PASS Information

Title	European Drug Usage Survey for Amyvid (I6E-MC-AVBF) [Protocol for an observational study to assess the usage pattern of Amyvid in the European Union]
Version identifier	1.0
Date of last version	Approval date can be found at the bottom of the page
EU PAS Register No:	ENCEPP/SDPP/6736
Active substance	florbetapir (^{18}F) V09AX05 Diagnostic Radiopharmaceuticals
Medicinal product(s):	Amyvid 800 MBq/mL solution for injection Amyvid 1900 MBq/mL solution for injection
Product reference:	EU/1/12/805/001-004
Procedure number:	EMEA/H/C/002422
Marketing authorisation holder(s)	Eli Lilly Nederland B.V. Grootslag 1-5 NL-3991 RA Houten The Netherlands
Joint PASS	No
Research question and objectives	To determine which types of patient are undergoing Amyvid PET scans. In particular to establish the usage patterns of Amyvid in European clinical practice and assess extent to which Amyvid is being used in off-label indications.
Country(-ies) of study	To be determined in part based on countries where Amyvid has become commercially available. Commercial availability has occurred in the United Kingdom and is projected to occur in Spain and Italy by the end of 2014.
Author	Claudia A. Salinas, PhD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S Delaware Street Indianapolis, IN 46225 United States Telephone: +1 317 433 9188 Charlotte Relf Principal, Brand Performance Management IMS Health® 210 Pentonville Road London N1 9JY United Kingdom Telephone: +44 (0)20 3075 5300

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V. Grootslag 1-5 NL-3991 RA Houten The Netherlands

1. Table of Contents

Section **Page**

List of Tables

List of Figures

List of Annexes

2. List of Abbreviations

Term	Definition
ABPI	The Association of the British Pharmaceutical Industry
AD	Alzheimer's Disease
ADR	Adverse Drug Reaction
AE	Adverse Event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
BHBIA	British Healthcare Business Intelligence Association
ERB	Ethical Review Board
EU	European Union
CAWI	Computer-Assisted Web Interview
CATI	Computer-Assisted Telephone Interview
CHMP	Committee for Medicinal Products for Human Use
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Market Research Association
ESOMAR	European Society for Opinion and Marketing Research
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professional
ICC	International Chamber of Commerce
IMS	IMS Health
MRS	Market Research Society
PET	Positron Emission Tomography
PS	Prescriber Survey
PSUR	Periodic Safety Update Report
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

STROBE	Strengthening The Reporting of Observational Studies in Epidemiology
UK	United Kingdom

3. Responsible Parties

Sponsor: Eli Lilly and Company

Project team:

Company Global Patient Safety Epidemiologist

Claudia A. Salinas, PhD
Global Patient Safety Epidemiologist
Eli Lilly and Company
893 S. Delaware Street
Indianapolis, IN 46225
United States
Telephone: +1 317 433 9188

Company Global Medical Director:

Mark Mintun, MD
Chief Medical Officer
Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Company
3711 Market Street, 7th Floor
Philadelphia, PA 19104
United States
Telephone: +1 215 298 0700

Company Qualified Person for Pharmacovigilance:

Valerie Simmons, MB BS FFPM
Eli Lilly and Company
Erl Wood Manor
Sunninghill Road
Windlesham, Surrey GU20 6PH
United Kingdom
Telephone: +44 1276 483320

Subcontractor: IMS

Charlotte Relf
Principal, Brand Performance Management
IMS Health
210 Pentonville Road
London N1 9JY
United Kingdom
Telephone: +44 (0)20 3075 5300

4. Abstract

Title: European Drug Usage Survey for Amyvid (I6E-MC-AVBF).

Version: 1.0. **Date:** See date stamped on cover page.

Rationale and background: Amyvid® (florbetapir ^{18}F) is a radiopharmaceutical indicated for positron-emission-tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. Physicians caring for such patients may be unfamiliar with amyloid imaging. While the Summary of Product Characteristics (SmPC) will provide clear guidance on the indication and limitations of Amyvid, it is important to gain a better understanding of the actual use of Amyvid PET scans in the everyday clinical setting.

In October 2012, Amyvid received a recommendation for marketing authorisation by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). This recommendation included a request from the CHMP for Eli Lilly and Company (Lilly) to evaluate usage patterns of Amyvid in routine clinical practice in Europe.

Research question and objectives: The overall project objective is to determine the characteristics of patients undergoing Amyvid PET scans, and specifically:

- To assess the usage patterns of Amyvid in European clinical practice;
- To assess the level of off-label use in European clinical practice

Study design: The study is a Prescriber Survey (PS). It is a cross-sectional, non-interventional census of physicians who have referred at least 1 patient for an Amyvid PET scan in European countries where the compound is available. Collection of study data will occur via a survey of referring physicians. The survey may be completed as a web-, telephone-, or paper-based questionnaire.

Enrolment of referring physicians will begin 1 year after first commercial availability anywhere in Europe. Countries will be added on a rolling basis as Amyvid becomes commercially available. The study will continue for 2 years or until the total number of referring physicians reaches 100 and the patient reports reach 300. If the study is open for 2 years (equivalent to 3 years after commercial availability) and these targets are not met, the study will continue until a minimum of 30 physicians and 100 patient reports are collected. In either scenario, the study will target enrolment of at least 10 physicians in the 3 major European Union (EU) countries where Amyvid is projected to become commercially available over the study period.

Population: This study will collect information from referring physicians on patients who have been sent for an Amyvid PET scan. Only physicians who have referred at least 1 patient for an Amyvid PET scan will be included in this study.

Information on clinicians likely to refer patients for Amyvid PET scans will be provided by Lilly based on projected use considering, for example, distance from manufacturing sites, association with private clinics or hospitals, etc. Additional information on physicians who may be eligible

for this study may be identified by considering typical referral patterns expected for imaging centres such as those where Amyvid PET scans occur. Information on referring clinics or hospitals and associated physicians may be available through IMS Health's (IMS) database of physicians. This database consists of physicians who have previously agreed to be contacted for surveys and may help identify potential referrers who would be screened for eligibility for this study. All local privacy laws will be observed in the process of identifying potential participants. Only physicians who have agreed to be contacted by IMS for purposes consistent with this survey will be approached.

Due to the limited number of physicians expected to refer patients for Amyvid PET scans, this will be a targeted, rather than a random, census. The generalisability of the study findings to the wider referring clinician population will be taken into consideration by comparing features of physicians who elect to participate with those who do not. Characteristics of physicians who decline to participate will be based on publicly available information or information those physicians have previously shared with IMS.

Variables: The primary goals of this protocol are to describe the pattern of use of Amvyid PET scans by referring physicians and referred patients and to evaluate the level of off-label use. The variables and survey questions for this purpose will be:

For Objective 1: (a) Characteristics of the referring physicians

(b) Characteristics of the patients who are referred.

For Objective 2: Evaluation of off-label use with respect to indication and population.

Descriptive statistics will characterise the pattern of use of Amyvid PET scans, especially with respect to (1) physician specialisation, experience managing patients with cognitive impairment, and understanding of the indication, and (2) patient demographics and disease history.

To be consistent with the label, patients referred for Amyvid PET scans should be adults who have had or will have a clinical evaluation and have evidence for cognitive impairment (either by objective evaluation or reported decline relative to the previous level of performance) and are suspected of currently having AD or other causes of dementia. Use in a population that is not indicated, such as asymptomatic individuals or children, would constitute off-label use.

A summary of variables addressed by the survey questions is presented below.

- **Characteristics of the Referring Physicians**
  Redacted in this version of the protocol.

- **Characteristics of the Referred Patients**
  Redacted in this version of the protocol.

- **Level of off-label use**
  Redacted in this version of the protocol.

Results will be reported by question and by patient. The finalisation of current questions and wording will depend on the result of survey piloting prior to implementation.

Data sources: In this survey, data on routine clinical use of Amyvid will be obtained from participating physicians who complete the survey. Information describing physicians (e.g., specialisation, physician awareness of Amyvid indication, etc.) will be collected at baseline only, whereas information on patients referred for Amyvid PET scans will be collected at 3-month intervals until a physician has provided a maximum of 5 patient reports or elects to stop participating. Only the physician's most recent patients referred for scans will be included, up to the maximum.

Study size: The target population for the study is patients who have been referred for an Amyvid PET scan, however, the number of patients who will be referred for an Amyvid PET scan in the first 3 years following commercial availability of Amyvid is not known. Therefore, clinicians identified as being potential referrers, as provided by Lilly, will be targeted to ascertain whether they have actually referred patients for an Amyvid PET scan.

By the beginning of the second year following commercial availability, Lilly projects that the total number of clinicians in the EU with the potential to refer patients for an Amyvid PET scan will be approximately 200. Although all clinicians identified as being potential referrers will be invited, based on response rates obtained in similar surveys conducted by IMS, only 10% to 33% of physicians will generally agree to participate. Based on these estimates and the assumption that each clinician will refer an average of 5 patients per year, the total number of patient reports that could be collected will range from 100 (assuming a 10% participation) to 330 (33% participation) which will provide a sampling error margin between 10% and 5%. This study will aim to survey 100 referring physicians, but in the event of low participation in the survey or lower than anticipated use, a minimum enrolment target will be set of 10 physicians in the 3 EU countries where Amyvid is projected to become commercially available over the study period, for a total of 30 enrolled physicians.

To increase the possibility that the physicians surveyed remain representative of all physicians who may refer patients for an Amyvid PET scan, recruitment and data collection will only be initiated in a country where the number of scans undertaken reaches 50. A scan will be identified based on an order for Amyvid where each order will equate to 1 scan/patient.

Data analysis: Analyses will focus first on describing the physicians who refer and the patients who undergo Amyvid PET scans in routine clinical practice. Usage patterns with respect to physicians will include specialisation, experience managing patients with cognitive impairment, as well as understanding of Amyvid indications and limitations. With respect to patients, the description will focus on demographic variables (gender, age at the time of the scan, and education), cognitive status at the time of the referral/scan, time since presentation for cognitive complaint that led to the Amyvid referral, and medical management including comorbidities and diagnostic procedures conducted.

Analyses will then focus on determining the level of off-label use by identifying responses that are not consistent with all of the following:

a) a clinical evaluation, that is, not monitoring,

b) of the indicated population, that is, adults with cognitive impairment, measured objectively or as reported by clinical decline relative to previous performance,

c) for AD or other causes of dementia.

Off-label use according to the above will be reported for each relevant question as a proportion of the total responses for that question and for each patient, by number of off-label responses. Further analyses, for example, by physician specialty, may be possible provided the sub-group stratification does not compromise the anonymity of the respondent. Statistical tests may be used to determine the significance of differences, for example, chi-square test. Analysis results by country will be presented in the same report in aggregate and separately, when not limited by small numbers.

Quantitative variables will be reported by standard statistics, that is, numbers, averages, standard deviation, median, minimum, maximum, first and third quartile. Qualitative variables will be described for each modality with associated percentages. Numbers relating to data entered and values missing will also be indicated. Missing values will be excluded from the calculation of percentages. Statistical tests may be used to determine the significance of differences and confidence intervals calculated for the key criteria.

Table 4.1. Study Milestones

Milestone	Planned date
Start of data collection	1 year after commercial availability, 15 December 2014
Interim Summary 1	Update to be included in PSUR, June 2015
Interim Summary 2	Update to be included in PSUR, June 2016
End of data collection	Collection will end after 2 years (3 years from commercial availability), estimated 15 December 2016
Final report of study results	6 months from end of data collection, estimated 31 March 2017 for inclusion in PSUR, June 2017

Abbreviation: PSUR: Periodic Safety Update Report.

5. Amendments and Updates

Not applicable.

6. Milestones

The study milestones are described in the table below (Table 6.1). As agreed during the Committee for Medicinal Products for Human Use (CHMP) review procedure, enrolment of referring clinicians and data collection will commence 1 year after the initial commercial availability of Amyvid (florbetapir ^{18}F) in the European Union (EU) to allow for an adequate number of Amyvid PET scans to be conducted. The number of physicians who are referring patients for Amyvid PET scans may be lowered by delays in reimbursement or radiopharmaceutical access. Interim updates on enrolment results will be included in the Periodic Safety Update Report (PSUR) planned for submission in June 2015 and 2016, along with information on the number of doses ordered in the first year after commercial availability. To provide time for data analysis and reporting, the final report will be provided 6 months from the end of data collection.

Table 6.1. Study Milestones

Milestone	Planned date
Start of data collection	1 year after commercial availability, estimated 15 December 2014
Interim Summary 1	Update to be included in PSUR, June 2015
Interim Summary 2	Update to be included in PSUR, June 2016
End of data collection	Collection will end after 2 years (3 years from commercial availability), estimated 15 December 2016
Final report of study results	6 months from end of data collection, estimated 31 March 2017 for inclusion in PSUR, June 2017

Abbreviation: PSUR: Periodic Safety Update Report.

7. Rationale and Background

7.1. Survey Context

It is estimated that there are currently 800,000 people with dementia in the United Kingdom (UK), 62% of whom are suffering with Alzheimer's disease (AD) (Alzheimer's Society 2013) with the vast majority aged 65 years or older. In Europe, AD affects 5 million people (Ferri et al. 2005). Accurate diagnosis of AD has been limited by a lack of diagnostic tests, with post-mortem biopsy being the main method for confirmation of clinical diagnosis to date.

Amyvid® [florbetapir (^{18}F)] is a diagnostic radiopharmaceutical that binds to β-amyloid neuritic plaques in the grey matter of the brain. β-Amyloid neuritic plaques occur in patients with AD and some other dementias. By binding to the plaques, Amyvid enables them to be imaged via Positron Emission Tomography (PET. A negative scan indicates sparse or no plaques and is not consistent with a diagnosis of AD, while a positive scan indicates moderate-to-frequent density and is consistent with the diagnosis of AD. However, a positive scan does not independently establish a diagnosis of AD or other cognitive disorder since neuritic plaque deposition in grey matter may be present in asymptomatic elderly and some neurodegenerative dementias (Lewy body dementia, Parkinson's disease dementia). For this reason, Amyvid should be used in conjunction with a clinical evaluation.

On 14 January 2013, the European Commission granted a marketing authorisation for Amyvid. The approved indication is for diagnostic use only and a risk management plan will be implemented as part of the marketing authorisation. The efficacy of Amyvid for predicting development of AD or monitoring response to therapy has not been established.

While the Summary of Product Characteristics (SmPC) will provide clear guidance on the indication and limitations of Amyvid, it is important to gain a better understanding of the actual use of Amyvid PET scans in the everyday clinical setting. The CHMP has asked Eli Lilly and Company (Lilly) to evaluate usage patterns of Amyvid in clinical practice. The survey will collect information regarding the context in which Amyvid is being used in order to assess the extent to which referrals fall within the licensed indication and population of adult patients with cognitive impairment being evaluated for AD and other causes of cognitive impairment. Cognitive impairment is defined as a decline in cognition level relative to previous level of performance or as established by a cognitive measurement. Amyvid PET scans for patients who fall outside this indication or population will be considered off-label use. The overall outline of this proposed study has been previously discussed and agreed with the CHMP. (See Annex 1 for Study Synopsis 2 – Evaluation of Amyvid Usage Patterns in Routine Clinical Use.)

7.2. Rationale for Country Selection

The selection of the countries in which the survey is to be conducted is based on:

- the countries where Amyvid will be registered and marketed during the period of the study,

- the extent of active referring physician utilisation of Amyvid in order to find the required sample of referrers and patients in the designated data collection time period.

For the purposes of this protocol, countries selected for this study be those within the European Union (EU). Amyvid is currently available in the UK and is anticipated to become available in Spain and Italy by the end of 2014. Since early adopters of Amyvid PET scans who refer patients in the first 6 months of availability may not adequately reflect the greater population of clinicians who will refer patients in routine clinical practice, only those countries in which at least 50 scans have been provided will be considered for selection. Updates on this threshold will be provided by Lilly, with the number of Amyvid orders serving as an approximate proxy for Amyvid PET scans.

7.3. Rationale for Clinician Selection

This study will evaluate cases from physicians who have referred patients for an Amyvid PET scan. This will be the sole criterion for establishing physician eligibility for the study.

Information on clinicians likely to refer patients for an Amyvid PET scan will be provided by Lilly based on projected use considering, for example, distance from manufacturing site, association with private clinics or hospitals, etc. Additional information on physicians who may be eligible for this study may be identified by considering typical referral patterns expected for imaging centres such as those where Amyvid PET scans occur. Information on expected referring clinics or hospitals and associated physicians may be available through IMS' database of physicians. This database consists of physicians who have previously consented to be included and may facilitate an identification of potential referrers who would be screened for eligibility for this survey. All local privacy laws will be observed in the process of identifying potential participants and only physicians who have agreed to be contacted by IMS for purposes consistent with this survey will be approached.

8. Research Question and Objectives

Amyvid is a member of a new class of diagnostic radiopharmaceuticals for PET imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive impairment. Physicians caring for such patients may be unfamiliar with amyloid imaging. While the SmPC will provide clear guidance on the indication and limitations of Amyvid, it is important to gain a better understanding of the actual use of Amyvid PET scans in the everyday clinical setting.

Thus, the overall goal of the present study shall be to understand the actual use of Amyvid PET scans in the everyday clinical setting in Europe. The specific objectives to be assessed are as follows:

Objective 1: To assess the usage patterns of Amyvid in European clinical practice;

Objective 2: To assess the level of off-label use in European clinical practice.

9. Research Methods

9.1. Study Design

The study is a Prescriber Survey (PS). It is a cross-sectional, non-interventional census that will be conducted among consenting physicians who have referred at least 1 patient for an Amyvid PET scan in European countries where Amyvid is available.

The study will commence recruitment at the end of the first year after commercial availability in the EU and continue for 2 years. Physicians who practice in countries where Amyvid is available during the course of the study will be invited to participate. Enrolled physicians will contribute information on patients they have referred in the preceding 3 months, except the first group of enrolees who will be invited to provide information on patients referred in the prior 6 months. Enrolment and data collection will then continue until at least 100 referring physicians have enrolled and 300 patient reports have been collected. If these targets are not achieved within 2 years, enrolment and data collection will continue until at least 30 physicians (no fewer than 10 referring physicians from each of 3 countries) and at least 100 patient reports have been collected.

To reduce the potential impact of selection bias, participating physicians will be able to choose among telephone-assisted interviews, a web-based questionnaire, or a paper version of the survey to contribute their data. At the time of the physician's enrolment into the protocol, they will answer questions that indicate their knowledge of the Amyvid indication, usage and limitations. Questions from Survey Questionnaire (Annex 3) Sections 1, 2 and 3 will be asked once, with questions from Sections 1 and 2 asked only at baseline, on the first occasion that the physician participates. Questions from Section 4 (that is, "Patient Reports") will invite clinicians to provide information for their most recent patient referrals for Amyvid PET scans. Participating physicians will be encouraged to contribute patient reports on at least a quarterly basis. Only the physician's most recent patients referred for scans will be included, with no more than 5 total patient reports accepted from any physician.

These questions will address the study goal of describing the pattern of Amyvid use in routine practice. Overall, the survey questions will fall into 4 categories addressing:

1. characteristics of referring physicians,
2. characteristics of patients who are referred,
3. time elapsed since product availability (calendar period or date of the scan), and
4. on-/off-label use.

No formal *a priori* hypothesis will be tested in this study. Descriptive statistics will be generated to describe the pattern of use of Amyvid with respect to the physician's practice and specialisation, and experience treating patients with cognitive impairment; the patient's cognitive status, severity of impairment, clinical features related to diagnosis, comorbidities (especially renal/hepatic impairment) and demographic description; and the level of off-label use described by the physician's knowledge of the indication, the patient's age, cognitive status, and suspected diagnosis. These descriptive measures will also be generated by the temporal period of the

Amyvid PET scan in relation to time elapsed since commercial availability, specifically at 1, 2, and 3 years. This will allow an analysis of the evolution of usage patterns over time after commercial availability.

9.2. Setting

This survey will analyse the profile of patients referred for Amyvid PET scans by healthcare providers. The survey will be carried out among referrers for Amyvid PET scans:

- physicians in active clinical practice
- hospital- or office-based,
- who practice in an EU country.

Amyvid use in clinical trials will not be included in this study.

9.2.1. Inclusion criteria

The survey will be carried out among physicians who have referred patients for at least 1 Amyvid PET scan, excluding any referrals to clinical trials involving Amyvid PET scans. Initially this will relate to any referrals, but if a physician participates in a subsequent wave of data collection, this will be limited to referrals taking place since the physician's last participation. This inclusion criterion, the sole one for this study, will be verified through the use of a screening question. Only those physicians passing the initial screening will be invited to participate in the study.

9.3. Variables

The primary goals of this protocol are to describe the pattern of use of Amyvid PET scans by referring physicians and referred patients and to evaluate the level of off-label use. The variables, and corresponding survey questions (See Sections 1 through 4 in Annex 3), that will address these goals will fall into 3 categories:

Objective 1: To assess the usage patterns of Amyvid in European clinical practice

1. Characteristics of the referring physicians,
2. Characteristics of the patients who are referred,

Objective 2: To assess the level of off-label use in European clinical practice

Descriptive statistics will be used to characterise the pattern of use of Amyvid, particularly with respect to (1) the physician setting (specialist versus generalist, type of specialty training, hospital or private practice, experience managing patients with cognitive impairment), (2) patient demographic characteristics (age, gender, comorbidities), and disease history (time since presentation, disease severity, diagnostic procedures performed prior to ordering Amyvid PET) and (3) temporal patterns relating to the elapsed time, that is, 1, 2, or 3 years, since commercial availability.

Off-label use will be defined as use in a population or for an indication that is not consistent with the label. Specifically, adult patients, with cognitive impairment (either by objective evaluation

or by reported decline relative to previous level of performance) must be undergoing evaluation for AD and other causes of cognitive impairment. [redacted]

Cognitive status/cognitive impairment will be assessed as normal cognition, cognitive decline without objective evidence of impairment, mild cognitive impairment, mild, moderate, or severe dementia.

The level of off-label use is the proportion of patient reports with an off-label indication divided by the total number of patient reports.

A summary of variables addressed by the survey questions is presented below.

1. **Characteristics of the Referring Physicians**

   Redacted in this version of the protocol.

2. **Characteristics of the Referred Patients**

   Redacted in this version of the protocol.

3. **Level of off-label use**
   Redacted in this version of the protocol.

9.4. Data Sources

In this survey, data on the pattern of Amyvid use in routine clinical practice will come from participating physicians who complete the survey via web-, post-, or telephone-based methods.

9.5. Study Size

There are 2 considerations for estimating the study size for this protocol: a pragmatic one and a statistical one. Over the study period, Amyvid is expected to reach commercial availability in 3 European countries, beginning with the UK in September 2013, and followed by Spain and Italy 6 or more months later. Since the UK will have commercial availability earlier with more imaging centres for Amyvid PET scans than other countries, we propose to launch the study there. Pragmatically, given expected reimbursement and availability, the UK is projected to potentially have 175 to 350 referring physicians in total ever. Based on 10% to 33% participation and the likelihood that referrals may be slower in the first year, this places a pragmatic bound of, at worst, 18, and, at best, 117, on the maximum possible study size with respect to physicians in one of the larger EU markets.

From a statistical perspective, since there are no *a priori* or other hypotheses for this descriptive study, the chief statistical concern relates to accuracy around a parameter estimate. The first study objective, to describe the pattern of use, may be addressed with information on either patient or physician or, ideally, both. However, the second study objective, to evaluate the level of off-label use, although requiring some information on physicians (e.g., understanding of the indication), relies mostly on patient-level information (see Section 4 in Annex 3.). One consideration is, thus, the number of patient reports required to achieve a satisfactory level of accuracy for a simple binary "Yes/No" question. In other words, we are interested in answering how many patient reports we need to collect to be reasonably confident that the true proportion (ie, the population parameter that we would have obtained had we been able to ask everyone) will lay within the interval we estimate with our smaller study sample. That question can be answered with the following formula:

$$n = \varepsilon^2 \, p \, (1\text{-}p) \, / \, i^2$$

where

ε = value (e.g., 1.96 for 95% confidence level)

p = percentage picking a choice, expressed as decimal (0.5 used for sample size needed).

i = confidence interval/ error margin expressed as decimal, e.g., 0.05 = ±5)

If the expected proportion *p* is not known, usually the value of 0.5 (or 50%) is used because it produces the largest sample size. In general, as the sample size increases, the error due to observing a sample of, rather than the whole of, the population decreases and the accuracy of the sample estimate increases.

So, relying on the default proportion of 50% to provide a conservative estimate for the number of patient reports needed to achieve 5%, 10%, or 15% confidence intervals (or error margins) around the sample estimate, the total number of patient reports, and number of physicians, that will be needed is summarised in Table 9.1.

Table 9.1. Number of Physicians or Patient Reports Corresponding to a Given Error Margin

Error margin	Number of Physicians / Patient reports
5%	385
10%	97
15%	43

Based on these results, an analysis of approximately 100 patients should provide sufficiently narrow confidence intervals, or error margins, for the primary analysis of a binomially distributed variable (that is, the proportion in a simple "Yes/No" question). However, we would expect the off-label use of Amyvid to fall far below 50%. Off-label use is often smaller at the beginning of a drug's market history than it is later when physicians become more familiar with it and, even later, 50% would represent a high proportion of off-label use. Other methods of calculating the sample size may be used to estimate confidence intervals when extreme proportions are expected. Application of the Wilson method suggests that a random sample of 177 patient reports will be needed to estimate a confidence interval with a half-width of 5%. Thus, the sample size required will depend on the proportion of off-label use, but regardless, will lie between the range of sample sizes required to achieve a 5% to 10% margin of error, that is, 100 to 381. A similar rationale may be used to establish the range of referring physicians who must be enrolled in order to achieve these error margins for a primary analysis of off-label use focusing on individual physicians, that is, 100 to 381 referring physicians.

Unfortunately, in the absence of reimbursement, even 100 patients may amount to approximately 30% of the first-year commercial sales within Europe and the upper bound of the range of

physicians that would be required may exceed the total number of physicians in the EU who may prescribe Amyvid® in the first or second year after commercial availability. Clearly, the target study size must take into account both the statistical requirements and the pragmatic limitations. Estimating that there will be 200 referrers by the second year after commercial availability of Amyvid, and assuming that each clinician will refer an average of 5 patients per year, the total number of patient reports that could be collected will range from 100 (assuming 10% participation) to 330 (assuming 33% participation). The total number of referring physicians who may participate by the second year after commercial availability of Amyvid will be considerably lower and would range from 20 (assuming 10% participation) to 66 (33% participation). In the absence of reimbursement it is unlikely that the number of referrers will continue to increase at a constant rate over time. Thus, assuming a conservative doubling of the number of participating physicians over the 2 years of the study, we would expect to enrol and collect data from approximately 40 to 132 referring physicians. Since the projections for anticipated patient reports align with the statistical determinations in Table 9.1, we propose 100 patients as the target sample size (see Figure 9.1 below). Further, since off-label use may represent an intrinsic characteristic of individual referring physicians, we propose an additional requirement of 100 referring physicians, with a minimum of 10 physicians per country to allow adequate representation across the EU. Ideally, at least 100 referring physicians would participate, but there may be pragmatic limits. At 10% participation, a reasonable level for a survey of this nature, 1000 active referrers would be required in the EU to achieve this number – a highly unlikely scenario over the course of this study.

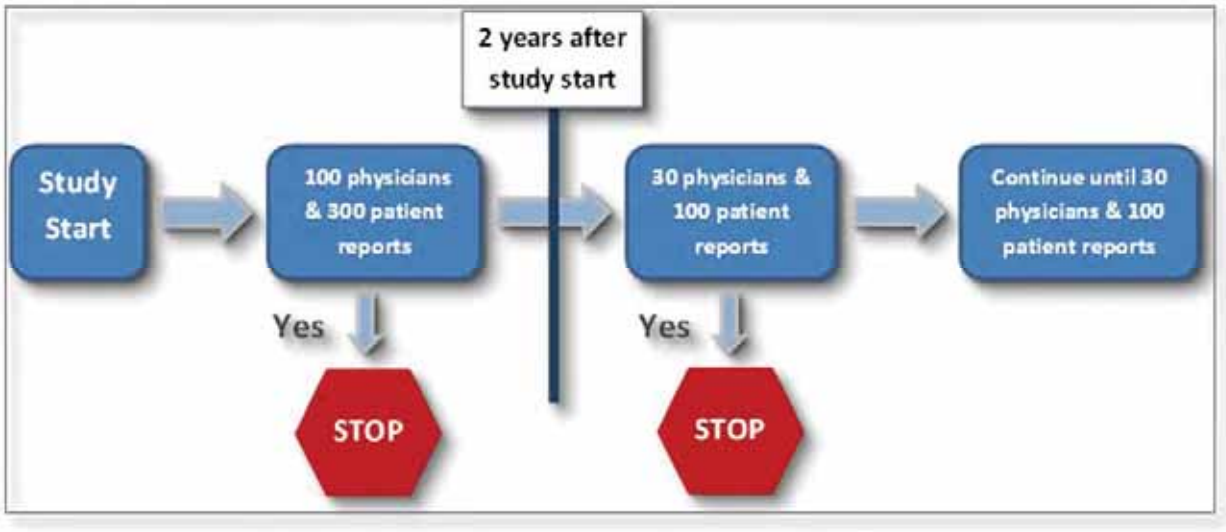

Figure 9.1. **Study size target and timeline from start of study 1 year after commercial EU availability to end of study ≥3 years after commercial availability.**

Thus, we propose a census of potential referring physicians commencing 1 year after commercial availability of Amyvid, initially in the UK, then expanding into Italy and Spain, as appropriate, based on meeting the target size and on-market availability of Amyvid during the

implementation phase of this study. Since early adopters of Amyvid PET scans who refer patients in the first 6 months of availability may not adequately reflect the greater population of clinicians who will refer patients in routine clinical practice, recruitment and data collection will only be initiated in those countries in which at least 50 scans have been undertaken. These countries will be identified based on the receipt of orders for Amyvid, with each order corresponding to 1 scan or patient. Information on the number of Amyvid orders will be provided by Lilly to IMS. Data collection will stop when 100 physicians are enrolled (with at least 10 per country) and the total number of patient reports reaches 300 unless 2 years have elapsed since the study began. After 2 years, data collection will continue until 30 referring physicians are enrolled in the 3 EU countries where Amyvid is projected to become commercially available over the study period and at least 100 patient reports are collected (see Figure 9.1 above). Thus, this study will enrol participants over 2 years and cover 3 years of Amyvid availability in the EU.

Each participating clinician will be limited to contributing a maximum of 5 patient reports during the study to ensure as broad coverage of clinical practice as possible. Clinicians agreeing to participate in the study will be invited to provide patient reports more than once during the data collection period at 3-month intervals.

9.6. Data Management

The survey will be conducted according to the standard operating procedures of IMS. In each country, recruitment will be conducted by IMS' dedicated team of native-speaking interviewers. Contact with clinicians will be made via telephone, e-mail, post, or fax.

Respondents' identities will not be disclosed. IMS will adhere to the Standard Code of Conduct adopted by the European Pharmaceutical Market Research Association (EphMRA), the Market Research Society (MRS), the associations of local market survey organisations and adheres to the International Chamber of Commerce/European Society for Opinion and Marketing Research (ICC/ESOMAR) International Code of Marketing and Social Research Practice. In addition, IMS will comply with the terms of the country Data Protection Act in all countries where the survey is conducted. During recruitment, it will be made clear to respondents that all personal data collected during the research project will be treated confidentially and used for the purposes of research in aggregate only. This may also reduce the likelihood of respondents only reporting on patient cases they know to be referred for on-label reasons.

Once a physician has agreed to take part in the study they will be provided with a method of contributing patient information, either a link to access a web-, paper-, or telephone-based survey. This will allow the collection of details from the physician's last consecutive cases who were referred for an Amyvid PET scan within the previous 3 months. All data collection will be managed by IMS, including the web-based questionnaire, which will be hosted via IMS' in-house computer-assisted web-based interviewing (CAWI) system. The beginning of the questionnaire will provide introductory text which will once again provide assurance regarding

confidentiality, in addition to reminding physicians of their responsibility regarding adverse event (AE) reporting (see Annex 3).

Participating clinicians will be contacted once every 3 months to ascertain whether they have referred any additional patients for Amyvid PET scans in the period since taking part previously/last being contacted. In the event that they have referred additional patients they will be invited to take part in the survey once again, until they have contributed a maximum of 5 patients. This process will be continued throughout the study period to cover at least 3 years post-commercial availability and until sufficient cases have been enrolled to meet the study's sample size requirements with respect to both referring physician numbers and patient reports.

IMS' field team will monitor survey initiations and conduct follow-up telephone calls with respondents after a certain amount of time to encourage completion for any that have failed to complete their surveys.

Data from completed interviews provided by participating physicians who fulfil the study entry criteria will be included in the analyses. For those physicians who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection. Data will be checked in terms of consistency before the data analysis.

The data collected will be stored in a database specific to the survey and the country on a secure IMS server. IMS will be responsible for the integrity of the data (ie, accuracy, completeness, legibility, and timeliness) reported to Lilly. Finally, data will be archived and retained as of applicable laws and regulations.

9.7. Data Analysis

9.7.1. *General Statistical Considerations*

The results of the statistical analysis for all countries will be presented in the same report. The response rates of each question of the questionnaire will be tracked in the results by country, overall and per specialty.

Continuous variables will be described by their number (number of valid cases, number of missing values), mean, standard deviation, median, Quartile 1, Quartile 3, minimum, and maximum.

Categorical variables will be described as the total number and relative percentage per category.

The number of missing data will be indicated. Missing values are expected to be non-substantial and distributed at random. This will be evaluated by assessing the proportion of missing values by key study variables: country, physician experience with Amyvid referrals (Section 3: Q. 1) and dichotomous off-/on-label use of Amyvid based on responses to Section 2: Q. 1 through 3). As no applicable methods of addressing missing values win unanimous support, no missing data will be replaced (Sterne et al. 2009). The reasons for non-response will be sought to ensure that missing data are reported with enough detail to strengthen the validity of the results, as

recommended by the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al. 2008).

Confidence intervals of 95% will be calculated, when relevant.

Calculations will be performed on raw data. Thus, no projection factor will be applied to generalise the results to the entire referrers' universe. As a consequence, the report will only show the results observed on the total sample of each country.

Summaries will be reported at country level according to the referrers' characteristics provided that the physicians' anonymity is in no way compromised.

Results will be analysed also according to prescribers' characteristics to check for possible selection bias. Finally, responses will also be analysed with respect to the time elapsed between the date of a scan and Amyvid commercial availability, for example, at 1-, 2-, and 3-year intervals.

9.7.2. *Assessment of the Representativeness of Participating Physicians*

The selection bias of physicians participating in a survey is an inherent potential limitation for any study based on voluntary participation. The existence of selection bias may result if physicians who agree to participate in the present study are not representative of the general population of physicians who prescribe Amyvid. In order to limit selection bias, the purpose of the survey, that is, to understand the pattern of use of Amyvid, will be presented to the physician without mentioning Lilly's name (unless the physician requests it). Physicians will also be given a choice of participating via a web-based survey, by telephone interview, or by mail on a paper questionnaire.

Questions on physician's years in practice and type of practice, that is, hospital versus office, are included in the questionnaire. An effort will be made to obtain this information from physicians even if they do not participate in the survey or do not refer patients for Amyvid PET scans. This information will allow the comparison of physicians participating in the survey with those who refuse to participate or who do not refer patients for Amyvid PET scans, in order to make sure the sample of respondents is representative of the general population of the applicable physician universe. The existence of statistically significant differences between these groups may indicate the presence of selection bias and affect the generalisability of the study results.

9.7.3. *Analysis of Non-Participation or Refusal to Participate*

Non-response is defined as the absence of an answer to a questionnaire and may include the following situations:

- the physician was not reachable,
- the physician refused to participate,
- the physician withdrew from the survey part way through completion (e.g., had to quit the interview because of an emergency),
- the questionnaire was lost or not analysable.

All cases of non-response will be analysed.

Various scenarios of overall non-response are shown in Figure 9.2 below.

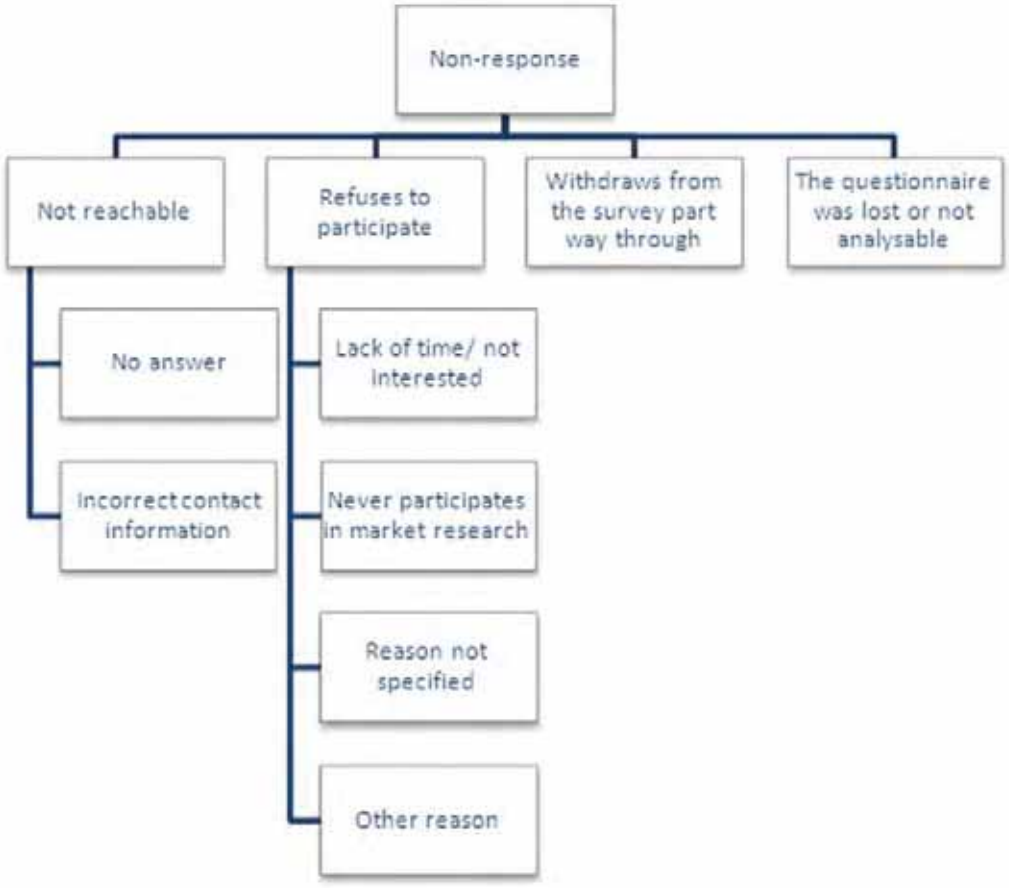

Figure 9.2. Description of the cases of non-response.

The following cases are defined:

- Target list of physicians identified for recruitment effort
- Physicians completing interview
- Physicians partially completing interview
- Physicians screening out during recruitment phase, e.g., not referring patients for Amyvid PET scans
- Physicians contacted who are unwilling/unable to participate
- Physicians with whom contact has not been possible, for example, failure to make contact after 5 calls, incorrect contact information

Participation in the survey will be analysed according to different ratios:

- The overall participation
- The effective proportion of participation among physicians contacted

- The overall proportion of non-response

The numerator of the overall proportion of non-response includes all possible forms of non-response (including cases where physicians could not be reached by phone).

The reasons why physicians could not be reached and the frequency of the reasons for refusal to participate in the survey will be analysed to explore any differences.

9.7.4. *Descriptive Analysis*

Analyses will focus on the overall study goal to describe the physicians who refer and the patients undergoing Amyvid PET scans. The first key objective to establish usage patterns of Amyvid in European clinical practice will focus on the reason for evaluation which will be analysed using responses to the following questions from the survey in Annex 3:

1. **Characteristics of the Referring Physicians** (*Survey Sections 1, 2 & 3*)
   Redacted in this version of the protocol.

2. **Characteristics of the Patients** (*Survey Section 4*)
   Redacted in this version of the protocol.

The second key objective to determine the level of off-label use of Amyvid PET scans will be met by identifying responses that are not consistent with:

a) a clinical evaluation, that is, not monitoring,
b) of the indicated population (adults with cognitive impairment, measured objectively or as reported by clinical decline relative to previous performance),

c) for AD or other causes of cognitive impairment.

Responses to the following questions will be analysed to meet this objective:

3. **Off-label use**

   Redacted in this version of the protocol.

The level of off-label use will be reported for each question as a proportion of the total responses received for that question and as the total number of questions consistent with off-label use by patients, that is, out of 10 total questions to address off-label use, how many had off-label responses. Sub-group analyses will be completed by physician specialty [redacted] experience with management of cognitively impaired patients [redacted] and number of previous Amyvid PET scans [redacted] to evaluate possible differences provided the stratification does not compromise the anonymity of the respondent. Given the potential limitations on the size of subgroups, simple statistical tests of proportions (unadjusted) will be used to determine the significance of differences. Analysis results by country will be presented in the same report in aggregate and separately, when not limited by small numbers. Results will also be analysed by temporal period since commercial launch of Amyvid in the EU, specifically at 1, 2, and 3 years after, to evaluate if there are temporal trends in patterns of use. If significant differences are detected between strata of variables, results will be reported separately for each stratum. The finalisation of current questions and wording will depend on the result of survey piloting prior to implementation.

Quantitative variables will be reported by standard statistics, that is, numbers, averages, standard deviation, median, minimum, maximum, first and third quartile. Qualitative variables will be

described for each modality with associated percentages. Numbers relating to data entered and values missing will be indicated. Missing values will be excluded from the calculation of percentages. Statistical tests can be used to determine the significance of differences and confidence intervals can be calculated for the key criteria.

9.8. Quality Control

Quality control for the collection of data through the web and telephone-based surveys will include the programming of key controls into the CAWI and computer-assisted telephone interview (CATI) systems to ensure that respondents are not able to submit responses which are not relevant to the question for any pre-coded and closed ended questions. The information provided via paper surveys will also be entered via the CAWI/CATI system. Certain checks can be built in relating to some open-ended questions requiring a numeric response. Answers to questions requiring a free-text response will be checked once the completed survey has been submitted by the respondent. In the event that there are any queries, the respondent will be contacted by telephone or e-mail to provide clarification. Any surveys which do not meet the quality control standards set for the project, for example, >50% missing or illegible information, will be excluded from the final analysis.

All survey data will be stored electronically on a secure server, with the original data maintained as originally entered by the clinician who participated in the survey. Coding of the data collected will follow a predetermined and documented process, with verification of coding confirmed by double data entry. The final analytical dataset and statistical programmes used for cleaning and analysing data will be preserved and maintained in electronic format and will be available for auditing at all times. All information collected through the survey will be traceable to specific login or participant identifiers, provided to each clinician at the time of their enrolment into the study. In order to preserve anonymity and confidentiality of the respondent, this information will not be shared with the client, Lilly, but will be used internally by IMS to collate data provided by each physician. All records, survey data, and analytical programmes will be securely maintained by IMS throughout the period of the study or longer, but may be shared with Lilly as long as this does not compromise participant anonymity or confidentiality.

9.8.1. *Safeguards, Security and Traceability of Calls*

Interviewers, specialised in health surveys, will be assigned to the project and briefed on the methodology prior to commencement of recruitment. Teams of interviewers undertaking telephone recruitment or data collection will be supervised at all times.

The data collected will be stored on a secure server and all telephone calls made will be logged.

All aspects of the survey from protocol development to the reporting of the results are conducted following standard operating procedures (SOPs).

9.9. Limitations of the Research Methods

9.9.1. *Possible Selection Bias Due to Voluntary Participation*

In common with any other survey, the voluntary participation of physicians in the survey can be a potential source of bias. As explained above, every effort has been undertaken to collect as much information as possible on those physicians who refuse to participate in the survey, so that the comparison of their characteristics with those of the participants may be possible.

During recruitment, physicians will be informed of the goal of the survey, that is, to describe the use of Amyvid in Europe. In order to prevent any bias regarding the responses provided, physicians will not be informed of Lilly's identity until the end of the survey and only if requested by the individual. However, due to the very specific subject matter of the interview there is a high probability that respondents will reach a conclusion as to which company is commissioning the project. This, in turn, may influence respondents in terms of the patient cases they report, thereby reducing the reporting of off-label referrals dependent on the clinician's understanding of the use of Amyvid.

9.9.2. *Missing Values*

We do not expect to have a substantial volume of missing values in this survey. Efforts will be made to follow up on surveys with substantial missing information, particularly for participants who elect to respond to the paper form of the survey. However, in case of missing values they will be mentioned and treated separately in the analyses. No missing value will be replaced.

9.10. Other Aspects

None.

10. Protection of Human Subjects

10.1. Regulatory and Ethics Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country or countries where the study is being conducted, as appropriate.

The survey is non-interventional and entirely anonymous. No identifying information about patients will be collected and data from physician participants will be de-identified. In addition, data collected will remain absolutely confidential and only aggregate data will be communicated or presented.

10.2. Physician Information

Physicians participating in the survey will be informed about the survey objectives, the type of data transmitted, the intended use of data, recipients of this data, and their right of access and rectification, and their right to object according to the European and national regulations.

10.3. Physician Compensation

Physicians will be compensated for time they spend participating in this survey, based on fair market value in their region for their specialisation and seniority during the period of this study. National guidance on reimbursement and remuneration of physicians will be followed for each country.

The time required to provide responses to baseline questions is estimated to be approximately 30 minutes and to complete each patient report is estimated to be approximately 30 to 45 minutes. The time for completion will be tested via pilot interviews prior to commencement of the main fieldwork.

11. Management and Reporting of Adverse Events/Adverse Reactions

During the collection or analysis of data for this study, information pertaining to suspected adverse reactions may be discovered. As described in Annex 4, all IMS interviewers undertake the British Healthcare Business Intelligence Association (BHBIA) AE reporting training course. In addition, IMS personnel will follow Lilly Adverse Event/Product Complaint procedures, which include directing the reader reporting an event to complete an adverse drug reaction (ADR) form for submission to Lilly Pharmacovigilance personnel. For the web-based survey, respondents will be provided with a link to an AE reporting form if they identify an AE relating to the information they have provided in the survey. This link will be provided at the end of the survey. Participants who elect the telephone- or paper-based survey versions will also be directed to an AE reporting form for submission to Lilly pharmacovigilance personnel.

12. Plans for Disseminating and Communicating Study Results

Interim summaries of data collected during the first year and second years of the study will be included in annual PSUR's and a final report, from the full data collected, will be prepared and submitted in accordance with the milestone dates provided in Section 6. This study protocol will also be submitted to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), but the questionnaire (Annex 3) will be omitted until the completion of the study to maintain the validity of the survey. Publications may result from this study.

13. References

Alzheimer's Society (UK). *Demography*. 2013. Available at: http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=412. Accessed February 21, 2014.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-2117.

Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61(4):344–349.

Annex 1. List of Stand-Alone Documents

1. Study Synopsis 2 – Evaluation of Amyvid Usage Patterns in Routine Clinical Use (Appendix 5 to Approved Amyvid Risk Management Plan 07 Nov 2012)

Annex 2. ENCePP Checklist for Study Protocols

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16
1.1.2 The objectives of the study?	☒	☐	☐	18
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☒	☐	☐	19

Comments:

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	16-17, 19, 20
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	15
2.2.2 Age and sex?	☐	☐	☒	

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.2.3 Country of origin?	☒	☐	☐	16, 17
2.2.4 Disease/indication?	☐	☐	☒	
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	29, 30, 31
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	19
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	29, 30
3.4 Is sample size considered?	☒	☐	☐	22, 23
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	20, 21, 22
4.1.3 Covariates?	☐	☐	☒	
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	29, 30, 31
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification				

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	29-30
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	23

Comments:

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	31, 32
7.1.2 Information biases?	☒	☐	☐	31, 32
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.3 Does the protocol address known effect modifiers?	☒	☐	☐	
(e.g. collection of data on known effect modifiers, anticipated direction of effect)				29, 30
7.4 Does the protocol address other limitations?	☒	☐	☐	31, 32

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	26-30
8.3 Are descriptive analyses included?	☒	☐	☐	29-31
8.4 Are stratified analyses included?	☒	☐	☐	27, 30
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☐	☐	☒	
8.5.2 Effect modifiers?	☐	☐	☒	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☐	☒	
8.6.2 Effect modification?	☐	☐	☒	

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	25, 31
9.2 Are methods of quality assurance described?	☒	☐	☐	25, 26, 31

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	25, 27, 28, 29
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	22-25
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	15, 24
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	15, 24
9.5.3 Study completion?	☒	☐	☐	15, 24
9.5.4 Reporting? (ie, interim reports, final study report)	☒	☐	☐	15
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14
9.7 Are communication methods to disseminate results described?	☒	☐	☐	35
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	33
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	25, 26, 31

Comments:

Name of principle investigators:

Claudia A. Salinas, PhD

Date: / / [DD/MM/YYYY]

Signature: Signature on file

Annex 3. Survey Questionnaire

This Annex (pages 48-59) has been removed in the current version of the protocol to maintain the scientific integrity of the study objectives. Upon completion of the study, the full protocol with the deleted information included will be uploaded.

Annex 4. IMS AE Reporting Procedure

IMS Medical Radar Adverse Events (AE) and Product Complaint (PC) procedures

The IMS Medical Radar Adverse Event (AE) and Product Complaint (PC) reporting process is compliant with the EphMRA and the British Healthcare Business Intelligence Association (BHBIA)-ABPI (Association of the British Pharmaceutical Industry) Adverse Event Guidelines as well as with the European Medicines Agency Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products, dated 22 June 2012 (EMA/873138/2011).

IMS Medical Radar uses an electronic system to report AEs/PCs. The system ensures high performance and security in our AE reporting procedures. The electronic AE-system is a closed internal system coupled to our interview programme. The system removes the problem of reading handwritten reports as they are entered directly into a computer. The electronic system also ensures that the minimum criteria for an AE-report are always recorded and it automatically saves all reports on a backed-up server.

Interviewers and QC personnel are trained according to the client's requirements. If preferred we will use the client's own educational material. In the absence of specific requirements, relevant personnel will go through an internal AE-training and/or the BHBIA ABPI online AE/PC-training. Both trainings contain working examples and/or tests. Training is refreshed every 12 months and confirmation of training is maintained.

If a suspected AE/PC is mentioned during an interview with a health care professional (HCP), a form that complies with the BHBIA-ABPI guidelines is used to capture the required information to complete the AE report. The HCP is asked to give permission for the client's drug safety team to contact him/her for further details. If consent is given, the HCP's contact information is included in the report. If consent is not given, the HCP remains anonymous. The HCP will then be identified by qualification, as recommended in the BHBIA-ABPI guidelines.

If a reportable AE/PC is discovered in the interview database of a web-survey, as much information as possible about the event is gathered from the web-answers, transferred to the electronic AE/PC-form and sent to the client.

All reports are sent to the client's drug safety team as soon as possible and always within one business day after IMS Medical Radar has become aware of the AE/PC. The reports are sent to the client via e-mail or fax, as requested by the client. When data collection for a project is finished an AE-reconciliation is performed with the client to make sure that all AE-reports were received.

IMS Medical Radar has personnel with special responsibility for adverse events reporting. This ensures a high level of compliance with procedures and educations. It also gives clients a fixed point of contact for questions regarding adverse events and product complaints.

Further information on security and internal quality control on AE-procedures:

All personnel that are involved in the AE-reporting process have access to written instructions for reference.

To help the interviewers comply with AE-reporting we add an AE-reminder that shows up in the beginning of each interview made for projects where AE-reporting is required. Also the clients' drugs are marked and interviewers have been shown how to access and fill in the electronic AE-form. To make the process of filling in the AE-form faster and more secure, the electronic form automatically picks up certain pieces of information from the interview, this includes, among other things, the project that generated the report and the date we became aware of the AE.

We have control procedures in place that ensure that we maintain high quality and security in our AE-reporting. For each project where AE reporting is required the Quality Control department goes through the interview database checking all answers that relate to the clients' drugs. AEs found in these answers are cross-checked against exports showing all reported AEs for the project. If an AE is found that has not been reported this is discussed with the responsible parties and the team supervisor to make sure that any misunderstandings are cleared and that the mistake is not repeated. If a missed AE is found, it is, of course also reported to the client. This procedure, which runs on a continuous basis, ensures that Adverse Events are being recognized and handled appropriately.

The electronic AE-system is internal and protected by a firewall. All reports are stored on an internal server that is incrementally backed up each day and fully backed up each weekend. Backup tapes are stored off-site in case of a fire or other disastrous events. At the moment, all AE- and PC-reports are stored forever. If in the future it becomes necessary, reports older than 5 years may be discarded, but only after enquiring if the client would like a copy.