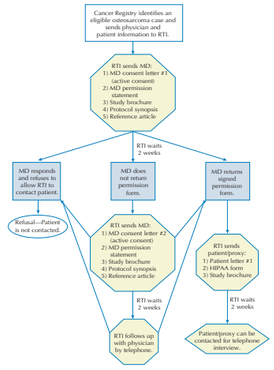


- Cancer registry sends patient and physician information to RTI
- RTI sends letter to physician
- Physician has 3 weeks to refuse contact with patient
- If no refusal from physician, RTI contacts patient (or proxy) to obtain permission to conduct interview

Results [4]

Figure 5. Active Physician Consent

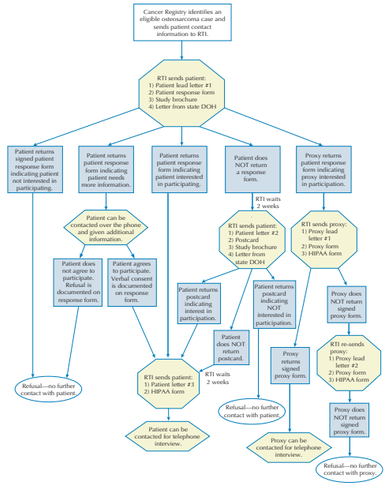
- Cancer registry sends patient and physician information to RTI
- RTI sends letter and consent form to physician
- Physician must return approval before RTI can contact patient



Results [5]

- Cancer registry sends patient information to RTI
- RTI sends letter and consent form to patient or proxy
- After patient or proxy returns consent form or after minimum of 4 weeks and 3 mailings to patient, RTI can contact patient

Figure 6. Direct Patient Consent



Results [6]

Time to Final Approval and Data Delivery

Figure 7. Time to Final Approval and Data Delivery

Task	Average Time Lapse
First IRB or registry submission to final approval*	5.2 months (range 1–2 months)
Approval to first data delivery	5 months (range < 1–9 months)

* Does not include additional lead time required prior to submission in order to recruit local site sponsor and complete application process.

Conclusions

- Final approval for multi-site surveillance studies requires persistence and the ability to adapt the study procedures to meet individual site requirements due to the following:
  - Confusion exists at IRB level surrounding HIPAA privacy considerations and possible safety studies.
  - Multiple approvals required from IRBs, scientific review committees and others—each with a unique format and content requirements.
  - Approval processes often extremely slow and complicated.
  - Local IRB membership turnover throughout approval process can lead to redundant questions and additional changes to study procedures.
- Two key challenges encountered were the following:
  - Some institutions lack an understanding of case-finding surveillance study methods (in contrast to clinical trials or case-control studies).
  - Privacy considerations exceeding HIPAA requirements led to detailed customization of the application for approval.
- Researchers should be aware of and plan for the increased resources and time required to launch post-marketing safety studies.
- For a long-term study of possible cancer risk using methods employed in this study, the lag time does not result in loss of cases because historical cases are maintained by ongoing registries. However, delays may lead to reporting bias due to increased patient mortality and proxy interviews.
- The lengthy lag time between site initiation and data collection can impede studies intended to address newly emerging safety issues requiring timely analyses.

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