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. 1 Amgen Center Drive Thousand Oaks, CA 91320-1799 Tel: 805-447-1000
Key Sponsor Contact:	**Susan Yue** **Clinical Scientist** 1 Amgen Center Drive Thousand Oaks, CA 91320-1799 Tel: 805-313-6304 Fax: 805-498-2481
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

---

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: Practice Fusion-Electronic Medical Record (PF-EMR): The PF-EMR database consists of medical information collected through the Practice Fusion (PF) cloud-based ambulatory EMR platform. A majority of PF 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 the PF-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 any PF 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 PF-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 PF-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 PF-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 annually to the FDA.**

Program Details:

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

Program Duration: The program **completion date is December 2021 and the final report will be submitted in June 2022 (per the terms of FDA postmarketing requirement [PMR] #2957-2).**

Data Processing: Amgen will be responsible for intake, processing, reviewing, and regulatory reporting according to Amgen **Standard Operating Procedures** for all **AESI** reports. **All PF 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 PF-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.**

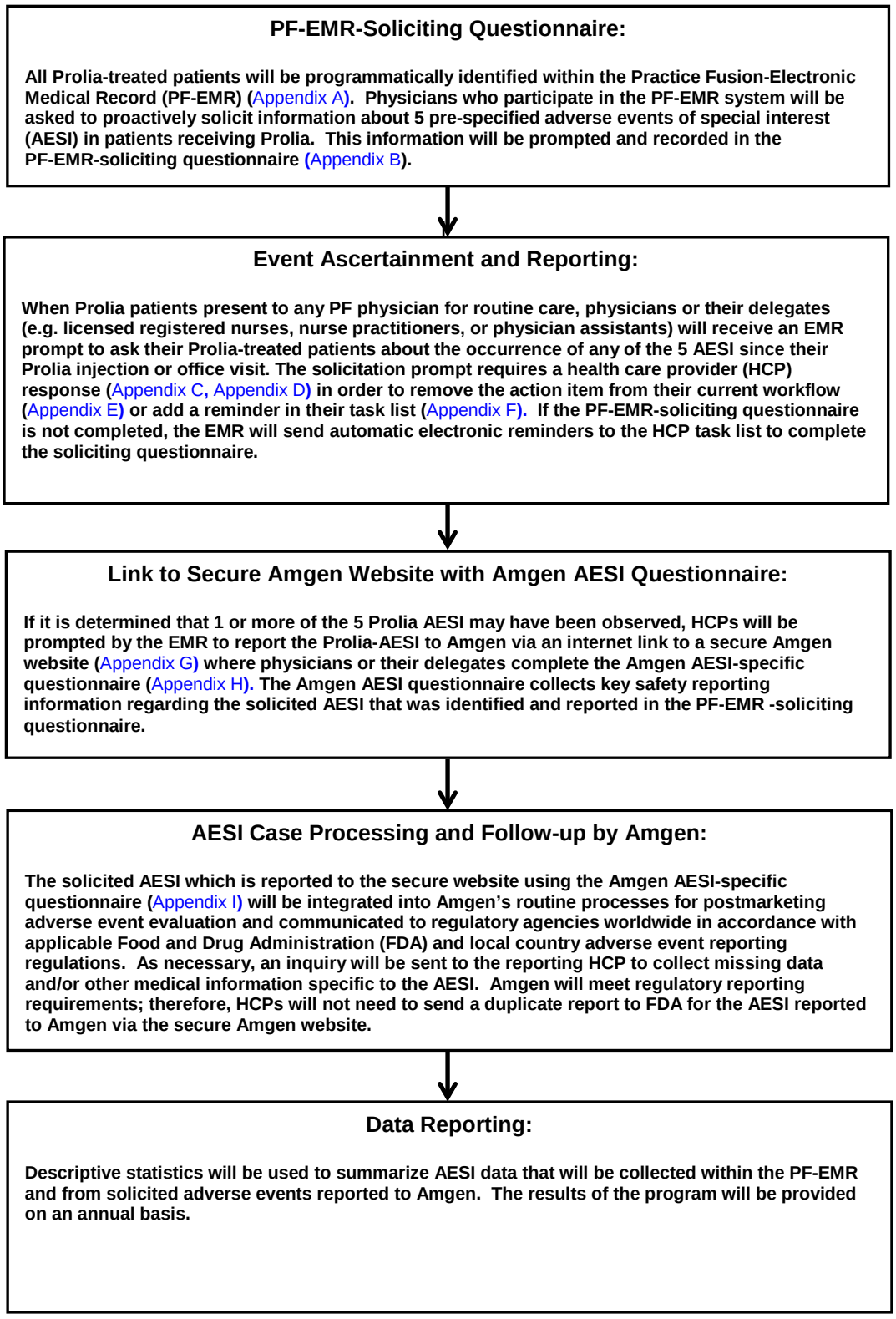
Amgen will meet regulatory reporting requirements; therefore, HCPs **will** not need to send a duplicate report to FDA for the AESI reported to Amgen.

Statistical Analysis: Descriptive statistics will be used to summarize AESI data that will be **collected within the PF-EMR and from solicited AESIs reported through the secure Amgen website. The results of the program will be reported on an annual basis to the FDA**. The analysis will include **annual** data summaries from the current reporting period as well as cumulative data. **The following key analyses will be provided by PF: number of Prolia-treated patients in the PF-EMR and number of AESIs reported to Amgen through PF-EMR-soliciting questionnaire. The report analyses and format will be similar to the annual reports previously submitted**.

A program design flowchart is presented in Figure 1.

Sponsor/Licensee: Amgen Inc

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**
PF	**Practice Fusion**
PF-EMR	**Practice Fusion-Electronic Medical Record**
PMR	**Postmarketing requirement**
RANKL	RANK ligand
REMS	**Risk Evaluation and Mitigation Strategy**
US	United States
VAERS	**Vaccination Adverse Event Reporting System**

TABLE OF CONTENTS

List of Figures

List of Appendices

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.

Practice Fusion-Electronic Medical Record (PF-EMR): The PF-EMR database consists of medical information collected through the Practice Fusion (PF) cloud-based ambulatory EMR platform. A majority of PF 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 PF–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 any PF 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 PF-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 PF-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).**

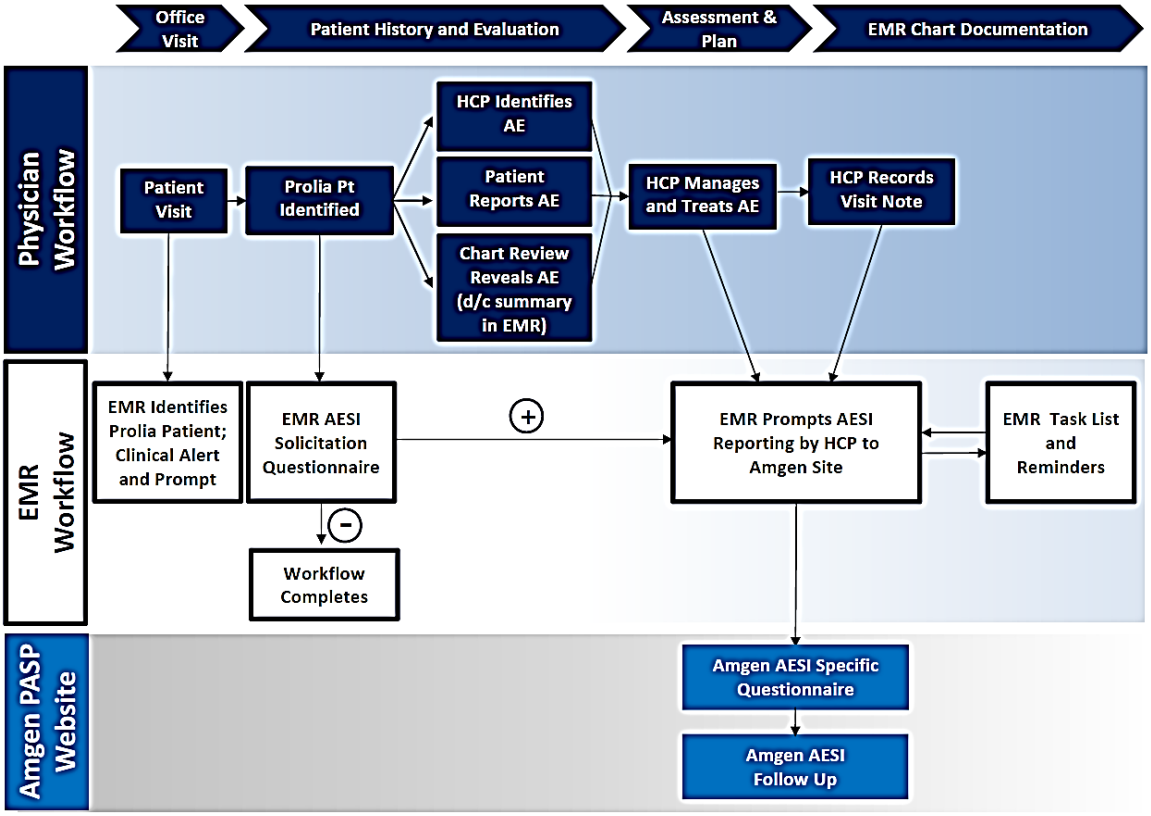
- If the PF-EMR-soliciting questionnaire is not completed, the EMR will send automatic electronic reminders to the HCP task list to complete the soliciting questionnaire.
- In addition, the PASP-EMR program also will instruct HCPs to counsel Prolia patients on the risks of Prolia treatment using the 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 annually 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:

- PF-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



Abbreviations: AESI = adverse events of special interest; EMR = electronic medical record; HCP = health care provider; PASP = Postmarketing Active Safety Surveillance Program; Pt = patient.

3.2 Program Targeted HCPs

Targeted HCPs will include US physicians and their delegates who use the cloud-based PF-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 PF-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 (PMR) #2957-2 (Biologics License Application 125320/0 Approval Letter, 01 June 2010), the program completion date is December 2021 and the final report will be submitted in June 2022.

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 PF-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 PF-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 PF-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 Practice Fusion

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), PF will make available to Amgen only aggregate and de-identified data from the EMR. The completion rates for PF-EMR-soliciting questionnaires and the physician responses to the questionnaire will be collected and will be reported via summary tables on a pre-specified basis for annual reporting purposes. Aggregated data from Prolia patients from PF-EMR will be analyzed annually to provide descriptive information of patient characteristics, distributions, and AESI information. Aggregate reports may be generated more frequently to determine the effectiveness of the active solicitation of AESI through the PASP-EMR program, as appropriate.

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. As necessary, an inquiry will be sent to the reporting HCP to collect missing data and/or other medical information specific to the AESI.

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 **using a tracking number** in order to fulfill reporting obligations for these AESI**. 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**.**

Events of ONJ and AFF reported to Amgen will be confirmed by an internal medical review at Amgen.

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 **annually**.

6. STATISTICAL ANALYSIS

Descriptive statistics will be used to summarize the program data. The following analyses will be conducted **annually**.

Practice Fusion EMR:

- **Number of Prolia-treated patients in the PF-EMR**
- **Number of Prolia-treated patients with at least 1 PF-EMR-soliciting questionnaire presented**
- **Number and percentage of Prolia-treated patients with at least 1 PF-EMR-soliciting questionnaire completed (at least 1 AESI box**, **or No AESI**, **is checked)**
- **Number and percentage of Prolia-treated patients with at least 1 AESI reported through PF-EMR-soliciting questionnaire**
- **Number of AESIs reported through PF-EMR-soliciting questionnaire**

Amgen AESI-Specific Questionnaire Via Secure Website:

- **Number of AESIs reported through the secure Amgen website via the link from the PF-EMR**
- **Number of potential ONJ and AFF events**
- **Number of events adjudicated as consistent with the definitions of ONJ and AFF**

The analysis will include annual data from the current reporting period as well as cumulative data **over the entire PASP-EMR program.**

Descriptive statistics will be used to summarize AESI data that will be collected within the PF-EMR and from solicited adverse events reported through the secure Amgen website. All PF-patient data will be analyzed and treated according to HIPAA. The results of the PASP-EMR program will be provided on an annual basis. The report analyses and format will be similar to the annual reports previously submitted.

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 PF-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 PF-EMR may also present educational materials from the Prolia REMS website

(http://www.proliahcp.com/risk-evaluation-mitigation-strategy/), including the Prolia REMS Patient Counseling Chart and Patient Brochure.

8. REFERENCES

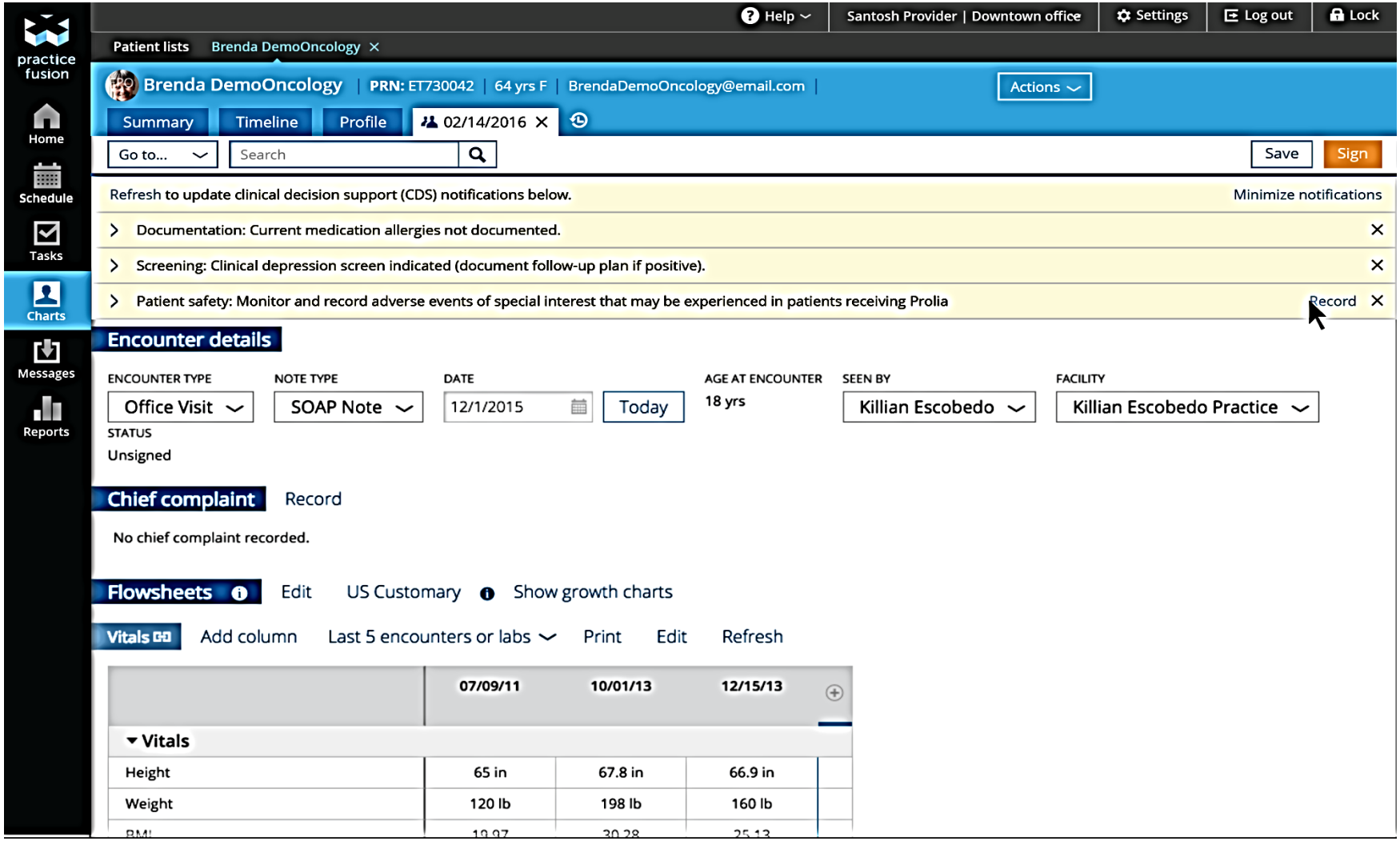
Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol.* Jan 1990;126(1):43-47.

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.

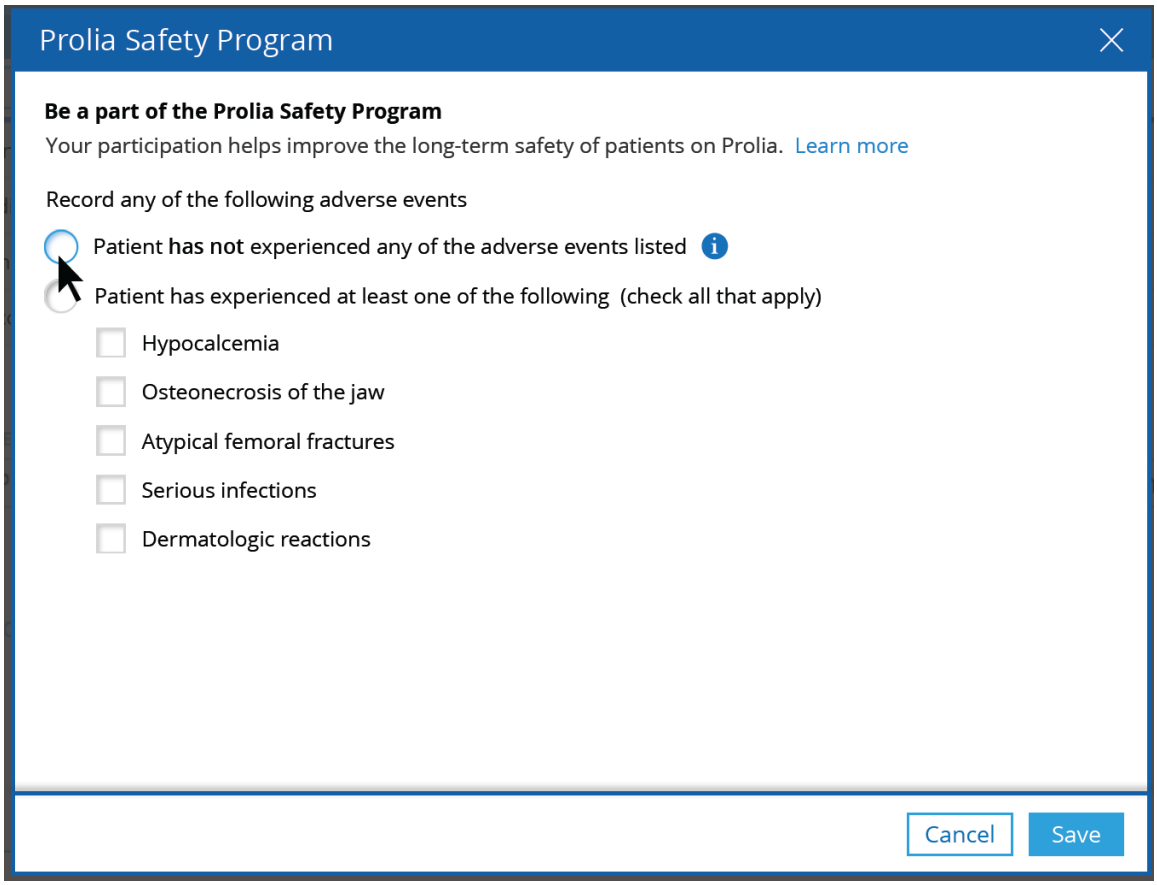
Shane E, Burr D, Abrahamson B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *JBMR*.2014;29(1):1-24.

9. APPENDICES

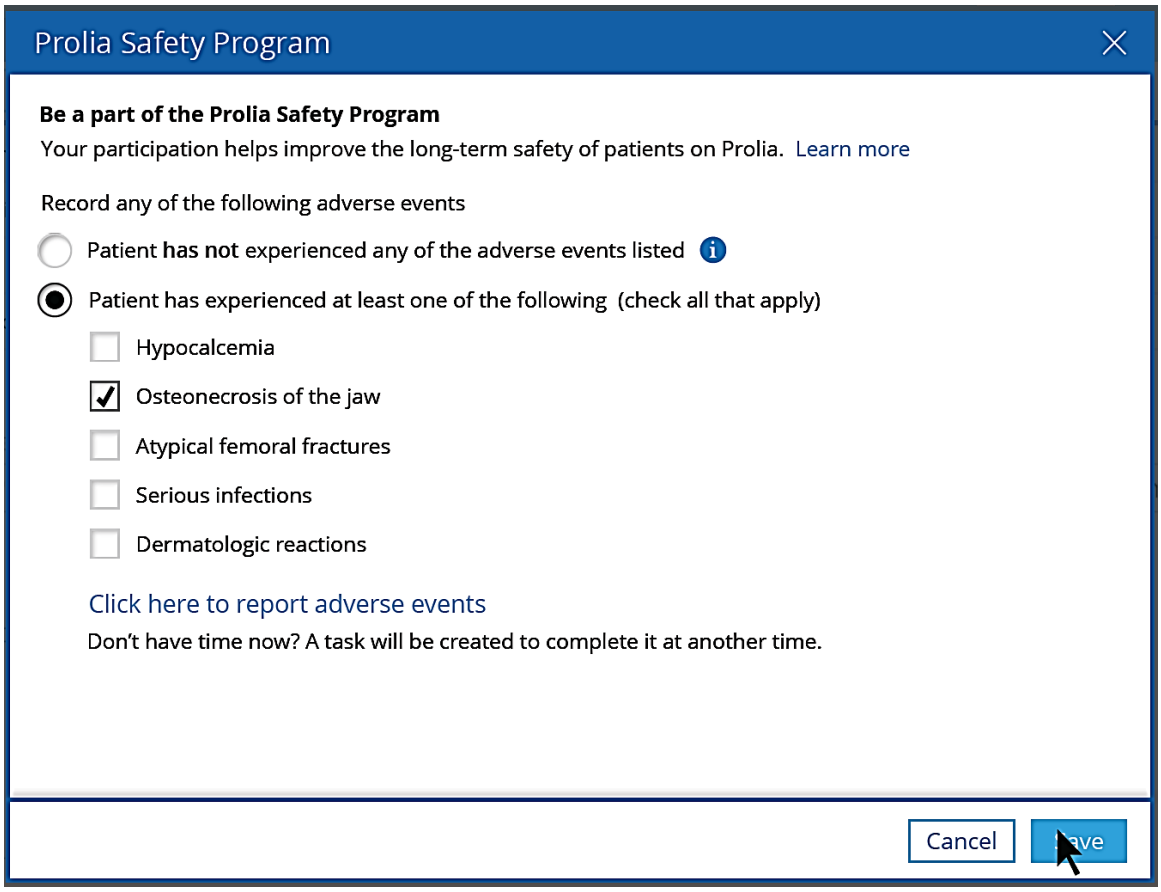
Appendix A. Clinical Decision Support Notification



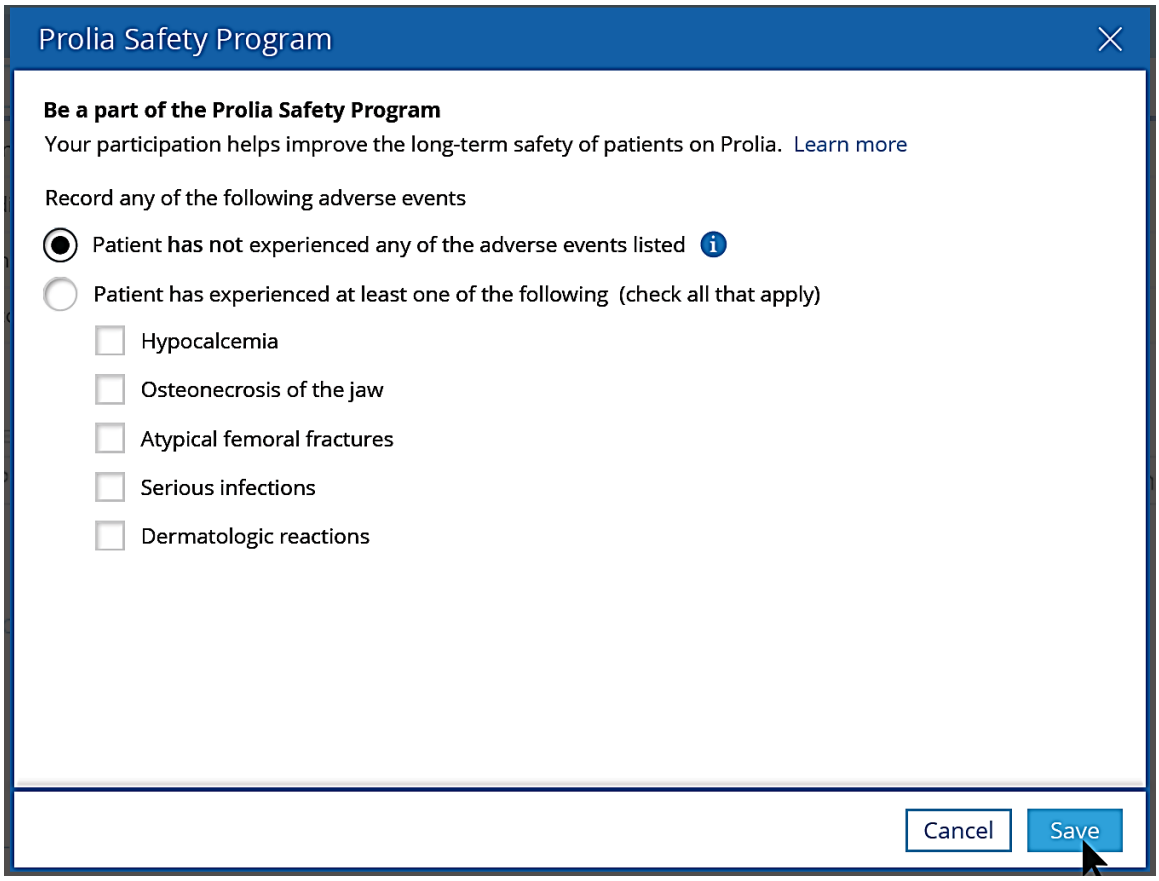
Appendix B. Adverse Events of Special Interest Soliciting Questionnaire



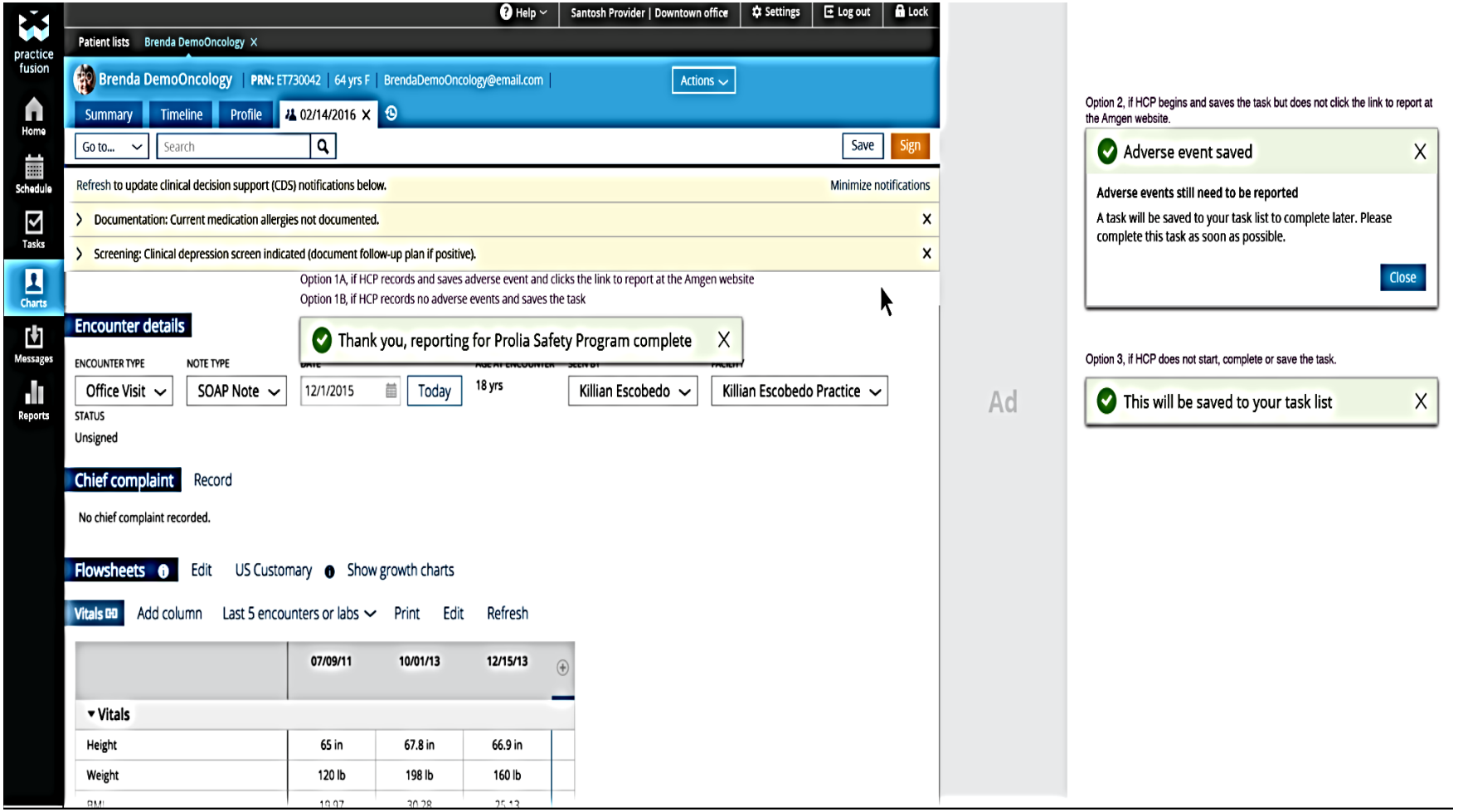
Appendix C. Positive Response



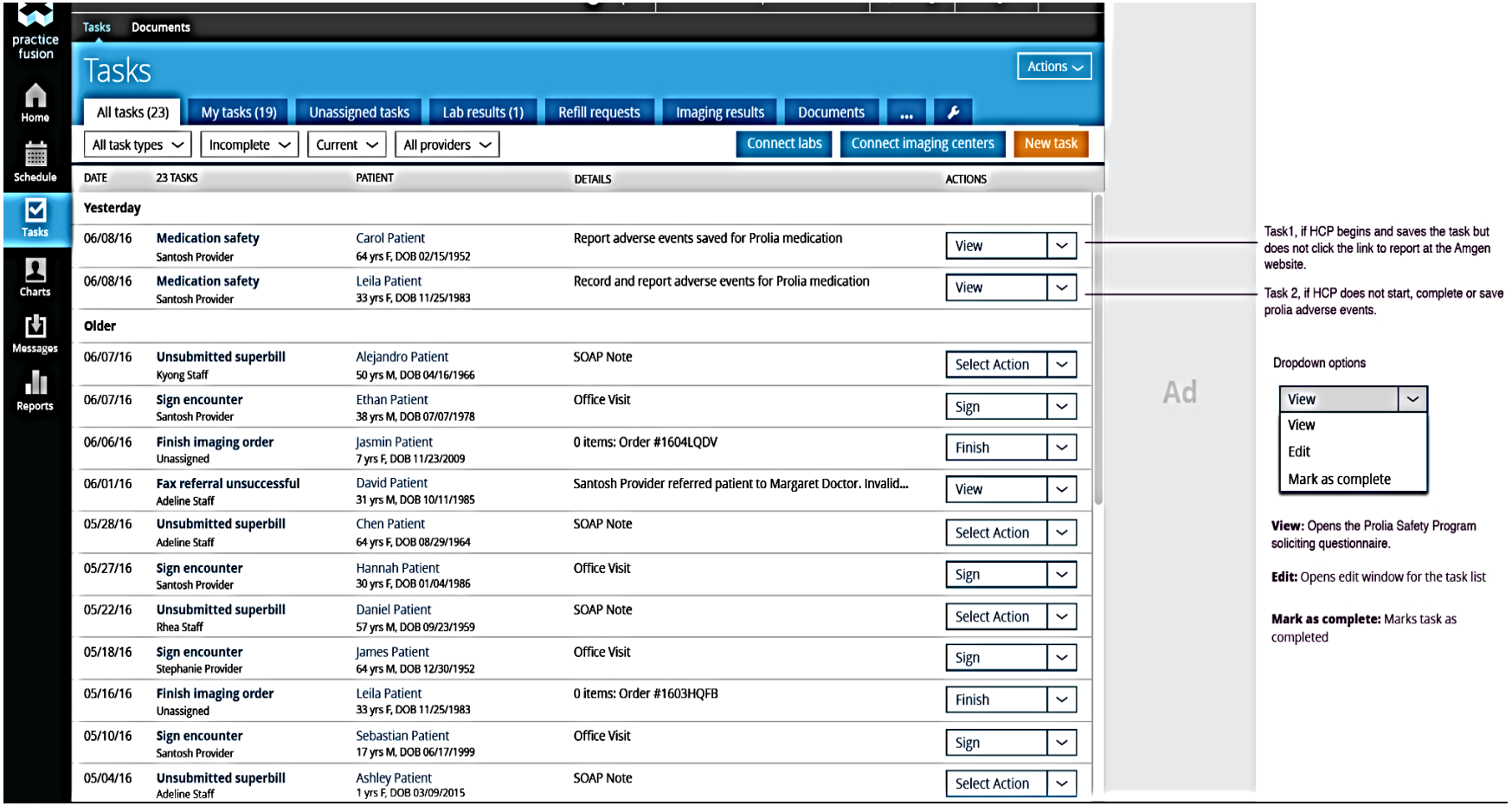
Appendix D. Negative Response



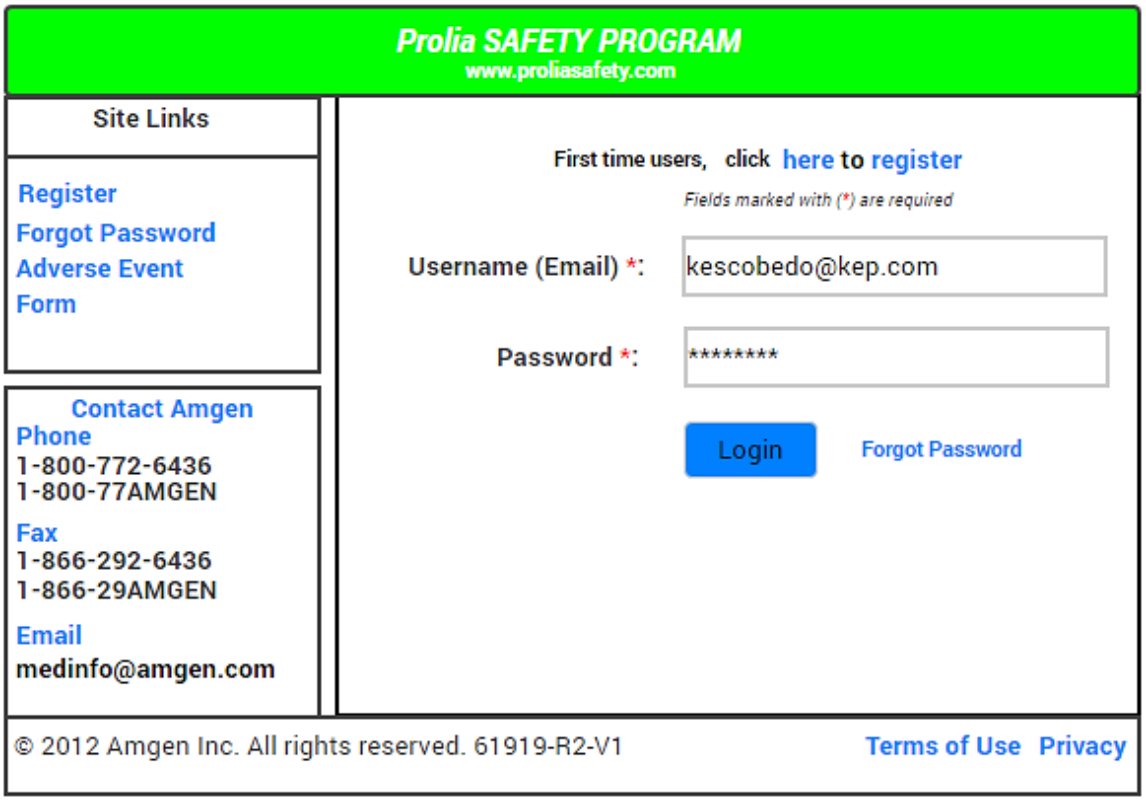
Appendix E. End of Point of Care Work Flow



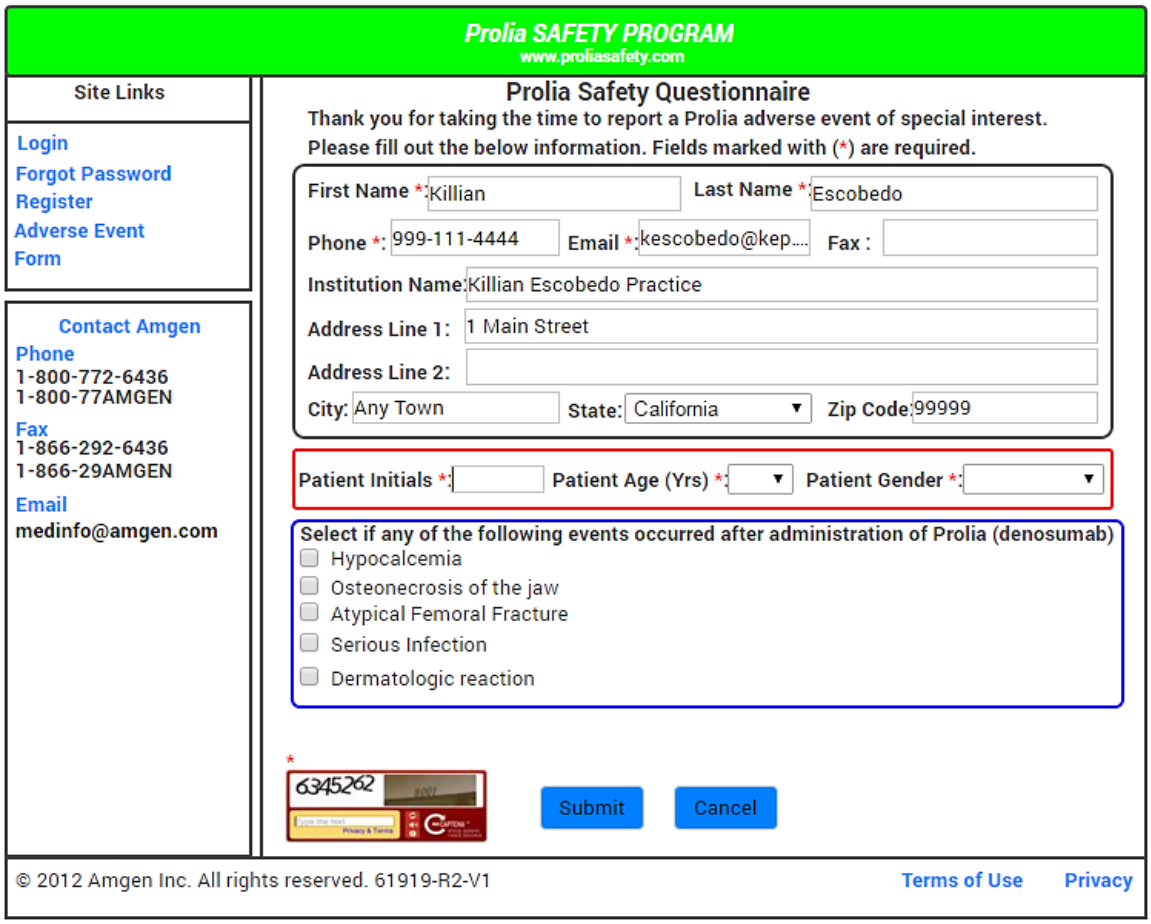
Appendix F. Electronic Medical Record Task List



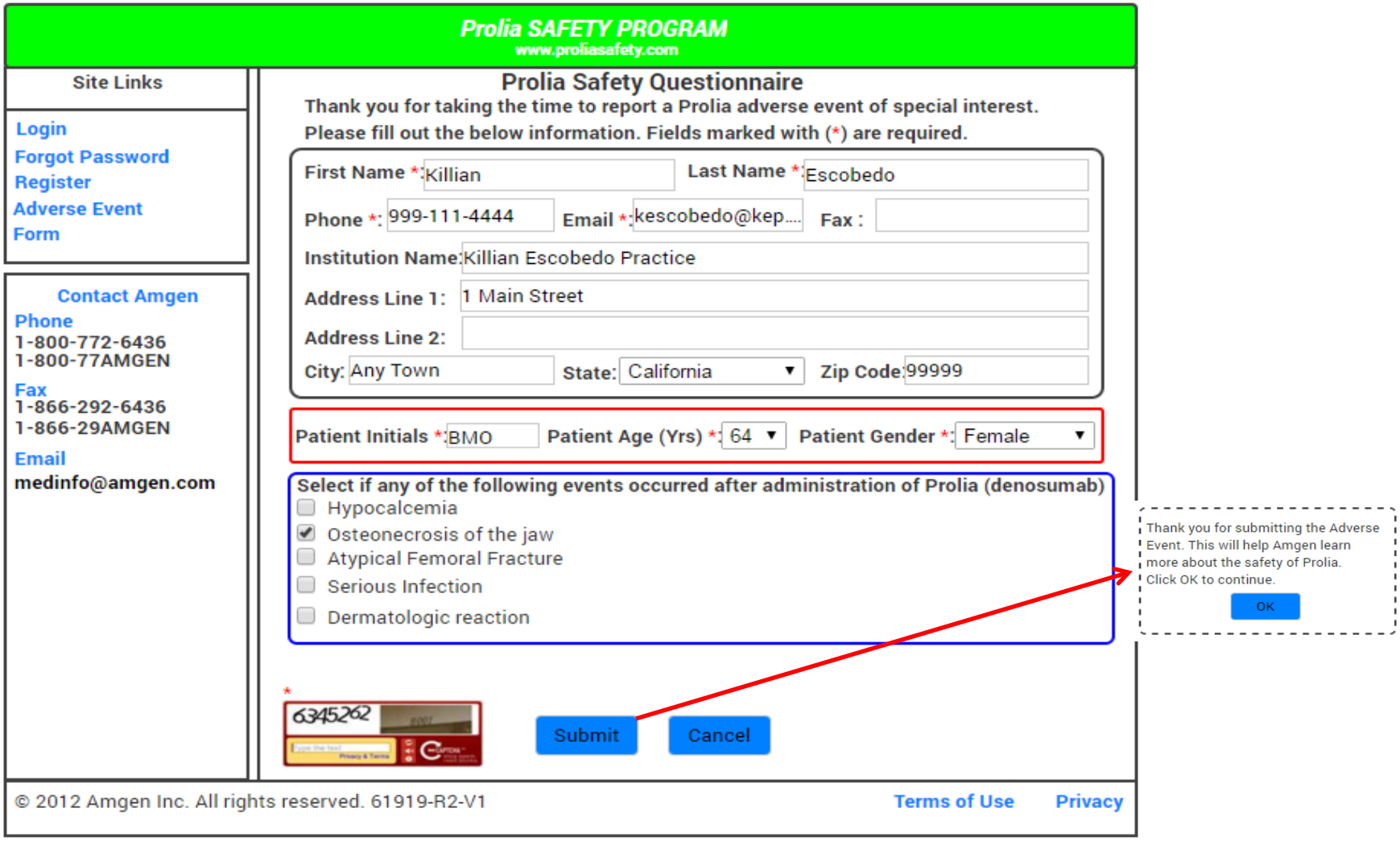
Appendix G Amgen Website Landing Page



Appendix H. Adverse Events of Special Interest-specific Questionnaire



Appendix I. Completed Adverse Event of Special Interest Reporting



Amendment 2

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

Amgen Product: Prolia® (denosumab) Program Number: 20090601

Amendment Date: 23 June 2016

Rationale:

The protocol is being amended to address the proposed modifications to the Prolia Postmarketing Active Surveillance Program (PASP), Program 20090601, as agreed to with the Food and Drug Administration (FDA) at the Type B meeting held on 22 February 2016 (FDA Meeting Minutes 15 March 2016, Reference ID: 3902154). The changes reflect the following key program modifications:

- The addition of a new electronic method of collecting Prolia adverse events of special interest (AESI) information using an electronic medical record (EMR) system based on Practice Fusion technology.
- The formal addition of a new target population to Program 20090601 covering the "indication for the treatment to increase bone mass in men with osteoporosis at high risk of fracture" (Supplemental Biologics License Application 125320/51, 20 September 2012). This amendment also removes 2 indications added to this protocol in Amendment 1 (18 Jan 2012, SN 0861), but which were not required by the FDA:
  - Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and
  - Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
- As agreed to with the FDA at the 22 February 2016 Type B Meeting, this amendment aligns the safety risks evaluated under Program 20090601 with the risks presented in the Risk Evaluation and Mitigation Strategy (REMS) Message Map. Specifically, the following 4 AESI have been removed from Program 20090601: fracture healing complications, acute pancreatitis leading to hospitalization or emergency room (ER) visit, hypersensitivity leading to hospitalization or ER visit, new primary malignancy (not including nonmelanoma skin cancer).
- Administration, typographical and formatting changes were made throughout the protocol.

Description of Changes:

Section: Title Page

Replace:

Product: Prolia® (denosumab)

With:

Product: Prolia® (denosumab) **20090601**

Section: Title Page

Replace:

Key Sponsor Contact:

John Spencer

With:

Susan Yue, Clinical Scientist

Section: Title Page

Add:

Date: **09 October 2009**

Section: Title Page

Replace:

Amendment No:

With:

Amendment **1 date:** 28 September 2011

Amendment 2 date: **23 June 2016**

Section: Program Synopsis

Replace:

Executive Summary

With:

Program Synopsis

Section: Program Synopsis, Indications

Replace:

Indications:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer and treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

With:

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

Section: Program Synopsis, Primary Objective of the Program

Replace:

To monitor the long-term safety of Prolia® and enhance the quality of data collection by proactively soliciting adverse event reporting of the 9 pre-specified Adverse Events of Special Interest (AESI) from United States (US) prescribers of Prolia® for an approved indication.

With:

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** 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)**.

Section: Program Synopsis, Background

Add:

Background: Practice Fusion-Electronic Medical Record (PF-EMR): The PF-EMR database consists of medical information collected through the Practice Fusion (PF) cloud-based ambulatory EMR platform. A majority of PF 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.

Section: Program Synopsis, Program Design

Add:

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.

Replace:

The program consists of elements to stimulate reporting of AESI and is intended to complement routine reporting systems. Prolia® prescribers in the US will be invited, through active communication activities, to participate in the voluntary Postmarketing Active Safety Surveillance Program (Appendix A). The program will proactively solicit adverse event reports for 9 pre-specified AESI occurring in patients receiving Prolia®.

Potential Prolia® prescribers will be made aware of the program through multiple activities including direct mailings, e-mail, materials from Amgen sales representatives, program references in the Product Prescribing Information, a link to the program website from the Amgen Prolia® Healthcare Provider (HCP) website, and US professional meetings and congresses. These communications will provide instructions on the program and will request Prolia® prescribers to register either online, by mail, by telephone, or by fax. Registration is requested in order to provide a secure mechanism for collection of adverse event information and to facilitate program-related correspondence and event follow-up.

Prolia® prescribers and their delegates (eg, licensed RNs, NPs, or PAs) are requested, as part of their routine medical practice, to ask their Prolia®-treated patients about the occurrence of an AESI since their last Prolia® injection. If an AESI has occurred, prescribers and their delegates are asked to report these events to Amgen via a secure website, a paper-based questionnaire, or telephone. The program questionnaires consist of an AESI-soliciting questionnaire (Appendix E) and an AESI-specific questionnaire (Appendix D and Appendix G). The paper-based initial solicitation questionnaire will be made available to potential Prolia® prescribers and their delegates by mail, Amgen sales representatives, and by downloading it from the program website. This soliciting questionnaire should be sent to Amgen upon completion. If a Prolia® prescriber or delegate reports an AESI utilizing the initial soliciting questionnaire, they will be provided with the AESI-specific questionnaire for completion to collect additional supporting information relevant to the AESI.

These solicited AESI will be integrated into Amgen's routine processes for serious adverse event collection, follow-up, evaluation, and reporting. Reported AESI cases will be processed at Amgen and reported to regulatory agencies worldwide in accordance with applicable FDA and local country adverse event reporting regulations. Descriptive statistics will be used to summarize AESI data that will be provided semi-annually for the first 3 years of the program and annually thereafter. In addition, AESI collected in this program will be included, along with all AESI collected globally, as part of the PSUR and reported to regulatory authorities worldwide according to the PSUR schedule.

With:

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 PF-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 any PF 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 PF-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 PF-EMR-soliciting prompt requires a HCP response to remove the action item from his or her current workflow or or add a reminder in the EMR task list.**
- **If the PF-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 annually to the FDA.**

Section: Program Synopsis, Targeted HCPs:

Replace:

Implementation and communication activities will target US physicians who have been identified as likely Prolia® prescribers and inform them of the opportunity to participate in the program. All Prolia® prescribers in the US are eligible to participate. Communication activities will be updated throughout the duration of the program that includes new indications to identify and educate new Prolia® prescribers about the program as appropriate.

With:

United States physicians and their delegates who use the cloud-based PF-EMR platform at the point of care when providing health care to Prolia-treated patients.

Section: Program Synopsis, Program Reporting Eligibility

Delete:

~~Program Reporting Eligibility: Prolia® prescribers or their delegates (e.g. licensed RNs, NPs, or PAs) may complete the program questionnaire for any patient who has received Prolia® and who subsequently develops an AESI.~~

Section: Program Synopsis, Program Duration

Replace:

The program will continue for approximately 10 years after Prolia® is available to prescribers in the US.

With:

The program completion date is December 2021 and the final report will be submitted in June 2022 (per the terms of FDA postmarketing requirement [PMR] #2957-2).

Section: Program Synopsis, Program Reminders

Delete:

~~Program Reminders: Program reminders will be sent to registered Prolia® prescribers and their delegates approximately every 3 months for the duration of the program.~~

Section: Program Synopsis, Data Processing

Replace:

Amgen will be responsible for intake, processing, reviewing, and regulatory reporting according to Amgen SOPs for all program adverse event reports. As necessary, an inquiry will be sent 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 (AER number) to facilitate processing and reporting of information.

All AESI reports that come in through the Program will be considered solicited events.

Amgen will meet regulatory reporting requirements; therefore, HCPs do not need to send a duplicate report to FDA for the AESI reported to Amgen via the soliciting questionnaire in this program.

With:

Amgen will be responsible for intake, processing, reviewing, and regulatory reporting according to Amgen **Standard Operating Procedures** for all **AESI** reports. **All PF 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 PF-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.

Section: Program Synopsis, Statistical Analysis

Replace

Data Analysis and Assessment Considerations for the Program: Descriptive statistics will be used to summarize AESI data that will be provided semi-annually for the first 3 years of the program and annually thereafter. The analysis will include semi-annual (for the first 3 years) or annual (after 3 years) data summaries from the current reporting period as well as cumulative data. Reports of ONJ and atypical fractures will be adjudicated by an external expert panel. The following analyses will be provided: total number of HCPs who registered for the active surveillance program; total number and time trend of each solicited pre-specified AESI; and total number of adjudicated ONJ and atypical fracture events.

With:

Descriptive statistics will be used to summarize AESI data that will be **collected within the PF-EMR and from solicited AESIs reported through the secure Amgen website. The results of the program will be reported on an annual basis to the FDA.** The analysis will include annual data summaries from the current reporting period as well as cumulative data. **The following key analyses will be provided by PF: number of Prolia-treated patients in the PF-EMR and number of AESIs reported to Amgen through PF-EMR-soliciting questionnaire. The report analyses and format will be similar to the annual reports previously submitted.**

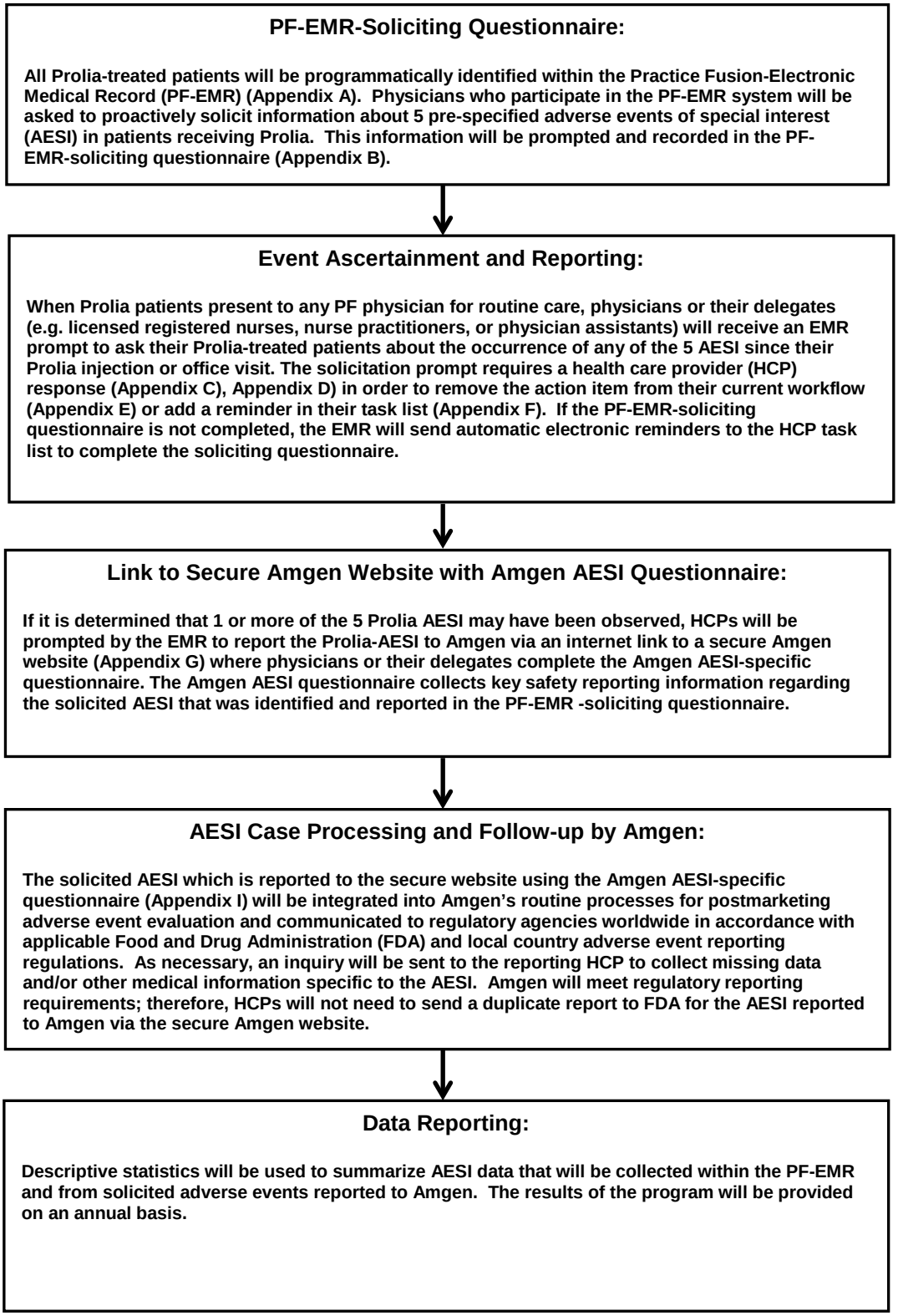
A program design flowchart is present in Figure 1.

Section: Figure 1. Program Design **Flowchart**

Replace Figure 1-1. Program Design Schema (figure contents)

With:

Figure 1. Program Design Flowchart



Section: Program Glossary

Update:

Updated List of Abbreviations as appropriate

Section: 1. OBJECTIVES

Replace:

To monitor the long-term safety of Prolia® and enhance the quality of data collection by proactively soliciting adverse event reporting of 9 pre-specified adverse events of special interest (AESI) from United States (US) prescribers of Prolia® in approved indications**.**

With:

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**.

Section: 2. BACKGROUND AND RATIONALE

Replace:

Prolia® (denosumab) is a fully human IgG_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 6 years. Amgen has committed to assess the occurrence of the following pre-specified AESI in the Postmarketing setting:

- Hypocalcemia leading to hospitalization or emergency room (ER) visit;
- Infection leading to hospitalization, ER visit, or administration of intravenous anti-infective medication;
- Dermatologic events leading to hospitalization or ER visit;

- Osteonecrosis of the jaw (ONJ);
- Atypical fracture;
- Fracture healing complications;
- Acute pancreatitis leading to hospitalization or ER visit;
- Hypersensitivity leading to hospitalization or ER visit;
- New primary malignancy (not including non-melanoma skin cancer)

With:

Prolia® (denosumab) is a fully human **immunoglobulin** ~~Ig~~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** ~~6~~ 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** fractures **(AFF)**
- **Serious i**nfectio**ns**
- Dermatologic **reactions**

Add:

Practice Fusion-Electronic Medical Record (PF-EMR): The PF-EMR database consists of medical information collected through the Practice Fusion (PF) cloud-based ambulatory EMR platform. A majority of PF 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.

Section: 3.1 Program Design

Replace:

The program consists of elements to stimulate reporting of AESI and is intended to complement routine reporting systems. Prolia® prescribers in the US will be invited, through active communication activities, to participate in the voluntary Prolia® Postmarketing Active Safety Surveillance Program. Prolia® prescribers may register either online, via mail, by telephone, or by fax. Prescribers can also authorize up to 5 delegate, non-prescriber healthcare providers to perform program related tasks including reporting AESIs. Delegates will register separately, must have an active state healthcare professional license (eg, registered nurse) and will receive all program communications and training materials. The program will proactively solicit reports on 9 pre-specified AESI occurring in patients receiving Prolia®. Data collection will include an AESI soliciting questionnaire (Appendix E) and AESI-specific questionnaires (Appendix F and Appendix G). Prolia® prescribers and their delegates are requested to, as part of their routine medical practice, solicit feedback regarding AESI from their Prolia®-treated patients. When the Prolia® prescriber or delegate reports an AESI in the soliciting questionnaire, they will be directed to complete the AESI-specific questionnaire to collect additional supporting information relevant to the AESI.

With:

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. T**he program will proactively solicit information from HCPs who participate in the PF–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 any PF 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 PF-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 PF-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 PF-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 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 PASP-EMR program and through the routine reporting system will be summarized and reported annually to the FDA. The program design flowchart is presented in Figure 1 and the program design schema is presented in Figure 2.

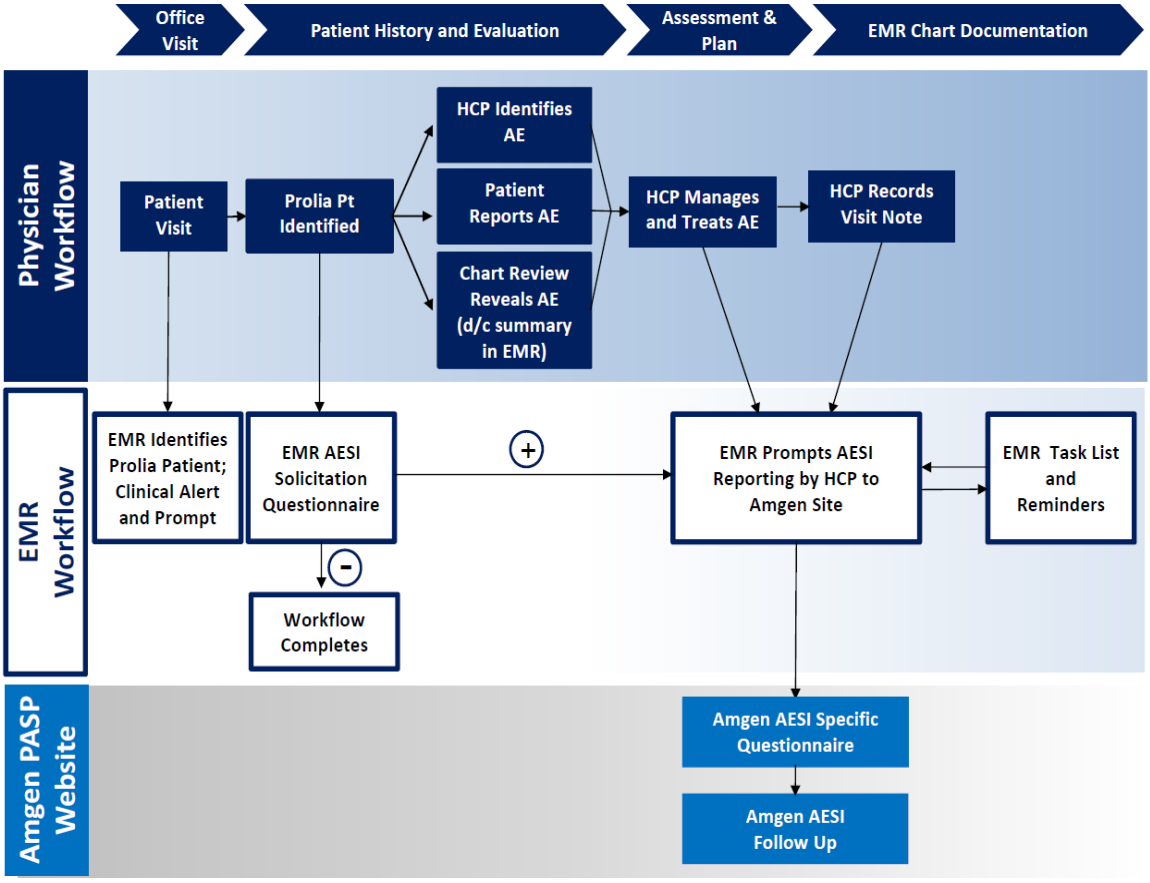
Data collection will include the following elements:

- **PF-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).**

Section: Figure 2. Program Design Schema

Add:

Figure 2. Program Design Schema



Abbreviations: AESI = adverse events of special interest; EMR = electronic medical record; HCP = health care provider; PASP = Postmarketing Active Safety Surveillance Program; Pt = patient.

Section: 3.2 Program Targeted HCPs

Replace:

Prescribers of Prolia® for approved indications will be made aware of the program through activities including, but not limited to, the following:

- Direct mailings and/or email to identified likely prescribers,
- Program materials provided by Amgen sales representatives,
- Program references in the Product Prescribing Information,
- A link to the program website from the Prolia® HCP website, and
- Program materials available at relevant US professional meetings and congresses.

These communications (Appendix A) will provide information on the Program and instructions on how to register either online or via mail or fax.

All Prolia® prescribers are eligible to participate. However, communication activities will target US physicians who have been identified as likely Prolia® prescribers and inform them of the opportunity to participate in the Program. HCPs will be targeted based on the likelihood of seeing patients with the conditions for which Prolia® is approved (eg, Internal Medicine, Oncologists, etc). Amgen will conduct an annual Prolia® Postmarketing Active Safety Surveillance Program awareness survey (Appendix H) to assess awareness of the Program among prescribers of Prolia®. Communication activities will be updated throughout the duration of the Program to identify new Prolia® prescribers and educate them about the Program as appropriate.

With:

Targeted HCPs will include US physicians and their delegates who use the cloud-based PF-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.

Section: 3.3 Program Reporting Eligibility

Replace:

Any Prolia® prescriber may complete an AESI soliciting questionnaire for any patient who has received Prolia® for an approved indication. Reports for patients who have not

yet received Prolia® are not eligible. HCPs 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. All AESI reports that come in through the Program will be considered solicited events.

With:

Any **physician or their delegate using the PF-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 AEs other than an AESI will be instructed to complete a MedWatch form and report it to Amgen or directly to the FDA.

Section: 3.4 Estimated Program Duration

Replace:

This program will last for approximately 10 years after Prolia® is available to US prescribers. Prescribers or their delegates may be contacted for follow-up, as appropriate, regarding individual AESI cases they have reported for detailed medical information and outcome.

With:

Per the terms of FDA postmarketing requirement (PMR) #2957-2 (Biologics License Application 125320/0 Approval Letter, 01 June 2010), the program completion date is December 2021 and the final report will be submitted in June 2022.

Section: 3.5 Definition of Adverse Events of Special Interest

Replace:

Hypocalcemic event leading to hospitalization or ER visit: 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.

Infectious event leading to hospitalization, ER visit, or administration of intravenous anti-infective medication:

Dermatologic events leading to hospitalization or ER visit:

Osteonecrosis of the jaw (ONJ): ONJ is defined as an area of exposed alveolar or palatal bone (eg, jaw or palate), associated with nonhealing after 8 weeks of appropriate care in a patient without prior history of radiation to the head, face, or mouth. This working definition has been adopted by the American Association of Oral and Maxillofacial Surgeons with regard to ONJ after bisphosphonate exposure. [9]

Atypical fracture: Atypical fractures are those occurring in the subtrochanteric (distal to the lesser trochanter) and diaphyseal (just proximal to the supracondylar region) femoral shaft with minimal or no trauma. They are usually transverse, but may have a short, oblique configuration (not described as spiral) and may be associated with a medial spike (beaking), cortical thickening, and prodromal symptoms, such as thigh pain. [5,6,10]

Fracture healing complications: Conceptually, a fracture healing complication is defined by a delay in the expected healing time. However, the expected healing time varies with the fracture site, fracture characteristics, and type of treatment.[1,3,7] The most clinically significant outcome related to delayed fracture healing is nonunion, which generally requires revision surgery. Reporting physicians will use their individual judgment to define what constitutes a fracture healing complication for each individual patient and fracture because no single definition is applicable.

Acute pancreatitis leading to hospitalization or ER visit: This is defined as any event of acute pancreatitis that is the primary reason for hospitalization or an ER visit.

New primary malignancy (not including basal skin cancer or benign neoplasms): A new primary malignancy is defined as any malignancy that is not a recurrence of a previous malignancy and is not a metastasis of an existing malignancy. New primary malignancies should be classified by the site of origin and cellular morphology

(eg, adenocarcinoma of the lung) and not by the location of a metastasis. Basal cell carcinomas of the skin and benign neoplasms are excluded. [4]

Hypersensitivity leading to hospitalization or ER visit: This is defined as any event of hypersensitivity that is the primary reason for hospitalization or an ER visit. Hypersensitivity reactions likely to lead to hospitalization or an ER visit include anaphylaxis and angioedema.[8]

With:

Hypocalcemi**a**: 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 has occurred 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 fracture: **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 infectio**ns:** 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)**

Section: 4.1 Registration

Delete:

~~Registration~~

~~The purpose of the registration process is to provide a secure mechanism to collect adverse event information and to obtain appropriate identification information for the reporter in order to facilitate program-related correspondence and event follow-up. Prescribers are encouraged to register for the Program either through the Program website, by mail, by telephone, or by fax as soon as they plan to prescribe Prolia® for an approved indication. Registration can occur before the prescriber or their delegates have any AESI reported by their patients who are receiving Prolia®. Registration in the Program is not required to report AESI.~~

~~The web-based registration is a simple procedure and includes an online training module for the program. Prescribers and up to two of their delegates may receive appropriate compensation for their time to complete the training module. Amgen reserves the right to discontinue the provision of compensation for training at its discretion.~~

~~The paper-based registration (Appendix D) is by mail or fax and may be completed before or at the time of completing the Program AESI soliciting questionnaire (Appendix E).~~

Section: 4.1 Solicitation of Pre-defined Adverse Events of Special Interest

Replace:

Prolia® prescribers or their delegates 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 last Prolia® injection. If one or more AESI have occurred, prescribers or their delegates are asked to report these events to Amgen utilizing the Program AESI solicitation questionnaire (Appendix E). Prescribers or their delegates can report AESI via the Program website or paper-based questionnaire. Prescribers or their delegates may also report adverse events, including AESI, using FDA's MedWatch program or by contacting Amgen Medical Information.

With:

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 last Prolia injection **or office visit**. If 1 or more AESI have occurred, **HCPs will be asked to identify these events in the PF-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 PF-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 events (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 AEs/SAEs 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.**

Section: 4.2 Program Data-Collection Procedures

Replace:

Prescribers or their delegates may report AESI utilizing the Program via any of the following mechanisms:

- Online at www.proliasafety.com, the Program website
- By mailing or faxing in the Program AESI Solicitation Questionnaire
- By telephone to Amgen at 1-800-77-Amgen

The program AESI soliciting questionnaire (Appendix E) and AESI-specific follow-up questionnaires (Appendix F and Appendix G) will collect basic demographic information, presentation and details of the specific AESI, treatment, outcome, and risk factors for the AESI. The information requested on the questionnaires will be the same in both the paper and electronic versions.

With:

The PF-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.

Section: 4.3.1 On Line Reporting

Delete:

~~Prescribers and their delegates who have registered with the Program will be instructed to complete and submit the Program AESI soliciting questionnaire as well as the applicable AESI-specific follow-up questionnaire at the same time. Program participants will be encouraged to report AESI using the electronic reporting system.~~

~~AESI reported through the Program website will follow Amgen standard processing procedures for adverse events, including data entry into Amgen's safety system and follow-up for additional information regarding the event.~~

Section: 4.3.2 Paper Reporting

Delete:

~~Paper Reporting~~

~~Prescribers or their delegates without access to the internet or who prefer to submit reports via paper may mail or fax completed questionnaires to Amgen. The AESI solicitation questionnaire (Appendix E) can be obtained:~~

1. By downloading and printing a copy of the form from the Program website (~~www.proliasafety.com~~)
2. From the Amgen mailed program materials
3. From an Amgen sales representative

~~Once completed, the questionnaire should be mailed or faxed to Amgen.~~

~~Upon receipt of the completed Program AESI soliciting questionnaire, the information will be processed per Amgen standard practices including data entry into Amgen's safety. The applicable AESI-specific questionnaire (Appendix F and Appendix G), will be sent to the reporting HCP for completion. Once completed, the reporting HCP will mail or fax the AESI-specific follow-up questionnaire to Amgen.~~

Section: 4.3.3 Telephone Reporting

Delete:

~~Telephone Reporting~~

~~HCPs may also report adverse events, including AESI, by phone at 1-800-772-6436. When prescribers or their delegates contact Amgen by phone to report an AESI, the information required to complete the Program AESI soliciting questionnaire as well as the applicable AESI-specific follow-up questionnaire will be collected by call center staff and entered into the appropriate Amgen system.~~

~~AESI reported via telephone will follow Amgen standard processing procedures for adverse events, including data entry into Amgen's safety system and follow-up for additional information regarding the event.~~

Section: 4.4 Follow-up Procedures

Delete:

~~Follow-up Procedures~~

~~Amgen will attempt any necessary follow-up to collect missing information and/or additional medical information, (e.g., x-ray and laboratory results and AESI outcome). Follow-up procedures will be conducted according to Amgen adverse event reporting follow-up SOPs.~~

Section: 4.5 Program Reminders

Delete:

~~Program Reminders~~

~~Program reminders will be sent by Amgen to registered Program participants approximately every 3 months for the duration of the program. For registrants whose e-mail addresses have been provided to Amgen, the reminders may be provided by e-mail. For registrants whose e-mail addresses are not provided to Amgen, a reminder will be sent via mail (Appendix B) or fax.~~

Section: 5.1 Data Processing at Practice Fusion

Replace:

Data Processing

Amgen will be responsible for the intake, processing, reviewing, and reporting of all pre-specified AESI according to Amgen SOPs for adverse event reporting. Each AESI will be assigned an AER number to facilitate processing and reporting of information. If necessary, an inquiry will be sent to the reporting HCP to collect missing data and/or other medical information specific to the AESI.

With:

Data Processing at **Practice Fusion**

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), PF will make available to Amgen only aggregate and de-identified data from the EMR. The completion rates for PF-EMR-soliciting questionnaires and the physician responses to the questionnaire will be collected and will be reported via summary tables on a pre-specified basis for annual reporting purposes. Aggregated data from Prolia patients from PF-EMR will be analyzed annually to provide descriptive information of patient characteristics, distributions, and AESI information. Aggregate reports may be generated more frequently to determine the effectiveness of the active solicitation of AESI through the PASP-EMR program, as appropriate.

Section: 5.2 Data Processing at Amgen

Added:

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. As necessary, an inquiry will be sent to the reporting HCP to collect missing data and/or other medical information specific to the AESI.

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.

Section: 5.3 Data Recording

Replace:

The data collected from the program will be entered into the Amgen Safety Database in order to fulfill reporting obligations for these AESI. AESIs reported by HCPs to Amgen via routine spontaneous reports using a MedWatch form will be processed as spontaneous cases. Follow-up for spontaneously reported AESI will request the same information contained in AESI-specific questionnaire as appropriate.

With:

The data collected from the **secure Amgen website with the Amgen AESI-specific questionnaire** will be entered **through** the Amgen Safety Database **using a tracking number** in order to fulfill reporting obligations for these AESI. **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.

Events of ONJ and AFF reported to Amgen will be confirmed by an internal medical review at Amgen.

Section: 5.4.1 Individual AESI Case Reporting

Replace:

Each AESI collected during the program will be reported to regulatory agencies worldwide as required according to the timeline specified in local country regulations for reported adverse events. Furthermore, all reports of ONJ and atypical fracture collected through Program channels will be reported to the FDA in expedited status throughout the duration of the Program (~10 years) regardless of whether or not these 2 events are in the Prolia® local label or the report meets routine criteria for seriousness. A line-listing of AESI will also be included as an attachment to the PSUR that is submitted to FDA and/or other regulatory agencies worldwide.

With:

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**.

Section: 5.4.2 Aggregate Data Assessment

Replace:

AESI collected through the program and AESI reported in the US through routine reporting systems (eg, FDA's MedWatch system) will be summarized in aggregate and provided to the FDA semi-annually for the first 3 years of the program and annually thereafter. In addition, AESI collected in this program will be included, along with those collected globally, in the PSUR and reported to regulatory authorities worldwide according to the PSUR schedule for approximately 10 years after Prolia® is first made available to US prescribers.

With:

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

Section: 6 Statistical Analysis

Replace:

Descriptive statistics will be used to summarize the program data. The following analyses will be conducted for each scheduled program report for approximately 10 years after Prolia® is approved in the US.

- Total number of Prescribers and delegates who have registered for the Program through the Program website, mail, telephone, or fax
- Total number of each solicited, pre-specified AESI
- Total number AESIs reported via the program
- Time trend for each solicited, pre-specified AESI measured by the number of each specific AESI over the years of the program period
- Number and proportion of specific sub-types of AESI (eg, malignancies) among a specific AESI
- Total number of adjudicated ONJ and atypical fractures

The analysis will include data from the current reporting period as well as cumulative data. ONJ and atypical fractures will be adjudicated by an external expert panel. Please refer to the statistical analysis plan (Appendix l) for further details.

With:

Descriptive statistics will be used to summarize the program data. The following analyses will be conducted **annually**.

Practice Fusion EMR:

- **Number of Prolia-treated patients in the PF-EMR**
- **Number of Prolia-treated patients with at least 1 PF-EMR-soliciting questionnaire presented**
- **Number and percentage of Prolia-treated patients with at least 1 PF-EMR-soliciting questionnaire completed (at least 1 AESI box, or NO AESI, is checked)**
- **Number and percentage of Prolia-treated patients with at least 1 AESI reported through PF-EMR-soliciting questionnaire**
- **Number of AESIs reported through PF-EMR-soliciting questionnaire**

Amgen AESI-Specific Questionnaire Via Secure Website:

- **Number of AESIs reported through the secure Amgen website via the link from the PF-EMR**
- **Number of potential ONJ and AFF events**
- **Number of events adjudicated as consistent with the definitions of ONJ and AFF**

The analysis will include data from the current reporting period as well as cumulative data **over the entire PASP-EMR program.**

Descriptive statistics will be used to summarize AESI data that will be collected within the PF-EMR and from solicited adverse events reported through the secure Amgen website. All PF-patient data will be analyzed and treated according to HIPAA. The results of the PASP-EMR program will be provided on an annual basis. The report analyses and format will be similar to the annual reports previously submitted.

Section: 7.1 Subject Confidentiality

Replace:

Collection of data in this program to stimulate and solicit the reporting of adverse events 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 Health Insurance Portability and Accountability Act (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.

Because this program fundamentally stimulates routine adverse event reporting by prescribers in the course of their medical practice, the program should not require IRB approval and patient informed consent.

With:

Collection of data in this program to stimulate and solicit the reporting of **AESIs** 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.

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.

Section: 7.2 Program Notifications

Replace:

Program Updates

Any updates to the program, including questionnaires, will be documented as appropriate.

With:

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 PF-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 PF-EMR may also present educational materials from the Prolia REMS website (http://www.proliahcp.com/risk-evaluation-mitigation-strategy/), including the Prolia REMS Patient Counseling Chart and Patient Brochure.

Section: 8 References

Updated References as appropriate.

Section: Appendix A

Replace:

Sample Introductory Letter/Postcard to Healthcare Prescriber

With:

Clinical Decision Support Notification

Section: Appendix B

Replace:

Sample Program Reminder E-mail/Postcard

With:

Adverse Events of Special Interest Soliciting Questionnaire

Section: Appendix C

Replace:

Sample Patient Chart Reminder

With:

Positive Response

Section: Appendix D

Replace:

Sample Program Registration Form

With:

Negative Response

Section: Appendix E

Replace:

AESI Soliciting Questionnaire

With:

End of Point of Care Work Flow

Section: Appendix F

Replace:

AESI-Specific Questionnaires

With:

Electronic Medical Record Task List

Section: Appendix G

Replace:

Malignancy-specific Questionnaires

With:

Amgen Website Landing Page

Section: Appendix H

Replace:

Sample Prolia® Postmarketing Active Safety Surveillance Program Awareness Survey

With:

Adverse Events of Special Interest-Specific Questionnaire

Section: Appendix I

Replace:

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

With:

Completed Adverse Event of Special Interest Reporting