What are the regulatory requirements for my NIS?

It Depends!
There are new European legal requirements for Post-Authorisation Safety Studies (PASS) effective from 21 July 2012:

- Regulation EU/520/2012
- Regulation EC/726/2004 (as amended by Regulation EU/1235/2010)
- Directive 2001/83/EC (as amended by Directive 2010/84/EU)
- EMA GVP Module VIII
- EMA Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (Sept 2012)

These requirements are more stringent than was previously seen for PASS. All obligatory PASS (and voluntary?!) must comply with the new PASS requirements.

Therefore, it is important that you correctly classify your study during the planning phase because there are significantly different requirements for non-interventional PASS than for other non-interventional studies.
STEP 1 - DETERMINE WHAT TYPE OF STUDY YOU INTEND TO CONDUCT

Before starting your study you first need to determine what type of study it is:

**Study Classification**

- **Interventional?**
  - Is your study an interventional clinical trial? → **X**
  - Is your study an interventional clinical trial? → **X**

- **PASS?**
  - Is your study a post-authorization safety study (PASS)? → **X**

- **Other NIS?**
  - Is your study a non-safety related non-interventional study? → **✓**

**Regulatory Framework**

- **Interventional?**
  - Clinical Trials Directive (2001/20/EC)

- **PASS?**
  - Pharmacovigilance Directive (2010/84/EU)

- **Other NIS?**
  - Country Specific!
STEP 1 - DETERMINE WHAT TYPE OF STUDY YOU INTEND TO CONDUCT

Is your Study Interventional?
- Is your study an interventional clinical trial?
- Refer to the Decision tree
STEP 1 - DETERMINE WHAT TYPE OF STUDY YOU INTEND TO CONDUCT

Is your Study a Post-Authorisation Safety Study (PASS)?

Your study is a PASS if the objectives include at least one of the following conditions:

1. Characterization of the safety profile (e.g. identifying the most frequent adverse reactions in a large population over time);
2. Providing reassurance about the absence of a safety concern related to a specific adverse reaction;
3. Investigating potential or identified risks, e.g. to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population and investigate risk factors and effect modifiers;
4. Evaluating risks of a product used in authorised indications by patients groups not studied in the pre-authorisation phase (e.g. pregnant woman, elderly patient);
5. Assessing patterns of drug utilisation and use of the product that may have an impact on its safety (e.g. co-medication, medication errors);
6. Evaluating the effectiveness of a risk mitigation activity (e.g. drug utilisation study, patient or physician survey)
STEP 1 - DETERMINE WHAT TYPE OF STUDY YOU INTEND TO CONDUCT

Is your Study a Post-Authorisation Safety Study (PASS)?

If your study falls within the scope/definition of a PASS and it isn’t a study that has been required by a Competent Authority as part of your Marketing Authorisation then it is a ‘voluntary’ PASS.

If you are the study sponsor you will need to determine, and document, what your policy is with regards to the notification and reporting considerations for these voluntary PASS.

The EMA encourages Companies to notify and register these study in the same way as Obligatory PASS. However, this is currently a business decision.
STEP 1 - DETERMINE WHAT TYPE OF STUDY YOU INTEND TO CONDUCT

Is Your Study a Non-Safety Related (‘Other’) Non-Interventional Study?

- If so, the requirements are not standardised and you will need to determine the country-specific considerations.
STEP 2 - DETERMINE THE COUNTRY-SPECIFIC REQUIREMENTS

The regulatory requirements for ‘Other’ NIS are very much dependent on a number of factors (see below), which is why there isn’t generally a single answer to the question, “what are the regulatory requirements for my non-interventional study?”

There are no short cuts. You will need to verify the country-specific regulations and considerations for each of the countries where you intend to conduct your non-interventional study.
**STEP 2 - DETERMINE THE COUNTRY-SPECIFIC REQUIREMENTS**

**NIS regulatory requirements include:**
- Competent Authority approvals, notifications and/or registration
- IRB/REC approval or notifications
- Data Protection Agency notifications or approvals
- Health Trust approvals

**The NIS requirements depend on:**
- The type of study
- The country where the study will be conducted
- The patient population
- What you intend to collect
- Non-routine requirements (e.g., patient diaries)
- What you intend to do with it
STEP 2 - DETERMINE THE COUNTRY-SPECIFIC REQUIREMENTS

Study Design
Prospective study?
Retrospective study?
Which countries?
Which patient populations?
Non-routine requirements?
Tissue collection?
Tissue export?
Biobanking?
DNA analysis?
Secondary use of data?
Secondary use of tissue?

Regulatory Requirements
Notifications
Approvals
Submissions procedures
Registration
Classification
Insurance requirements

‘Other’ NIS
Need to verify requirements for each country

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CHCUK NIS Tools and Resources

CHCUK has prepared a comprehensive range of detailed country-specific ‘NIS Considerations’ reports and training modules which aim to provide you with the support you need to start-up and conduct NIS in the country of your choice.

**Country-Specific NIS Reports**

- NIS Considerations (Europe: Part 1 - 2012)*
- NIS Considerations (Europe: Part 2 - 2011)*
- NIS Considerations (Argentina - 2012)
- NIS Considerations (Australia - 2012)
- NIS Considerations (Brazil - 2012)
- NIS Considerations (Canada - 2012)
- NIS Considerations (Israel - 2012)
- NIS Considerations (India - 2012)
- NIS Considerations (Luxembourg - 2012)
- NIS Considerations (Mexico - 2012)
- NIS Considerations (Russia - 2012)
- NIS Considerations (Taiwan - 2012)
- NIS Considerations (USA - 2012)

**Free Resources**

- NIS Considerations - Newsletter
- NIS Considerations - Regulatory Maps
- NIS Considerations - Regulatory Definitions
- NIS Considerations - Monitoring Guidelines

*The NIS Considerations (Europe) reports only provide an overview of the regulatory requirements that need to be considered when conducting NIS in Europe. More detailed country-specific reports are available for each of the countries that provide information on submission documents, approval timeframes, practical operational considerations, biosample collection etc.
Non-Interventional Study Standards, Guidelines and Resources

There is a vast range of guidelines that are applicable to the conduct of non-interventional studies. The following sections lists some of the key guidance documents.

- **Ethical Standards & Guidelines**
  - ICH E2E
  - ICH E6 (ICH GCP)
  - ISPE: Guidelines for Good Pharmacoepidemiology Practices (GPP)
  - CIOMS International Ethical Guidelines for Epidemiological Studies, 2008

- **Ethical Standards & Guidelines**
  - ISPE: Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health

- **Free NIS Study Conduct Standards & Guidelines**
  - ISPE: Guidelines for Good Pharmacoepidemiology Practices (GPP)
  - ISPE: Guidelines for Good Database Selection and Use in Pharmacoepidemiology Research - July 2011
  - IEA Guidelines for Proper Conduct in Epidemiological Research, November 2007
  - ENCePP Guide on Methodological Standards in Pharmacoepidemiology (2011)

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Non-Interventional Study Standards, Guidelines and Resources

There is a vast range of guidelines that are applicable to the conduct of non-interventional studies. The following sections lists some of the key guidance documents:

- **Study Protocol Guidelines and Checklists**
  - ISPE: Guidelines for Good Pharmacoepidemiology Practices (GPP)
  - ENCepP Checklist for Study Protocols (2011)

- **Observational Study Reporting Guidelines and Checklists**
  - STROBE Observational Study Report Checklists (2007)
  - STROBE checklist for cohort, case-control, and cross-sectional studies (combined)
    - [download](#) PDF / Word
  - Checklist for cohort studies
    - [download](#) PDF / Word
  - Checklist for case-control studies
    - [download](#) PDF / Word
  - Checklist for cross-sectional studies
    - [download](#) PDF / Word
  - Draft STROBE checklist for conference abstracts
    - [download](#) PDF

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Non-Interventional Study Standards, Guidelines and Resources

There is a vast range of guidelines that are applicable to the conduct of non-interventional studies. The following sections lists some of the key guidance documents:

- **European Post-Authorisation Safety Study (PASS) Regulations, Standards and Guidelines**
  - EMA Guidance on the 2010 Pharmacovigilance Legislation
  - EMA Regulatory and Procedural Pharmacovigilance Guidance
  - EMA Good Pharmacovigilance Practices (GVPs)
  - EMA Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies (Sept 2012)
  - Implementation Timeframe for the Pharmacovigilance Legislation
  - Regulation EC/726/2004 (as amended)


- **2001/83/EC** (Marketed Products Directive – as amended)

- **Eudralex Volume 9a**

- **The EU Pharmacovigilance System**
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