Title: Prolia® Postmarketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States

Product: Prolia® (denosumab) 20090601

Program Sponsor: Amgen Inc.
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Date: **09 October 2009**
Amendment **1 Date:** 28 September 2011
Amendment 2 Date: **23 June 2016**

Program Synopsis

Title: Prolia® Postmarketing Active Safety Surveillance Program for Soliciting Adverse Events of Special Interest in the United States

Indications:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men **with osteoporosis** at high risk for fracture

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Primary Objective of the Program: To monitor the long-term safety of Prolia® **(denosumab)** and enhance the quality of data collection by proactively soliciting adverse event reporting of the **5 pre-specified adverse events** of special interest (AESI) from United States (US) **health care providers (HCPs) of Prolia-treated postmenopausal women and men with osteoporosis within the Postmarketing Active Safety Surveillance Program (PASP) Electronic Medical Record (EMR) (PASP-EMR program)**.

Background: [redacted] The [redacted] EMR database consists of medical information collected through the [redacted] ambulatory EMR platform. A majority of [redacted] practices are single-provider or small-group practices. Patient data are available for over 25 million unique patients since 2005, of which over 14 million are currently active on the platform. Data validation and quality checks are performed as part of this process.

Program Design: This PASP is a commitment with the US Food and Drug Administration (FDA). As such, the design of the program is to solicit pre-specified AESI. The program is not designed to capture all adverse events. The study is non-interventional and Prolia is an established product with a known safety profile. Adverse events that are not pre-specified may be captured through standard spontaneous reporting processes. Therefore, only the pre-specified AESI will be captured and reported per this protocol.

The program consists of elements to stimulate reporting of AESI and is intended to complement routine reporting systems. **The program will proactively solicit information from HCPs who participate in [redacted] EMR system about 5 pre-specified AESI in patients receiving Prolia. The office visit and querying will commence as follows:**

- **When Prolia patients present to [redacted] physician or their delegate (eg, licensed registered nurses, nurse practitioners, or physician assistants) for routine care, HCPs will receive an EMR prompt to ask their Prolia-treated patients about the occurrence of any of the 5 AESI since their Prolia injection or office visit.**
- **As part of the user interface of the EMR, the physician or delegate will automatically be prompted to solicit information on the Prolia AESI from Prolia-treated patients using the [redacted] EMR-soliciting questionnaire.**
- **If it is determined that 1 or more of the 5 Prolia AESI may have been observed, HCPs will be prompted by the EMR to report the Prolia-AESI to Amgen via an internet link to a secure Amgen website.**
- **At the secure Amgen website, the Prolia physician or delegate will be instructed to complete an AESI-specific questionnaire.**
- **The [redacted] EMR-soliciting prompt requires a HCP response to remove the action item from his or her current workflow or add a reminder in the EMR task list.**
- **If the [redacted] EMR-soliciting questionnaire is not completed, the EMR will send automatic electronic reminders to the HCP task list to complete the soliciting questionnaire.**
- **In addition, the PASP-EMR program will also instruct HCPs to counsel Prolia patients on the risks of Prolia treatment using the Prolia Risk Evaluation and Mitigation Strategy (REMS) Patient Counselling Chart and Patient Brochure.**

Solicited AESI will be integrated into Amgen's routine processes for **postmarketing adverse event** collection, follow-up, evaluation, and reporting. Reported AESI cases will be processed at

Amgen and reported to **the US FDA and other** regulatory agencies worldwide in accordance with applicable FDA and local country adverse event reporting regulations. **Adverse events of special interest collected through the PASP-EMR program and through the routine reporting system will be summarized and reported [redacted] to the FDA.**

Program Details:

Targeted HCPs: United States physicians and their delegates who use the [redacted] EMR platform at the point of care when providing health care to Prolia-treated patients.

Program Duration: The program **completion date is [redacted] (per the terms of FDA postmarketing requirement [redacted]**

Data Processing: Amgen will be responsible for intake, processing, reviewing, and regulatory reporting according to Amgen **Standard Operating Procedures** for all **AESI** reports. **All [redacted] patient data will be aggregated and de-identified, and will be analyzed and treated according to Health Insurance Portability and Accountability Act (HIPAA). If a [redacted] EMR-soliciting questionnaire for an AESI is captured, the EMR will automatically send an electronic prompt to the HCP task list to complete the AESI reporting at the secure Amgen website.**

All reports that **are submitted** through the **secure Amgen website** will be considered solicited events**. As necessary, an inquiry will be sent by Amgen to the reporting HCP to collect missing data and/or other medical information specific to the AESI. Each reported event will be assigned a tracking number to facilitate processing and reporting of information.**

Amgen will meet regulatory reporting requirements; therefore, HCPs **will** not need to send a duplicate report to FDA for the AESI reported to Amgen.

Statistical Analysis: Descriptive statistics will be used to summarize AESI data that will be **collected within the [redacted] EMR and from solicited AESIs reported through the secure Amgen website. [redacted]**

A program design flowchart is presented in Figure 1.

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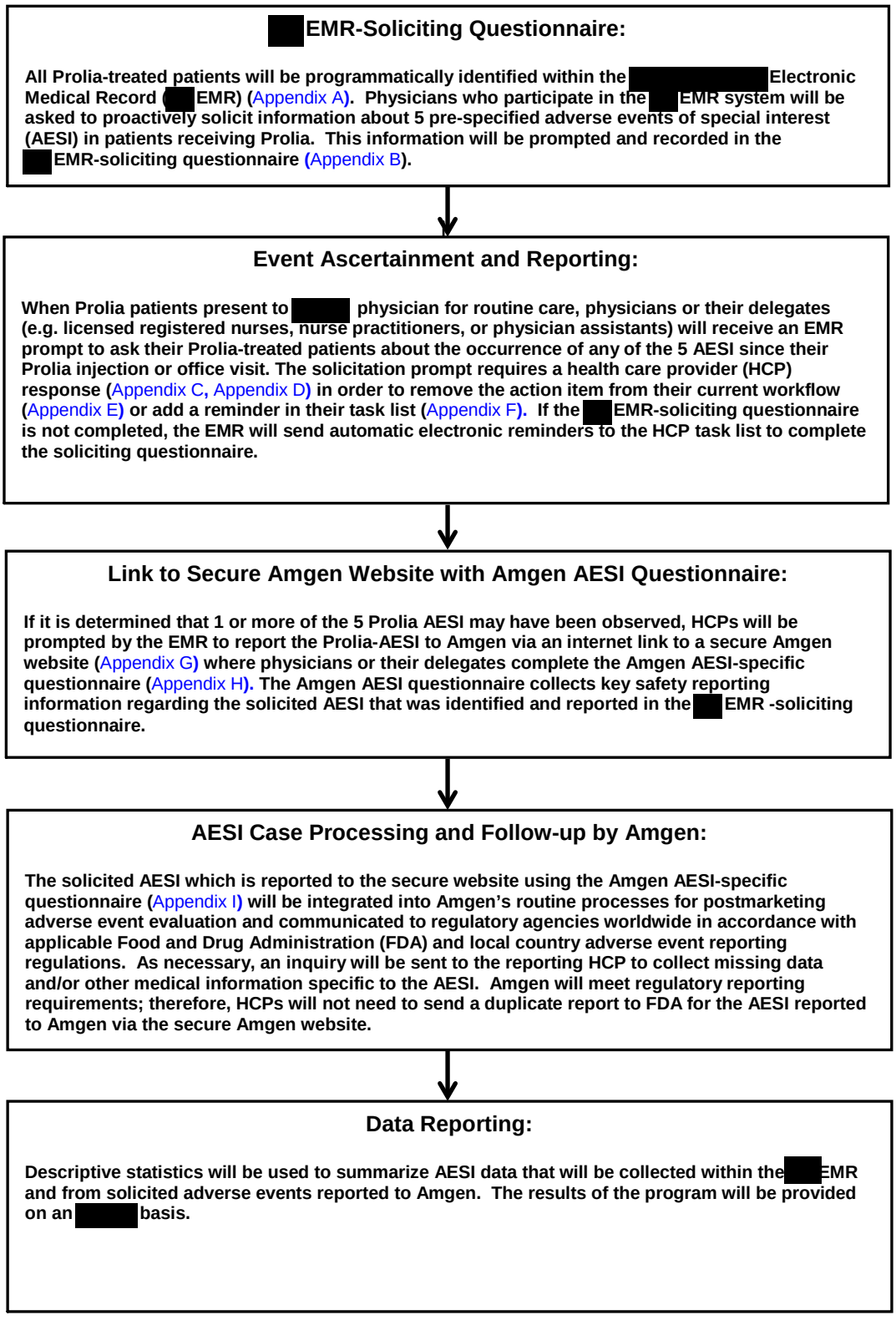
Figure 1. Program Design Flowchart



Program Glossary

Abbreviation/Acronym	Definition
AESI	Adverse event of special interest
AFF	**Atypical femoral fractures**
EMR	**Electronic medical record**
ER	Emergency room
FDA	Food and Drug Administration
HCP	Health care provider
HIPAA	**Health Insurance Portability and Accountability Act**
ONJ	Osteonecrosis of the jaw
PASP	**Postmarketing Active Safety Surveillance Program**
PASP-EMR	**Postmarketing Active Safety Surveillance Program-Electronic Medical Record program**
[redacted]	
PMR	**Postmarketing requirement**
RANKL	RANK ligand
REMS	**Risk Evaluation and Mitigation Strategy**
US	United States
VAERS	**Vaccination Adverse Event Reporting System**

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1. OBJECTIVES

To monitor the long-term safety of Prolia® **(denosumab)** and enhance the quality of data collection by proactively soliciting adverse event reporting of **the 5** pre-specified adverse events of special interest (AESI) from United States (US) **health care providers (HCPs eg, licensed registered nurses, nurse practitioners, or physician assistants) of Prolia-treated postmenopausal women and men with osteoporosis within the Postmarketing Active Safety Surveillance Program (PASP) Electronic Medical Record (EMR) (PASP-EMR) program .**

2. BACKGROUND AND RATIONALE

Prolia® (denosumab) is a fully human **immunoglobulin** G_2 monoclonal antibody that binds with high affinity to RANK ligand (RANKL) and prevents activation of RANK, thereby inhibiting osteoclast formation, function, and survival, and thus reducing the number of osteoclasts. Denosumab thereby decreases bone resorption and increases cortical and trabecular bone mass and bone strength.

Clinical studies have demonstrated that Prolia® has a favorable benefit: risk profile in patients followed for up to **10** years. Amgen has committed to assess the occurrence of the following pre-specified AESI in the **p**ostmarketing setting **which are consistent with the risks of Prolia therapy that are communicated through the Prolia Risk Evaluation and Mitigation Strategy (REMS)**:

- Hypocalcemia
- Osteonecrosis of the jaw (ONJ)
- Atypical **femoral** fracture**s (AFF)**
- **Serious** infectio**ns**
- Dermatologic **reactions**

Results from the program described in this document will supplement information on the safety profile of Prolia® obtained from clinical trials, observational studies, and other pharmacovigilance activities.

[redacted] **The [redacted] EMR database consists of medical information collected through [redacted] [redacted] ambulatory EMR platform. A majority of [redacted] practices are single-provider or small-group practices. Patient data are available for over**

25 million unique patients since 2005, of which over 14 million are currently active on the platform. Data validation and quality checks are performed as part of this process.

3. PROGRAM PLAN

3.1 Program Design

This PASP is a commitment with the US Food and Drug Administration (FDA). As such, the design of the program is to solicit pre-specified AESI. The program is not designed to capture all adverse events. The study is non-interventional and Prolia is an established product with a known safety profile. Adverse events that are not pre-specified may be captured through standard spontaneous reporting processes. Therefore, only the pre-specified AESI will be captured and reported per this protocol.

The program consists of elements to stimulate reporting of AESI and is intended to complement routine reporting systems. **The program will proactively solicit information from HCPs who participate in the [redacted] EMR system about 5 pre-specified AESI in patients receiving Prolia. The office visit and querying will commence as follows:**

- **When Prolia patients present to [redacted] physician or their delegate for routine care, HCPs will receive an EMR prompt (Appendix A) to ask their Prolia-treated patients about the occurrence of any of the 5 AESI since their last Prolia injection or office visit.**
- **As part of the user interface of the EMR, the physician or delegate will automatically be prompted to solicit information on the Prolia AESI from Prolia-treated patients using the [redacted] EMR-soliciting questionnaire (Appendix B).**
- **If it is determined that 1 or more of the 5 Prolia AESI may have been observed (Appendix C and Appendix D), HCPs will be prompted by the EMR to report the Prolia-AESI to Amgen via an internet link to a secure Amgen website.**
- **At the secure Amgen website (Appendix G), the Prolia physician or delegate will be instructed to complete an AESI-specific questionnaire (Appendix H and Appendix I).**
- **The [redacted] EMR-soliciting prompt requires a HCP response to remove the action item from his or her current workflow (Appendix E) or the reminder in the task list (Appendix F).**

- **If the [redacted] EMR-soliciting questionnaire is not completed, the EMR will send automatic electronic reminders to the HCP task list to complete the soliciting questionnaire.**
- **In addition, the PASP-EMR program also will instruct HCPs to counsel Prolia patients on the risks of Prolia treatment using the Prolia REMS Patient Counselling Chart and Patient Brochure.**

Solicited AESI will be integrated into Amgen's routine processes for postmarketing adverse event collection, follow-up, evaluation, and reporting. Reported AESI cases will be processed at Amgen and reported to the US FDA and other regulatory agencies worldwide in accordance with applicable FDA and local country adverse event reporting regulations. Adverse events of special interest collected through the PASP-EMR program and through the routine reporting system will be summarized and reported [redacted] to the FDA. The program design flowchart is presented in Figure 1 and the program design schema is presented in Figure 2.

Data collection will include the following elements:

- **[redacted] EMR AESI-soliciting questionnaire (Appendix B)**
- **EMR task list and reminders (Appendix F)**
- **Secure website with Amgen AESI-specific questionnaire and adverse event follow-up per Amgen's routine processes (Appendix H)**

Figure 2. Program Design Schema

3.2 Program Targeted HCPs

Targeted HCPs will include US physicians and their delegates who use the [redacted] EMR at the point of care while providing health care to patients who are being treated with Prolia. The soliciting process is integrated into the normal EMR workflow and participation is automatic, thus, there is no requirement for enrollment or registration to participate.

3.3 Program Reporting Eligibility

Any **physician or their delegate using the [redacted] EMR** may complete an AESI-soliciting questionnaire for any patient who has received Prolia **for 1 of the following** approved indications **for Prolia:**

1) **Treatment of postmenopausal women with osteoporosis at high risk for fracture.**
2) **Treatment to increase bone mass in men with osteoporosis at high risk for fracture.**

All reports that are submitted through the secure Amgen website will be considered solicited events.

Health care providers who wish to report adverse events other than an AESI will be instructed to complete a MedWatch form and report it to Amgen or directly to the FDA.

3.4 Estimated Program Duration

Per the terms of FDA postmarketing requirement [redacted]

3.5 Definition of Adverse Events of Special Interest

Hypocalcemia: This is defined as any event of hypocalcemia that, in the opinion of the reporting physician, is the primary reason for hospitalization or an emergency room (ER) visit.

Osteonecrosis of the jaw: Osteonecrosis of the jaw is defined as exposed **bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks. Osteonecrosis of the jaw occurs in the absence of radiotherapy to the jaw or metastatic disease to the jaws, and in the presence of current or previous treatment with antiresorptive medication or antiangiogenic agents.** This working definition has been adopted by the American Association of Oral and Maxillofacial Surgeons with regard to ONJ after bisphosphonate **exposure.(Ruggiero, 2014)**

Atypical femoral fractures: **Atypical femoral fractures are those occurring in the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare and having at least 4 of the 5 major features as described by the 2013 case definition adopted by the American Society for Bone and Mineral Research.(Shane, 2014)**

Serious infections: An infectious event leading to hospitalization or ER visit is defined as any event of infection that is the primary reason for hospitalization or an ER visit. An infectious event requiring intravenous anti-infective medication is defined as any event of infection requiring intravenously administered anti-infective medication as an outpatient. Skin infections are considered a subgroup of all infections for purposes of analysis.

Dermatologic reactions: This is defined as any dermatologic event that is the primary reason for hospitalization or an ER visit. Dermatologic events that are likely to lead to

hospitalization include erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.(**Chan, 1990**)

4. DATA COLLECTION PROCEDURES

4.1 Solicitation of Pre-defined Adverse Events of Special Interest

Health care providers who provide care to postmenopausal women or men with osteoporosis at high risk for fracture are requested, as part of their routine medical practice, to ask their patients who are receiving Prolia about the occurrence of an AESI since their Prolia injection or **office visit.** If 1 or more AESI have occurred**, HCPs will be asked to identify these events in the [redacted] EMR AESI-soliciting questionnaire (Appendix B). The soliciting questionnaire will prompt the HCP to complete the AESI reporting to Amgen via a link to a secure Amgen website. Data collected through the [redacted] EMR AESI-soliciting questionnaire will be de-identified and summarized in aggregate whereas patient, HCP, and AESI-specific information will be received at Amgen once the HCP has completed this information on the secure Amgen website (Appendix I).**

Once the AESI has been reported to Amgen, Amgen will follow the routine process for serious adverse event processing and follow-up. Instructions will also be provided within the PASP-EMR program for HCPs to report other adverse events/serious adverse event (not falling under the AESI category) using the FDA's MedWatch program or by contacting Amgen Medical Information**, although these reports would be outside the scope of the program for solicited AESI. The AESI and adverse events/serious adverse events reported outside of the secure Amgen website will be managed as usual spontaneous case reporting rather than as a component of the PASP-EMR program**.

4.2 Program Data-collection Procedures

The [redacted] EMR AESI-soliciting questionnaire (Appendix B) allows for collection of aggregated and de-identified demographic information. The Amgen AESI-specific questionnaires (Appendix H) and routine processes for adverse event follow-up will collect information for adverse event reporting.

The solicited AESI which are reported to the secure Amgen website will be integrated into Amgen's routine processes for postmarketing adverse event evaluation and communicated to regulatory agencies worldwide in accordance with applicable FDA and local country adverse event reporting regulations.

5. DATA PROCESSING, RECORDING, AND REPORTING

5.1 Data Processing at [redacted]

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), [redacted] will make available to Amgen only aggregate and de-identified data from the EMR. The completion rates for [redacted] EMR-soliciting questionnaires and the physician responses to the questionnaire will be collected and will be reported [redacted]

Aggregated data from Prolia patients from [redacted] EMR will be analyzed [redacted] to [redacted]

5.2 Data Processing at Amgen

Amgen will be responsible for the intake, processing, reviewing, and reporting of all pre-specified AESI reported to the secure website with the Amgen AESI-specific questionnaire, according to Standard Operating Procedures for adverse event reporting. [redacted]

Amgen will meet regulatory reporting requirements for information submitted on the AESI-specific questionnaires. Therefore, HCPs do not need to send a duplicate report to FDA for the AESI reported via the secure Amgen website in this program.

5.3 Data Recording

The data collected from the **secure Amgen website with the Amgen AESI-specific questionnaire** will be entered **through** the Amgen Safety Database [redacted] **Adverse events of special interest** reported by HCPs to Amgen via routine spontaneous reports using a MedWatch form **or by contacting Amgen Medical Information (ie, reporting outside of PASP-EMR program)** will be processed as spontaneous cases**.** Follow-up for spontaneously reported AESI **and those reported through the secure website with the Amgen AESI-specific questionnaire** will request the same information**.**

[redacted]

5.4 Data Reporting

5.4.1 Individual AESI Case Reporting

Each AESI collected **from the secure Amgen website** will be reported to regulatory agencies worldwide as required according to the timeline specified in local country regulations for reported adverse events.

5.4.2 Aggregate Data Assessment

Solicited AESI collected through the **secure Amgen website and** AESI reported **through routine US** reporting systems (eg, FDA's MedWatch system) will be summarized [redacted]

6. STATISTICAL ANALYSIS

Descriptive statistics will be used to summarize the program data. The following analyses will be conducted [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7. REGULATORY AND ADMINISTRATIVE OBLIGATIONS

7.1 Subject Confidentiality

Collection of data in this program to stimulate and solicit the reporting of **AESI**s is similar to adverse event reporting for the Vaccination Adverse Event Reporting System (VAERS) and MedWatch programs. Physicians can continue to make adverse event reports under the HIPAA Privacy Rule. The HIPAA Privacy Rule is not intended to disrupt or discourage adverse event reporting. The Privacy Rule specifically permits covered entities (such as physicians) to report adverse events and other information related to the safety of FDA-regulated products both to the manufacturer and directly to FDA. Amgen will collect only the information on the patient that is necessary in follow-up correspondence to allow the reporting physician to re-identify the patient in the initial report. Amgen will protect patient confidentiality and will not collect or disclose other patient identifying information such as patient's full name, social security number, address, or phone number.

Because this program fundamentally stimulates routine adverse event reporting by **HCPs** in the course of their medical practice, the program should not require **institutional review board** approval and patient informed consent.

7.2 Program Notifications

Any updates to the program, including questionnaires, will be documented as appropriate. **These notifications will provide relevant background information on PASP-EMR, encourage prescribers to complete the [redacted] EMR AESI-soliciting questionnaire when prompted, inform HCPs to counsel patients about the risks associated with Prolia, and facilitate adverse event reporting to Amgen.**

The information on the 5 Prolia AESI evaluated under the PASP-EMR program is consistent with the 5 serious risks communicated by the approved Prolia Risk Evaluation and Mitigation Strategy (REMS) program. Notifications in the [redacted] EMR may also present educational materials [redacted]

[redacted]

8. REFERENCES

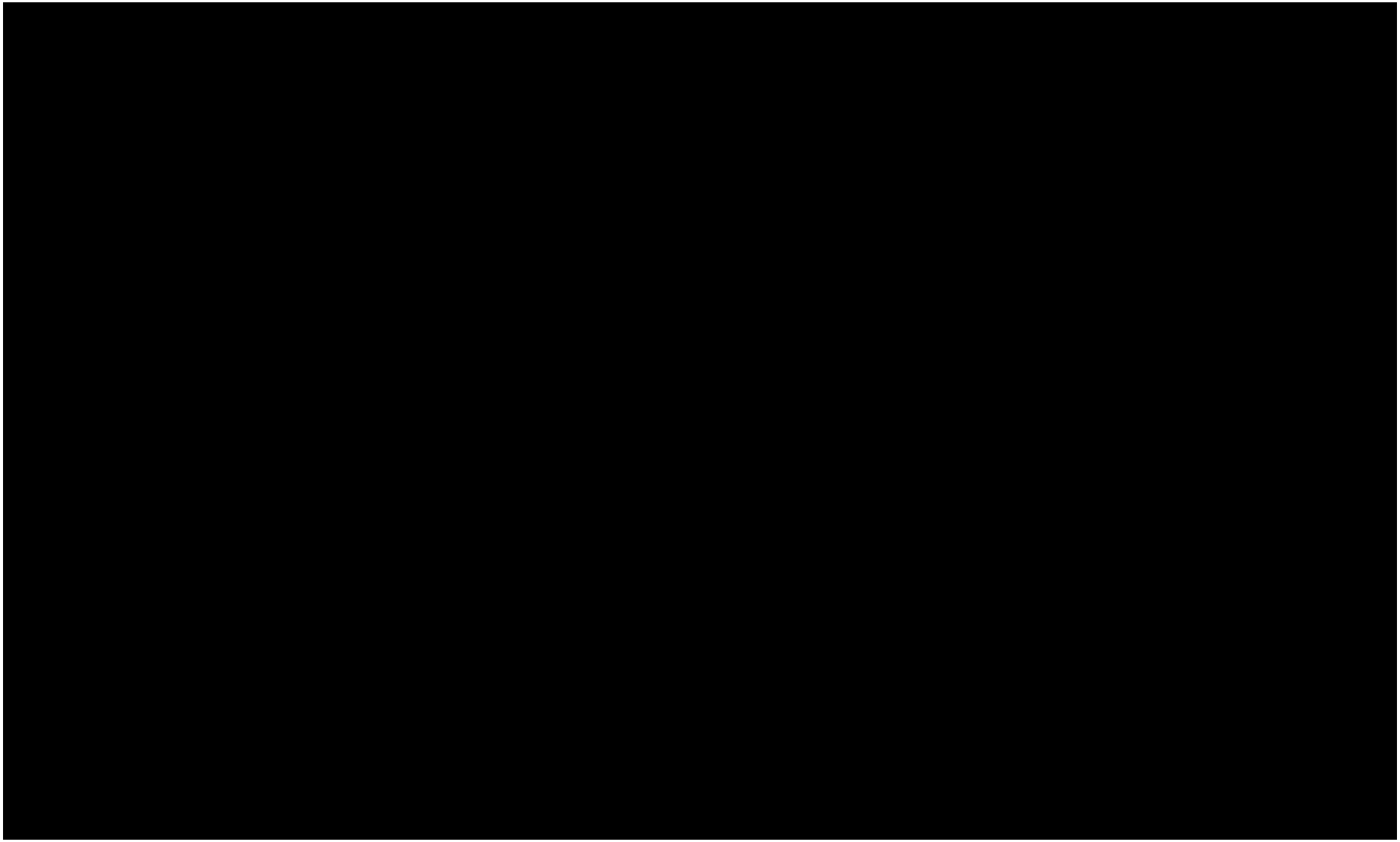
Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol.* Jan 1990;126(1):43-47.

Ruggiero SL, Dodson T, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaws–2014 update. *J Oral Maxillofac Surg.* 2014;72:38-56.

Shane E, Burr D, Abrahamson B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *JBMR*.2014;29(1):1-24.

9. APPENDICES

Appendix A. Clinical Decision Support Notification



Appendix B. Adverse Events of Special Interest Soliciting Questionnaire

[redacted]

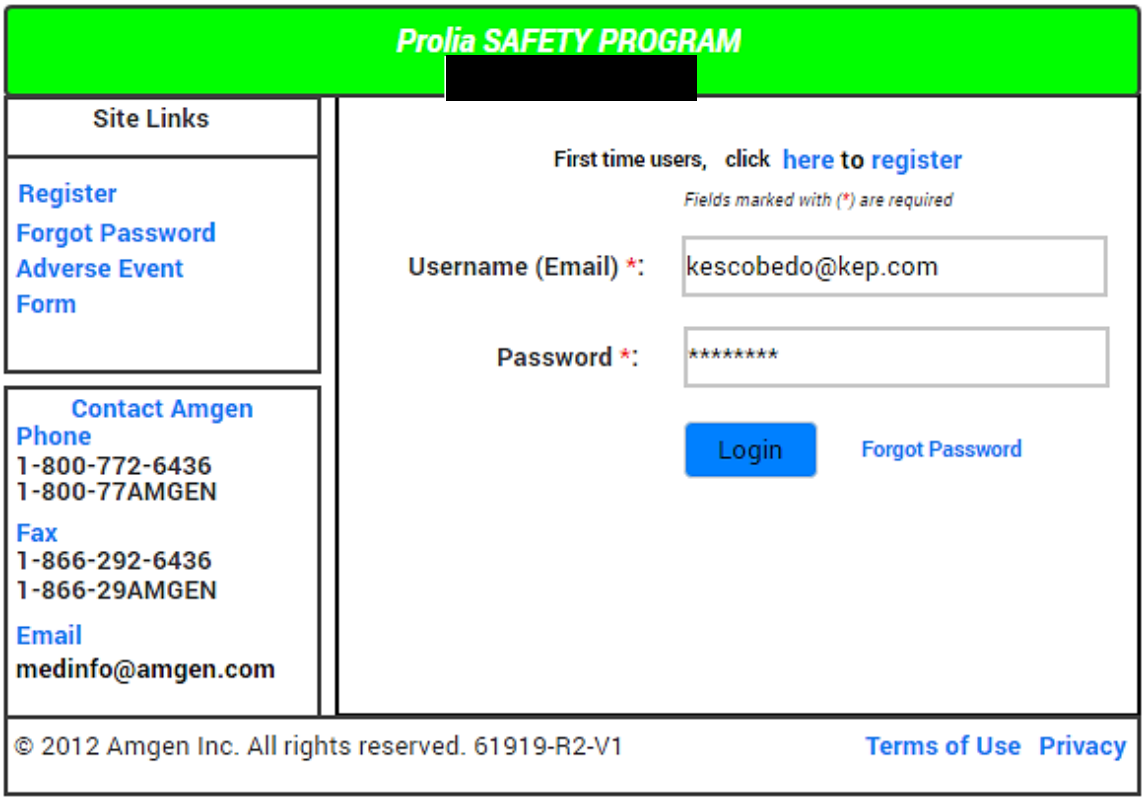
Appendix C. Positive Response

Appendix D. Negative Response

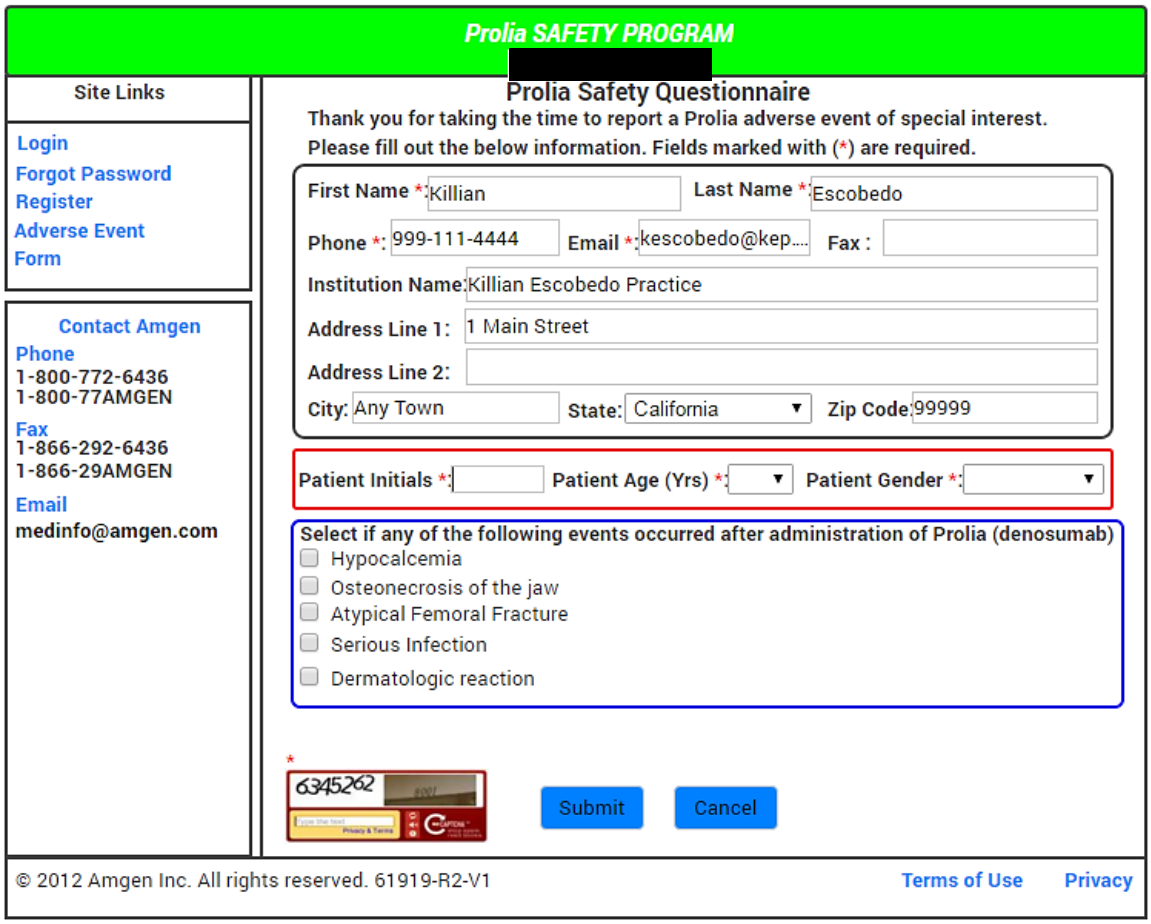
Appendix E. End of Point of Care Work Flow

Appendix F. Electronic Medical Record Task List

Appendix G Amgen Website Landing Page



Appendix H. Adverse Events of Special Interest-specific Questionnaire



Appendix I. Completed Adverse Event of Special Interest Reporting