NIS Considerations: Basics – 2013
An introduction to the considerations when planning, conducting and reporting non-interventional studies (NIS)

Stuart McCully • Compliance Healthcheck Consulting UK Ltd • NIS-C-BASICS-2013
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Ethical Considerations when Conducting Non-Interventional Studies

WHICH ETHICAL STANDARDS ARE APPLICABLE TO NIS?

World War II Nazi Medical Experiments (1939 - 1945)

The Declaration of Helsinki (1964)

The Need to Harmonise the Clinical Trials Regulations (1964 - 1996)

The Birth of the ICH (1989)

ICH Guideline for Good Clinical Practice (ICH GCP - 1996)

Applicability of Clinical Trials Regulations and ICH GCP to NIS (1996 to Present)

Why don’t we apply GCP in it’s entirety to NIS?

The Tuskegee Syphilis Observational Study (1932 - 1972)

Statement from Fred D Gray – Attorney (8th April 1997)

Statement from President Bill Clinton (16th May 1997)

Statement from Vice President Al Gore (16th May 1997)

DO WE APPLY GCP, GEP OR GPP TO NIS?

So What are the Scientific and Ethical Quality Standards that are Applicable to NIS?

NIS GUIDELINES - ETHICS, DATA OWNERSHIP AND PRIVACY

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) - Harmonised Tripartite Guideline for Good Clinical Practice (ICH GCP)

International Society for Pharmacoepidemiology (ISPE) guideline for Good Pharmacoepidemiology Practices (GPP)

International Epidemiological Association (IEA) Good Epidemiological Practice (GEP) Guideline

The Council for International Organizations of Medical Sciences (CIOMS) 2009 International Ethical Guidelines for Epidemiological Studies

The Agency for Healthcare Research and Quality (AHRQ) of the United States

The International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals

ETHICAL CONSIDERATIONS - USEFUL LINKS

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Recommendations for the Planning, Conduct and Reporting Considerations for Non-Interventional Studies

- **WHAT IS A NON-INTERVENTIONAL STUDY?**
  - Definition

- **Why Perform Non-Interventional Studies?**

- **THE COMPLEX SIMPLICITY OF NON-INTERVENTIONAL STUDIES**
  - Comparison of the Considerations when Conducting Interventional Clinical Trials versus Non-Interventional Studies
  - Why aren’t Non-Interventional Studies Simpler and Easier to Manage and Perform than Interventional Clinical Trials?

- **GOOD PHARMACOEPIDEMIOLOGY PRACTICES (GPP)**
  - Study Classification
  - Regulatory Assessment
  - Protocol Development
  - Responsibilities
  - Personnel
  - Facilities
  - Resource Commitment
  - Contracts
  - Contractors
  - Study Conduct
  - Protection of Human Subjects
  - Data Collection, Management and Verification
  - Data Privacy Requirements in Europe
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Disclaimer

Although this Compilation contains information of a legal nature, it has been developed for informational purposes only and does not constitute legal advice or opinions as to the current operative laws, regulations, or guidelines of any jurisdiction. In addition, because new standards are issued on a continuing basis, this Compilation is not an exhaustive source of all current applicable laws, regulations, and guidelines relating to non-interventional studies. While reasonable efforts have been made to assure the accuracy and completeness of the information provided, researchers and other individuals should check with local authorities and/or research ethics committees before starting research activities.
SUMMARY OF CHANGES SINCE PREVIOUS VERSION

Summary of the changes since the previous of the NIS Basics report (NIS-B-EU-2012).

<table>
<thead>
<tr>
<th>Area Impacted</th>
<th>Details</th>
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<tbody>
<tr>
<td>Report Format</td>
<td>The report has been reformatted, indexed and bookmarked to create a more intuitive and user-friendly resource</td>
</tr>
<tr>
<td>Report Content</td>
<td>The report is no longer a 13 page collection of useful links but is now a 112 page comprehensive introduction to non-interventional studies and covers the following key elements:</td>
</tr>
<tr>
<td></td>
<td>1. Ethical Considerations</td>
</tr>
<tr>
<td></td>
<td>2. Recommendations for the Planning, Conduction and Reporting Considerations for NIS</td>
</tr>
<tr>
<td></td>
<td>3. Study Classification</td>
</tr>
<tr>
<td></td>
<td>4. NIS Standards, Guidelines and Resources</td>
</tr>
<tr>
<td></td>
<td>5. Recommended Quality Standards for NIS</td>
</tr>
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<td>6. NIS Definitions</td>
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<tr>
<td></td>
<td>7. Common NIS Terminology</td>
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Summary

SCOPE & APPLICATION

This resource compliments 'NIS Basics - 2013' elearning course and is intended as an operational reference source for researchers who are involved in the planning, conduct and reporting of voluntary non-interventional studies i.e., non-interventional studies that are not mandated non-interventional post-authorisation safety studies (PASS).

All citations have been hyperlinked to the original sources (where cloud-based sources are available).

FORMAT

The report is organized as follows:

1. Ethical Considerations
2. Recommendations for the Planning, Conduct and Reporting Considerations for NIS
3. Study Classification
4. NIS Standards, Guidelines and Resources
5. Recommended Quality Standards for NIS
6. NIS Definitions
7. Common NIS Terminology
ETHICAL CONSIDERATIONS

So What are the Scientific and Ethical Quality Standards that are Applicable to NIS?

So what quality standards should we apply to non-interventional studies? Do we apply Good Clinical Practice (GCP), Good Epidemiological Practice (GEP) or Good Pharmacoepidemiological Practice (GPP)?

In reality, the answer is that we apply all the elements of the above GXPs that are applicable. GEP and GPP are operational adaptations of GCP and specifically address (although not in as much detail as GCP) the requirements of drug-related NIS (GPP) and non-drug related NIS (GEP). Of course, the national regulations and requirements, where present, take precedence. In short, non-interventional studies should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, with GCP/GEP/GPP and the applicable regulatory requirements.

Why don’t we apply GCP in its entirety to NIS?

Simply put, NIS are different types of studies, with different approaches, designs and risks to interventional clinical trials. It’s not about ethical compromise, it’s all about ethical applicability. Many of the requirements stipulated in GCP aren’t applicable to non-interventional studies e.g., IMP, drug labeling and drug accountability; Investigator’s Brochure; study-related insurance in case of injury to patients as a result of novel interventions etc.

Regardless of whether the study is interventional or non-interventional, the general ethical requirements are based on the original requirements stipulated in the Declaration of Helsinki, namely:

- The patient must provide their voluntary informed consent, or in the case of legal incompetence consent should be obtained from the legal representative
- They are free to withdraw from the study at any moment
- The benefit to the patient should outweigh the risk to the patient
- The rights, safety and welfare of the patient must be protected and the interest of the patient must always prevail over the interests of science and society
- The study must be scientifically valid and the purpose described in a protocol
The protocol should always include a statement of the ethical considerations involved

The protocol must be reviewed by an independent ethics committee

The research must be conducted by scientifically qualified persons under the supervision of a clinically competent medical person

There is a wide range of guidelines for the protection of human subjects. All are consistent with the ethical principles that have their origin in the Declaration of Helsinki (see diagram below).

RECOMMENDATIONS FOR THE PLANNING, CONDUCT AND REPORTING CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

What Is Non-Interventional Study

Definition

A non-interventional study is a study fulfilling cumulatively the following requirements:
The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;

The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and

No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (e.g. case-control, cross-sectional and cohort studies). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met (as per Annex I of the EMA Guideline on good pharmacovigilance practices (GVP), 2012).

In this context, interviews, questionnaires and blood samples may be performed as normal clinical practice (as per Annex I of the EMA Guideline on good pharmacovigilance practices (GVP), 2012).

**Why Perform Non-Interventional Studies?**

Many questions in medical research are investigated in observational studies. Much of the research into the cause of diseases relies on cohort, case control, or cross-sectional studies. Observational studies also have a role in research into the benefits and harms of medical interventions. Randomized trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable to detect rare or late adverse effects of treatments and are more likely to provide an indication of what is achieved in daily medical practice (von Elm et al., 2008).

**THE COMPLEX SIMPLICITY OF NON-INTERVENTIONAL STUDIES**

A large majority of researchers that participate in the performance of non-interventional studies have come from a clinical trials background. They often come with the expectation
that non-interventional studies (NIS), are simpler and easier to manage and perform than interventional clinical trials. It therefore comes as a shock when they realise that this isn’t the case. Welcome to the exciting and challenging world of non-interventional studies!

The table below illustrates the similarities and differences between interventional clinical trials and non-interventional studies.

**Comparison of the Considerations when Conducting Interventional Clinical Trials versus Non-Interventional Studies**

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Intervventional Clinical Trial (Higher Risk)</th>
<th>Non-Interventional Study (Low Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethical Standards</td>
<td>• Declaration of Helsinki</td>
<td>• Declaration of Helsinki</td>
</tr>
<tr>
<td></td>
<td>• ICH GCP etc</td>
<td>• ISPE GPP</td>
</tr>
<tr>
<td></td>
<td>• ICH GCP</td>
<td>• ICH GCP</td>
</tr>
<tr>
<td></td>
<td>• Dependent on country</td>
<td>• Dependent on country</td>
</tr>
<tr>
<td>Regulatory Approvals</td>
<td>• National Competent Authority</td>
<td>• IRB/IEC - often unfamiliar with NIS which can lead to delays in the review and approval process.</td>
</tr>
<tr>
<td></td>
<td>• IRB/IEC</td>
<td>• National Competent Authority - Dependent on country</td>
</tr>
<tr>
<td></td>
<td>• Data Protection Agency - Dependent on Country</td>
<td>• Data Protection Agency - Dependent on country</td>
</tr>
<tr>
<td></td>
<td>• Harmonised framework</td>
<td>• No harmonised framework - country-specific requirements</td>
</tr>
<tr>
<td>Regulatory Submission Documents</td>
<td>• Comprehensive harmonised submission package</td>
<td>• Country dependent</td>
</tr>
<tr>
<td></td>
<td>• ICH GCP compliant</td>
<td>• Usually limited/streamlined submission package</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No harmonised submission package - Compliant with local legislation</td>
</tr>
<tr>
<td>Registration</td>
<td>• Mandatory</td>
<td>• Dependent on country</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Considerations</th>
<th>Interventional Clinical Trial (Higher Risk)</th>
<th>Non-Interventional Study (Low Risk)</th>
</tr>
</thead>
</table>
| Monitoring                     | • Requirements dictated by Section 4.18 of ICH GCP  
• Usually on-site monitoring with extra ‘triggered’ visits when required                                                                                                                                                                      | • Dependent on study type and country-specific requirements  
• Primarily remote monitoring with scheduled on-site monitoring as needed                                                                                                                                                                                                                                                                                         |
| Risk to Patient                | • Exposure to novel interventional treatment (diagnostic or therapeutic)                                                                                                                                                                       | • Compromised data privacy  
• Possible psychological trauma -                                                                                                                                                                                                                                                                                                                        |
| Patient Enrollment             | • Strict inclusion and exclusion criteria as trying to reduce as many variables as possible                                                                                                                                                   | • Very few inclusion and exclusion criteria as trying to capture ‘real life’ use of drug                                                                                                                                                                                                                                                                                         |
| Physicians                     | • Usually are already GCP trained and have previous clinical trials experience                                                                                                                                                                  | • Often naive to clinical research                                                                                                                                                                                                                                                                                                                                 |
| Treatment                      | • Dictated by protocol                                                                                                                                                                                                                      | • Dictated by Physician. Patient must already be prescribed the drug of interest prior to enrollment                                                                                                                                                                                                                     |
| Study Visits                   | • Dictated by protocol                                                                                                                                                                                                                      | • As per normal clinical practice  
• Not dictated by protocol                                                                                                                                                                                                                                                                                                                                 |
| Drug Supplied by Study Sponsor | • Always  
• Need to account for all IMP  
• Needs to be labelled as IMP                                                                                                                                                                                                               | • Never  
• Prescribed by treating Physician and used according to SmPC i.e., not an investigational drug  
• No need to account for the drug  
• No need for special labelling                                                                                                                                                                                                                                                                                          |
<table>
<thead>
<tr>
<th>Considerations</th>
<th>Interventionsal Clinical Trial (Higher Risk)</th>
<th>Non-Interventionsal Study (Low Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator Brochure (IB)</td>
<td>• Required for all pre-approval IMPs</td>
<td>• Not required as drugs approved</td>
</tr>
<tr>
<td></td>
<td>• To be review annually</td>
<td>• Physicians have access to SmPCs of prescribed drugs as standard - not supplied by study Sponsor</td>
</tr>
<tr>
<td></td>
<td>• Need to demonstrate that IBs have been received by participating Physicians</td>
<td></td>
</tr>
<tr>
<td>Study-Specific Insurance</td>
<td>• Study Sponsor legally required to provide insurance to patients for IMP/study-related adverse reactions</td>
<td>• Generally not required for NIS as drug is approved and is used in accordance with SmPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Some exceptions e.g., Belgium</td>
</tr>
<tr>
<td>Data Collection</td>
<td>• Generally large CRFs with text fields as needed</td>
<td>• Limited/minimal CRFs with limited text fields</td>
</tr>
<tr>
<td></td>
<td>• Usually includes lots of ‘nice to have’ fields which results in multiple and often excessive and unnecessary data queries</td>
<td>• Should include only ‘must have’ data to reduce data queries and burden to site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Imperative that impact of data collection on site is limited to a minimum</td>
</tr>
<tr>
<td>Safety Reporting</td>
<td>• Requirements dictated by ICH E2 series</td>
<td>• Requirements dictated by local requirements - as a general rule, comply with post-authorisation safety reporting requirements e.g., spontaneous reporting within 15 days of knowledge of reaction</td>
</tr>
<tr>
<td></td>
<td>• Terminal and life-threatening SUSARs reported to NCA and IRB/IEC within 7 days of becoming aware of reaction</td>
<td>• Specific reporting requirements in Europe - as per EMA GVP module VI and VIII</td>
</tr>
<tr>
<td></td>
<td>• All other SUSARs to be reported within 15 days</td>
<td></td>
</tr>
<tr>
<td>Considerations</td>
<td>Intervventional Clinical Trial (Higher Risk)</td>
<td>Non-Interventional Study (Low Risk)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study Report</td>
<td>• Format dictated by ICH E3</td>
<td>• Format dependent on study type and country-specific requirements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Specific requirements for mandated EU non-interventional PASS</td>
</tr>
<tr>
<td>Audits</td>
<td>• Generally a legal imperative derived from implementation of Section 5.1 of ICH GCP into national legislation</td>
<td>• Generally a recommendation based on stipulations from the Codes of Practice of Pharmaceutical Self-Regulatory Bodies (e.g., EFPIA) and generic guidelines such as ISPE GPP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Legal imperative in countries such as Spain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Legal Imperative for NCA mandated Post-Authorisation Safety Studies (PASS)</td>
</tr>
<tr>
<td>NCA Inspection</td>
<td>• Generally a legal requirement based on national clinical trials regulations</td>
<td>• Legal Imperative for NCA mandated Post-Authorisation Safety Studies (PASS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dependent on country</td>
</tr>
</tbody>
</table>

Why aren’t Non-Interventional Studies Simpler and Easier to Manage and Perform than Intervventional Clinical Trials?

It’s a valid question. In theory, non-interventional studies should be more simple to manage and perform than interventional clinical trials because the purpose of the studies is to observe the use of drugs in ‘real life’ situations. As a researcher you aren’t influencing how a patient is being treated. You are merely observing the outcome of that treatment.

The simple fact is that the operational standards and requirements for the planning, conduct and reporting of interventional clinical trials were harmonised through the implementation of
ICH GCP in 1996 and the subsequent adoption into national legislation. Whereas, the operational standards and requirements for the planning, conduct and reporting of non-interventional studies have not been harmonised. The results is that each country around the world governs non-interventional studies according to their own standards and requirements.

This report highlights the generic ethical and scientific standards that are applicable to all non-interventional studies. These then need to be supplement with the country-specific requirements for your study which will be dependent on a variety of factors including, but not limited to, the design of the study (retrospective or prospective), the purpose of the study, the patient population, what you intend to collect, what you intend to do with the samples and/or data you collect, and where you intend to conduct the study.

GOOD PHARMACOEPIDEMIOLOGY PRACTICES (GPP)

The ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) are regarded as the foundational guidelines for non-interventional studies and as such form the core of the NIS activity recommendations listed below:

- Study Classification
- Protocol Development
- Responsibilities
- Personnel
- Facilities
- Resource commitment
- Contracts
- Contractors
- Study conduct
- Protection of human subjects
- Data collection, management and verification
- Monitoring

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STUDY CLASSIFICATION

The first step when assessing the specific requirements for a study is to determine what type of study it is that you intend to conduct.

- Where do you intended to conduct the study?
- Has the study ben mandated by a national competent authority (NCA)?
- What is the purpose of the study?
- What do you intend to collect - sensitive health information and/or biological samples?
- What do you intend to do with the data and/or biological samples you collect
- How do you intend to collect the data - are the intended questionnaires/ patient reported outcomes (PROs) part of routine practice in the country/site where you intend to conduct the study?
- Is your study interventional or non-interventional?

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.
RECOMMENDED QUALITY STANDARDS FOR NIS

In the light of the recent financial turmoil, companies are increasingly outsourcing processes and activities to external vendors. There is an ever increasing loss of expertise within organisations due to downsizing, mergers and acquisitions. Furthermore, vendors have the capacity and bandwidth to provide increasingly diverse services in response to the current financial and regulatory climate. They have the ability to provide quick start-up services by utilising either internal or client systems, processes and procedures (Politis and Delgra, 2012).

Furthermore, the ever changing regulatory landscape requires industry to ensure that oversight and quality of deliverables are maintained in all instances and in particular when significant processes have been outsourced. As the ultimate accountability for compliance rests with the company, assessment of vendors’ quality management systems (QMS) are becoming more common as a means to identify potential risks for consideration and remediation (Politis and Delgra, 2012).

The principles of an adequate QMS can be summarised as follows:

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

Notifications
Approvals
Submissions procedures
Registration
Classification
Insurance requirements

Need to verify requirements for each country
Defines customer requirements
Ensure products are processes are developed and verified to meet requirements
Measures performance
Addresses quality issues and improves quality
Improves productivity
Ensures that acceptable product is delivered to the customer

Quality Standards for Epidemiological Research

Basic principles for this kind of research are laid down in guidelines and recommendations for assurance of good epidemiological practice (GEP) and other additional international guidelines. The aim of GEP is to establish a quality standard for epidemiological research. The guidelines contain partially detailed recommendations regarding the topics ethic, research questions (e.g. a priori defined hypothesis), study plan, biological sample databases, quality assurance, data storing and data documentation, analysis, data protection, contractual provisions and interpretation of research results (Theobold et al., 2009).

Quality Assurance in Non-Interventional Studies

The aim of quality assurance is to make valid, scientific statements based on the results in NIS, meaning to avoid possible bias of results by using an appropriate study design and an adequate data analysis, assure authenticity, completeness and validity of the data and to identify and resolve deficiencies at an early stage (Theobold et al., 2009).

Laws, guidelines and recommendations relating to NIS are very helpful to implement quality assurance measures (Theobold et al., 2009).

General quality assurance measures include:

Employ SOPs specifically designed for managing the planning, operational, and evaluation processes involved in non-interventional studies (NIS);
Keep the study staff/project management team apprised of legal and regulatory requirements and recommendations for NIS;

Ensure that the protocol and study-related management processes do not interfere with the non-interventional premise of NIS;

Implement a quality plan that describes which quality control and quality assurance activities should be conducted.

(Source: Theobold et al., 2009).
<table>
<thead>
<tr>
<th>Useful Links</th>
<th>Accessed From</th>
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<tbody>
<tr>
<td>Politis and Delgra, 2012</td>
<td>Politis H and Delgra CJ. Industry Perspective on Quality Management Systems and Outsourcing - Challenges and Expectations. Quasar, October 2012</td>
</tr>
<tr>
<td>Useful Links</td>
<td>Accessed From</td>
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<tr>
<td>SJ, Poole C, Schleselman JJ, Egger M; STROBE Initiative. Strengthening the</td>
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<tr>
<td>Reporting of Observational Studies in Epidemiology (STROBE): explanation and</td>
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<td>STROBE Initiative. The Strengthening the Reporting of Observational Studies</td>
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<tr>
<td>in Epidemiology (STROBE) statement: guidelines for reporting observational</td>
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</tbody>
</table>
Ethical Considerations when Conducting Non-Interventional Studies

WHICH ETHICAL STANDARDS ARE APPLICABLE TO NIS?

As a general rule we have ethical standards because at some point in the past there was a lack of such standards that resulted in a detrimental impact on the credibility of the medical experiments and/or the health and welfare of patients. It’s a case of cause and effect.

In order to understand the impact and applicability of the effect (ethical standard) it helps to understand why it was necessary i.e., what caused it.

For most of you, the following history lesson won’t be new. However, bear with me because it helps to explain the general ethical scientific and ethical quality standard that is applicable to non-interventional studies.

World War II Nazi Medical Experiments (1939 - 1945)

During the second world war (1939 to 1945), the German Nazi’s performed many medical experiments on prisoners with a view to either ‘advancing science’ or aiding their soldiers in the battle.

Many of these experiments were terminal, none were in the best interests of those subjected to the experiments and none of the prisoners had a choice as to whether they would participate or not.

At the end of the second world war some of the Nazi doctors who had performed human experiments were tried at a war crimes tribunal in Nuremberg. During the Nuremberg War
Crime Trials, the ‘Nuremberg code’ was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype/foundation of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner (The Belmont Report).

The Declaration of Helsinki (1964)

In 1947, the World Medical Association (WMA) was formed with a view to preventing a reoccurrence of such atrocities and in 1964, the WMA expanded the ‘Nuremberg Code’, which although a good start as an ethical code for human research, was too short to be of practical use. And so was born the ‘Declaration of Helsinki’ which still forms the ethical foundation for biomedical research.

According to the Declaration of Helsinki:

- The interests of the research subject must always prevail over the interests of science and society
- Voluntary consent is essential
- When the subject is legally incapacitated, the consent of their legal guardian should be obtained
- Research subjects must have the right to withdraw
- Research studies must be scientifically sound
- The design and performance of the study must be clearly stated in a protocol
- The study protocol should be independently reviewed
- The protocol should always include a statement of the ethical considerations involved
- Researchers must be appropriately qualified
- The privacy of the research subject must be respected
The importance of the research must be proportional to the risk to the research subject.

The Need to Harmonise the Clinical Trials Regulations (1964 - 1996)

Between 1964 and 1996, each nation conducted clinical trials implemented their own operational interpretation of of the Declaration of Helsinki. The result was that each country had different, and often conflicting requirements, for the approval, conduct and reporting of clinical trials (as per the History of the ICH).

The realisation that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. However in many cases the realisation was driven by tragedies, such as that with thalidomide in Europe in the 1960s (as per the History of the ICH).

For most countries, whether or not they had initiated product registration controls earlier, the 1960s and 1970s saw a rapid increase in laws, regulations and guidelines for reporting and evaluating the data on safety, quality and efficacy of new medicinal products. The industry, at the time, was becoming more international and seeking new global markets, however the divergence in technical requirements from country to country was such that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally (as per the History of the ICH).

The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of health care, escalation of the cost of R&D and the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need (as per the History of the ICH).

The Birth of the ICH (1989)

Harmonisation of regulatory requirements was pioneered by the European Community (EC), in the 1980s, as the EC (now the European Union) moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonisation was feasible. At the same time there were bilateral discussions between Europe, Japan and the US on possibilities for harmonisation. It was, however, at the WHO Conference of Drug Regulatory Authorities...
(ICDRA), in Paris, in 1989, that specific plans for action began to materialise. Soon afterwards, the authorities approached IFPMA to discuss a joint regulatory-industry initiative on international harmonisation, and ICH was conceived (as per the History of the ICH).

The birth of ICH took place at a meeting in April 1990, hosted by EFPIA in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH (as per the History of the ICH).

At the first ICH Steering Committee (SC) meeting of ICH the Terms of Reference were agreed and it was decided that the Topics selected for harmonisation would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorising new medicinal products (as per the History of the ICH).

ICH Guideline for Good Clinical Practice (ICH GCP - 1996)

In 1996, the harmonised tripartite guideline for good clinical practice (ICH GCP) was adopted in Europe and in 1997 in Japan and the USA. This began the process for harmonising the ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

And what ethical principles is ICH GCP based on? The ethical principles that have their origin in the Declaration of Helsinki (as per Section 2.1 of ICH GCP).

In Europe, the ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects was adopted as the Clinical Trials Directive in 2001 (2001/20/EC), with the legal directive that European member states transposed these requirements into national legislation by 2004. Thus, the requirements of ICH GCP became legally binding for clinical trials in Europe and all other regions where ICH GCP was adopted into national legislation.
Applicability of Clinical Trials Regulations and ICH GCP to NIS (1996 to Present)

The implementation, in whole or part, of ICH GCP into national legislations was great news for interventional clinical trials, but it left a regulatory gap for non-interventional studies. For example, in Europe Article 1.1 of the Clinical Trials Directive states “This Directive does not apply to non-interventional trials”.

Furthermore, ICH GCP was developed to provide detailed harmonised operational guidelines for clinical trials and as such many of the elements aren’t applicable to non-interventional studies e.g., IMP, drug labelling and drug accountability; Investigator’s Brochure; study-related insurance in case of injury to patients as a result of novel interventions etc.

The regulation of non-interventional studies is addressed at a national level. The requirements aren’t harmonised and as such, the current situation for non-interventional studies is similar to pre-1996 ICH GCP era for interventional clinical trials.
Why don’t we apply GCP in its entirety to NIS?

Simply put, NIS are different types of studies, with different approaches, designs and risks to interventional clinical trials. It’s not about ethical compromise, it’s all about ethical applicability. Many of the requirements stipulated in GCP aren’t applicable to non-interventional studies (see below).

For example:

- The protocol does not dictate the treatment of the patients
  - The purpose of a non-interventional studies is to ‘observe’ the real life use of an approved drug. As such, the inclusion and exclusion criteria are very minimal – we aren’t trying to reduce variables, as per clinical trials, we’re trying to understand the impact of these variables on the use, efficacy and safety of the drugs in real patients who are likely to be on multiple concomitant medications and suffer from a range of ailments.
  - The NIS protocol dictates the methodology for data collection, not the treatment of the patient
  - The purpose is to observe the outcomes of patients undergoing routine clinical practice. The protocol must therefore be designed to accommodate this and ensure that the prescribing pattern of the treating Physician isn’t influenced by the study. This is the reason why the patient must already be prescribed the drug before they can participate in the study

- There is no investigational medicinal product (IMP), the drug is prescribed by the Physician as per normal clinical practice
  - No drug is supplied by the study Sponsor
  - There is therefore no need for study-specific drug accountability

- There is no Investigator’s Brochure (IB)
  - The drug is approved and information is therefore provided through the Summary of Product Characteristics (SmPC)
- There is therefore no need to track the SmPC

The main risk to patients is a breach of data privacy and the direct impact that this may have on them e.g., increased life or health insurance premiums, genetic discrimination etc

There is no need to provide study-specific insurance against adverse reactions to the IMP, as the drug is approved and being used in accordance with the marketing authorisation

Safety reporting is conducted in accordance with the standard procedures for marketed products (unless collection of safety information is an objective of the NIS)

The Tuskegee Syphilis Observational Study (1932 - 1972)

The Tuskegee Syphilis Study demonstrated that observational studies aren’t exempt from abuse. The US government conducted an observational study on African-Americans with the purpose of learning more about the disease progression of syphilis. The ‘participants’ believed they were receiving government aid, they didn’t know they were part of a research study for 40 years they were observed by the US government researchers. Treatment was withheld from the ‘participants’ for 40 years, even though they could have been cured of the disease.
The public outcry from this study resulted in the implementation of the National Research Act in 1974 in the US and the drafting of the Belmont Report in 1979 on the ‘Ethical Principles and Guidelines for the Protection of Human Subjects of Research’.

**Statement from Fred D Gray – Attorney (8th April 1997)**

“In 1932 the US Government misled 623 African-Americans into participating into a study of untreated syphilis. The government induced these men to participate in a study in which the government represented that the participants were being treated for whatever their ailments were. They were never told what their ailment was. They never gave their consent to be involved in a study, nor did they realise they were part of a study until the story broke in July 1972. Treatment was knowingly withheld for 40 years.”


**Statement from President Bill Clinton (16th May 1997)**

“Men who were poor and African American, without resources and with few alternatives believed they had found hope when they were offered free medical care by the United States Public Health Service. They were betrayed.

For 40 years, hundreds of men were betrayed, along with their wives and children, along with a community in Macon County, Alabama, the City of Tuskegee, the fine university there, and the larger African American community. The United States government did something that
was wrong – deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all of our citizens.”

(Source: [http://www.cdc.gov/tuskegee/clintonp.htm](http://www.cdc.gov/tuskegee/clintonp.htm))

**Statement from Vice President Al Gore (16th May 1997)**

“Medical professionals willingly and intentionally let human beings suffer from a treatable, and then later a curable illness. These researchers knew that mercury and arsenic compounds could treat the disease, but the Tuskegee men did not receive the medicine. Later the researchers knew that penicillin could cure the disease, but again, the Tuskegee men did not get the medicine. They didn’t get treated until the 40 year study was discovered and stopped amid public outcry in 1972. It was a disgraceful episode for American Scientists.”

(Source: [http://www.cdc.gov/tuskegee/clintonp.htm](http://www.cdc.gov/tuskegee/clintonp.htm))

**DO WE APPLY GCP, GEP OR GPP TO NIS?**

**So What are the Scientific and Ethical Quality Standards that are Applicable to NIS?**

So what quality standards should we apply to non-interventional studies? Do we apply Good Clinical Practice (GCP), Good Epidemiological Practice (GEP) or Good Pharmacoepidemiological Practice (GPP)?

In reality, the answer is that we apply all the elements of the above GXPs that are applicable. GEP and GPP are operational adaptations of GCP and specifically address (although not in as much detail as GCP) the requirements drug-related NIS (GPP) and non-drug related NIS (GEP). Of course, the national regulations and requirements, where present, take precedence. In short, non-interventional studies should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, with GCP/GEP/GPP and the applicable regulatory requirements.

The next chapter provides a systematic overview of the scientific and ethical quality standards that are (GPP/GEP) that should be considered when planning, conducting and reporting non-interventional studies.
Regardless of whether the study is interventional or non-interventional, the general ethical requirements are based on the original requirements stipulated in the Declaration of Helsinki, namely:

- The patient must provide their voluntary informed consent, or in the case of legal incompetence consent should be obtained from the legal representative.
- They are free to withdraw from the study at any moment.
- The benefit to the patient should outweigh the risk to the patient.
- The rights, safety and welfare of the patient must be protected and the interest of the patient must always prevail over the interests of science and society.
- The study must be scientifically valid and the purpose described in a protocol.
- The protocol should always include a statement of the ethical considerations involved.
- The protocol must be reviewed by an independent ethics committee.
- The research must be conducted by scientifically qualified persons under the supervision of a clinically competent medical person.

**NIS GUIDELINES - ETHICS, DATA OWNERSHIP AND PRIVACY**

There is a wide range of guidelines for the protection of human subjects. All are consistent with the ethical principles that have their origin in the Declaration of Helsinki (see diagram below). The applicability of ethical requirements varies based on the nature of the inquiry and the studies to be conducted. Certain human subject protections applicable to clinical studies (e.g. full informed consent) would not apply to other kinds of research (e.g. review of data from de-identified medical records) ([ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010](https://www.ema.europa.eu/en/medicines-humans/epar-human-medication-guidelines/encpp-guide-methodological-standards-pharmacoepidemiology)).
Below is a short, and by no means complete, list of the ethical guidelines applicable to the conduct of non-interventional studies:

- **ICH GCP**
- **ISPE GPP**
- **IEA GEP**
- **CIOMS International Ethical Guidelines for Epidemiological Studies**
- **AHRQ**
- **ICJME Uniform Requirements for Manuscripts Submitted to Biomedical Journals**
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) - Harmonised Tripartite Guideline for Good Clinical Practice (ICH GCP)

This Good Clinical Practices document (ICH GCP or ICH E6) describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. GCPs cover aspects of monitoring, reporting and archiving of clinical trials and incorporating addenda on the Essential Documents and on the Investigator’s Brochure which had been agreed earlier through the ICH process.

The GCP guideline was specifically developed to harmonise the operational considerations of clinical trials. As such, many elements are not applicable to non-interventional studies.

International Society for Pharmacoepidemiology (ISPE) guideline for Good Pharmacoepidemiology Practices (GPP)

Consideration of ethical issues, data ownership and privacy is an important part of the International Society for Pharmacoepidemiology (ISPE) guideline for Good Pharmacoepidemiology Practices (GPP), section IV. It includes a sub-section (IV.A) on protection of human subjects and a reference to the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health. The GPP also recommends a stand-alone section within the protocol containing a description of plans for protecting human subjects that includes consideration of the need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee and the requirement of informed consent in accordance with local law (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

International Epidemiological Association (IEA) Good Epidemiological Practice (GEP) Guideline

The main scope of the International Epidemiological Association (IEA) Good Epidemiological Practice (GEP) guideline for proper conduct in epidemiological research is on the ethical principles of pharmacoepidemiological field studies, which could also apply to interventional studies, such as the role of ethics committees, patients’ informed consent, use and storage of personal data and publication of results (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).
The Council for International Organizations of Medical Sciences (CIOMS) 2009 International Ethical Guidelines for Epidemiological Studies

The Council for International Organizations of Medical Sciences (CIOMS) 2009 International Ethical Guidelines for Epidemiological Studies have as their objective the preparation of guidelines to indicate how the ethical principles that should govern the conduct of biomedical research involving human subjects could be effectively applied. The Guidelines set forth ethical guidance on how epidemiologists - as well as those who sponsor, review, or participate in the studies they conduct - should identify and respond to the ethical issues that are raised by the process of producing this information (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

The Agency for Healthcare Research and Quality (AHRQ) of the United States

The Agency for Healthcare Research and Quality (AHRQ) of the United States has published Registries to Evaluate Patient Outcomes: a User’s guide, Second Edition, which is a reference for establishing, maintaining and evaluating the success of registries created to collect data about patient outcomes. In Section 1: ‘Creating a registry’ is a specific chapter dedicated to ethics, data ownership, and privacy. The concepts are useful although the authors indicate that this section focuses solely on United States (US) law (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

The International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals

The Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (ICJME) includes clear statements on ethical principles related to publication in biomedical journals addressing authorship and contributorship, editorship, peer review, conflicts of interest, privacy and confidentiality and protection of human subjects and animals in research (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).
<table>
<thead>
<tr>
<th>Useful Links</th>
<th>Accessed From</th>
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<tr>
<td>Pharmacoepidemiologic Assessment (March 2005)</td>
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<td>Useful Links</td>
<td>Accessed From</td>
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<tr>
<td>ICH Website - History of the ICH</td>
<td><a href="http://www.ich.org/about/history.html">http://www.ich.org/about/history.html</a></td>
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<tr>
<td>International Committee of Medical Journal Editors</td>
<td><a href="http://www.icmje.org/">http://www.icmje.org/</a></td>
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<tr>
<td>Politis and Delgra, 2012</td>
<td>Politis H and Delgra CJ. Industry Perspective on Quality Management Systems and Outsourcing - Challenges and Expectations. Quasar, October 2012</td>
</tr>
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<td>The Nuremberg Code</td>
<td><a href="http://www.hhs.gov/ohrp/archive/nurcode.html">http://www.hhs.gov/ohrp/archive/nurcode.html</a></td>
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<td>The Tuskegee Syphilis Observational Study</td>
<td><a href="http://www.cdc.gov/tuskegee/clintonp.htm">http://www.cdc.gov/tuskegee/clintonp.htm</a></td>
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Recommendations for the Planning, Conduct and Reporting Considerations for Non-Interventional Studies

WHAT IS A NON-INTERVENTIONAL STUDY?

Definition

A non-interventional study is a study fulfilling cumulatively the following requirements:

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and
- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (e.g. case-control, cross-sectional and cohort studies). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met (as per Annex I of the EMA Guideline on good pharmacovigilance practices (GVP), 2012).

In this context, interviews, questionnaires and blood samples may be performed as normal clinical practice (as per Annex I of the EMA Guideline on good pharmacovigilance practices (GVP), 2012).
**Why Perform Non-Interventional Studies?**

Many questions in medical research are investigated in observational studies. Much of the research into the cause of diseases relies on cohort, case control, or cross-sectional studies. Observational studies also have a role in research into the benefits and harms of medical interventions. Randomized trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable to detect rare or late adverse effects of treatments and are more likely to provide an indication of what is achieved in daily medical practice (von Elm et al., 2008).

**THE COMPLEX SIMPLICITY OF NON-INTERVENTIONAL STUDIES**

A large majority of researchers that participate in the performance of non-interventional studies have come from a clinical trials background. They often come with the expectation that non-interventional studies (NIS), are simpler and easier to manage and perform than interventional clinical trials. It therefore comes as a shock when they realise that this isn’t the case. Welcome to the exciting and challenging world of non-interventional studies!

The table below illustrates the similarities and differences between interventional clinical trials and non-interventional studies.

**Comparison of the Considerations when Conducting Interventional Clinical Trials versus Non-Interventional Studies**

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Interventional Clinical Trial (Higher Risk)</th>
<th>Non-Interventional Study (Low Risk)</th>
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<tbody>
<tr>
<td>Ethical Standards</td>
<td>• Declaration of Helsinki</td>
<td>• Declaration of Helsinki</td>
</tr>
<tr>
<td></td>
<td>• ICH GCP etc</td>
<td>• ISPE GPP</td>
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<tr>
<td></td>
<td></td>
<td>• ICH GCP</td>
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<tr>
<td></td>
<td></td>
<td>• Dependent on country</td>
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<tr>
<td>Considerations</td>
<td>Interventional Clinical Trial (Higher Risk)</td>
<td>Non-Interventional Study (Low Risk)</td>
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</tr>
<tr>
<td>Regulatory Approvals</td>
<td>• National Competent Authority</td>
<td>• IRB/IEC - often unfamiliar with NIS which can lead to delays in the review and approval process.</td>
</tr>
<tr>
<td></td>
<td>• IRB/IEC</td>
<td>• National Competent Authority - Dependent on country</td>
</tr>
<tr>
<td></td>
<td>• Data Protection Agency - Dependent on Country</td>
<td>• Data Protection Agency - Dependent on country</td>
</tr>
<tr>
<td></td>
<td>• Harmonised framework</td>
<td>• No harmonised framework - country-specific requirements</td>
</tr>
<tr>
<td>Regulatory Submission Documents</td>
<td>• Comprehensive harmonised submission package</td>
<td>• Country dependent</td>
</tr>
<tr>
<td></td>
<td>• ICH GCP compliant</td>
<td>• Usually limited/streamlined submission package</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No harmonised submission package - Compliant with local legislation</td>
</tr>
<tr>
<td>Registration</td>
<td>• Mandatory</td>
<td>• Dependent on country</td>
</tr>
<tr>
<td>Monitoring</td>
<td>• Requirements dictated by Section 4.18 of ICH GCP</td>
<td>• Dependent on study type and country-specific requirements</td>
</tr>
<tr>
<td></td>
<td>• Usually on-site monitoring with extra ‘triggered’ visits when required</td>
<td>• Primarily remote monitoring with scheduled on-site monitoring as needed</td>
</tr>
<tr>
<td>Risk to Patient</td>
<td>• Exposure to novel interventional treatment (diagnostic or therapeutic)</td>
<td>• Compromised data privacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Possible psychological trauma -</td>
</tr>
<tr>
<td>Patient Enrollment</td>
<td>• Strict inclusion and exclusion criteria as trying to reduce as many variables as possible</td>
<td>• Very few inclusion and exclusion criteria as trying to capture ‘real life’ use of drug</td>
</tr>
<tr>
<td>Physicians</td>
<td>• Usually are already GCP trained and have previous clinical trials experience</td>
<td>• Often naive to clinical research</td>
</tr>
<tr>
<td>Considerations</td>
<td>Intervventional Clinical Trial (Higher Risk)</td>
<td>Non-Interventional Study (Low Risk)</td>
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<td>---------------------------------</td>
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</tr>
<tr>
<td>Treatment</td>
<td>• Dictated by protocol</td>
<td>• Dictated by Physician. Patient must already be prescribed the drug of interest prior to enrollment</td>
</tr>
<tr>
<td>Study Visits</td>
<td>• Dictated by protocol</td>
<td>• As per normal clinical practice</td>
</tr>
<tr>
<td>Drug Supplied by Study Sponsor</td>
<td>• Always</td>
<td>• Never</td>
</tr>
<tr>
<td></td>
<td>• Need to account for all IMP</td>
<td>• Prescribed by treating Physician and used according to SmPC i.e., not an investigational drug</td>
</tr>
<tr>
<td></td>
<td>• Needs to be labelled as IMP</td>
<td>• No need to account for the drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No need for special labelling</td>
</tr>
<tr>
<td>Investigator Brochure (IB)</td>
<td>• Required for all pre-approval IMPs</td>
<td>• Not required as drugs approved</td>
</tr>
<tr>
<td></td>
<td>• To be review annually</td>
<td>• Physicians have access to SmPCs of prescribed drugs as standard - not supplied by study Sponsor</td>
</tr>
<tr>
<td></td>
<td>• Need to demonstrate that IBs have been received by participating Physicians</td>
<td></td>
</tr>
<tr>
<td>Study-Specific Insurance</td>
<td>• Study Sponsor legally required to provide insurance to patients for IMP/study-related adverse reactions</td>
<td>• Generally not required for NIS as drug is approved and is used in accordance with SmPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Some exceptions e.g., Belgium</td>
</tr>
<tr>
<td>Data Collection</td>
<td>• Generally large CRFs with text fields as needed</td>
<td>• Limited/minimal CRFs with limited text fields</td>
</tr>
<tr>
<td></td>
<td>• Usually includes lots of ‘nice to have’ fields which results in multiple and often excessive and unnecessary data queries</td>
<td>• Should include only ‘must have’ data to reduce data queries and burden to site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Imperative that impact of data collection on site is limited to a minimum</td>
</tr>
<tr>
<td>Considerations</td>
<td>Interventional Clinical Trial (Higher Risk)</td>
<td>Non-Interventional Study (Low Risk)</td>
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</tbody>
</table>
| Safety Reporting   | • Requirements dictated by ICH E2 series  
• Terminal and life-threatening SUSARs reported to NCA and IRB/IEC within 7 days of becoming aware of reaction  
• All other SUSARs to be reported within 15 days | • Requirements dictated by local requirements - as a general rule, comply with post-authorisation safety reporting requirements e.g., spontaneous reporting within 15 days of knowledge of reaction  
• Specific reporting requirements in Europe - as per EMA GVP module VI and VIII |
| Study Report       | • Format dictated by ICH E3 | • Format dependent on study type and country-specific requirements  
• Specific requirements for mandated EU non-interventional PASS |
| Audits             | • Generally a legal imperative derived from implementation of Section 5.1 of ICH GCP into national legislation | • Generally a recommendation based on stipulations from the Codes of Practice of Pharmaceutical Self-Regulatory Bodies (e.g., EFPIA) and generic guidelines such as ISPE GPP  
• Legal imperative in countries such as Spain  
• Legal Imperative for NCA mandated Post-Authorisation Safety Studies (PASS) |
| NCA Inspection     | • Generally a legal requirement based on national clinical trials regulations | • Legal Imperative for NCA mandated Post-Authorisation Safety Studies (PASS)  
• Dependent on country |
Why aren’t Non-Interventional Studies Simpler and Easier to Manage and Perform than Interventional Clinical Trials?

It’s a valid question. In theory, non-interventional studies should be more simple to manage and perform than interventional clinical trials because the purpose of the studies is to observe the use of drugs in ‘real life’ situations. As a researcher you aren’t influencing how a patient is being treated. You are merely observing the outcome of that treatment.

The simple fact is that the operational standards and requirements for the planning, conduct and reporting of interventional clinical trials were harmonised through the implementation of ICH GCP in 1996 and the subsequent adoption into national legislation.

Whereas, the operational standards and requirements for the planning, conduct and reporting of non-interventional studies have not been harmonised. The results is that each country around the world governs non-interventional studies according to their own standards and requirements.

This report highlights the generic ethical and scientific standards that are applicable to all non-interventional studies. These then need to be supplement with the country-specific requirements for your study which will be dependent on a variety of factors including, but not limited to, the design of the study (retrospective or prospective), the purpose of the study, the patient population, what you intend to collect, what you intend to do with the samples and/or data you collect, and where you intend to conduct the study.

GOOD PHARMACOEPIDEMIOLOGY PRACTICES (GPP)

The ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP) are regarded as the foundational guidelines for non-interventional studies and as such form the core of the NIS activity recommendations listed below:

- Study Classification
- Protocol Development
- Responsibilities
- Personnel
- Facilities
- Resource commitment
- Contracts
- Contractors
- Study conduct
- Protection of human subjects
- Data collection, management and verification
- Monitoring
- Analysis
- Study Reports
- Communication
- Adverse Event Reporting
- Archiving
STUDY CLASSIFICATION

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

**Study Classification**

<table>
<thead>
<tr>
<th>Interventional?</th>
<th>Is your study an interventional clinical trial?</th>
<th>Regulatory Framework</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASS?</td>
<td>Is your study a post-authorization safety study (PASS)?</td>
<td>Clinical Trials Directive (2001/20/EC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Country Specific!</td>
</tr>
</tbody>
</table>

REGULATORY ASSESSMENT

A key part of conducting non-interventional studies is understanding the country-specific regulatory requirements, which in themselves will be dependent on the type of study you intend to conduct. Hence, the need for the initial study classification step (above).

Once the study has been classified, the requirements per country need to be assessed and may include approvals, notifications and/or registration with the following:

- Competent Authority
- IRBs/ RECs
- Data Protection Agencies
- Hospitals/ Institutions

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NIS-C-BASICS-2013
PROTOCOL DEVELOPMENT

Each study should have a written protocol. A protocol should be drafted as one of the first steps in any research project, and the protocol should be amended and updated as needed throughout the course of the study. The protocol should include the following elements:

A. A descriptive title and version identifier (e.g., date);

B. The names, titles, degrees, addresses, and affiliations of all responsible parties, including the principal investigator, co-investigators, and a list of all collaborating primary institutions and other relevant study sites;

C. The name and address of each sponsor;

D. An abstract of the protocol;

E. The proposed study tasks, milestones, and timeline;

F. A statement of research objectives, specific aims, and rationale;
   i. Research objectives describe the knowledge or information to be gained from the study. Specific aims list key exposures and outcomes of interest, and any hypotheses to be evaluated. The protocol should distinguish between a limited number of a priori research hypotheses and hypotheses that are generated based on knowledge of the source data. The rationale explains how achievement of the specific aims will further the research objectives.

G. A critical review of the literature to evaluate pertinent information and gaps in knowledge;
   i. The literature review should describe specific gaps in knowledge that the study is intended to fill. The literature review might encompass relevant animal and human experiments, clinical studies, vital statistics, and previous epidemiological studies. The literature review should also cite the findings of similar studies, and the expected contribution of the current study.

H. A description of the research methods, including:
   i. The overall research design, strategy, and reasons for choosing the proposed study design;
• Research designs include, for example, case-control, cohort, cross-sectional, nested case-control, safety trials or hybrid designs.

ii. The population or sample to be studied;

• The population is defined in terms of persons, place, time period, and selection criteria. The rationale for the inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, description of the population and details of sampling methods should be provided.

iii. The strategies and data sources for determining exposures, health outcomes, and all other variables relevant to the study objectives, such as potential confounding variables and effect measure modifiers;

• Data sources might include, for example, questionnaires, hospital discharge files, abstracts of primary clinical records, electronic medical records, ad hoc clinical databases, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews, or exposure/disease registries. Use validated instruments and measures whenever such exist, and describe the validation method. If data collection methods or instruments will be tested in a pilot study, plans for the pilot study should be described. Any expert committees and evaluation procedures to be used to validate diagnosis should be described.

iv. Clear operational definitions of health outcomes, exposures, and other measured risk factors as well as selection criteria and comparison groups;

• An operational definition is one that can be implemented independently using the data available in the proposed study. For example "pneumocystis carinii pneumonia, episode" is not an operational definition; a better description would be "hospitalization with a primary discharge diagnosis of ICD-9-CM code 136.3.”

v. Projected study size, statistical precision, and the basis for their determination;
• Describe the relation between the specific aims of the study and the projected study size in relation to each outcome. In most circumstances it is desirable to express study goals in terms of precision sought for study estimates rather than statistical power. For safety studies, it may be useful to specify the sample size that can minimally detect a pre-specified risk with a pre-specified power. For example, “the study has an 80% power to detect a relative risk of 3 or greater for drug x compared to treatment with other drugs commonly used in this condition.”

vi. Methods used in assembling the study data;

• This should include a description of, or reference to any pre-testing procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders, or data entry personnel. This should also include procedures for linkage and data mining of administrative databases.

vii. Procedures for data management;

• Describe data management and statistical software programs and hardware to be used in the study. Describe data preparation and analytical procedures as well as the methods for data retrieval and collection.

viii. Methods for data analysis; Data analysis includes all the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, or modify raw data.

• Data analysis comprises comparisons and methods for analyzing and presenting results, categorizations, and procedures to control sources of bias and their influence on results, e.g., possible impact of biases due to selection bias, misclassification, confounding, and missing data. The statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, for instance, should be presented. Any sensitivity analyses should be described.

ix. A description of quality assurance and quality control procedures for all phases of the study;
Mechanisms to ensure data quality and integrity should be described, including, for example, abstraction of original documents, extent of source data verification, and validation of endpoints. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups.

x. Limitations of the study design, data sources, and analytic methods;

• At a minimum, issues relating to confounding, misclassification, selection bias, generalizability, and random error should be considered. The likely success of efforts taken to reduce errors should be discussed.

I. A description of plans for protecting human subjects;

i. This section should include information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects, and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study. Conditions under which a clinical trial would be terminated for ethical reasons (stopping rules) should be described. Procedures for monitoring results should be described, and the use of a Data Safety Monitoring Board (DSMB) for clinical trials should be considered for this purpose. The need for submitting the protocol to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the requirement of informed consent should be considered in accordance with local law. See Section IV A.

J. A description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication;

i. There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g., results pertaining to the safety of a marketed medication). Authorship should follow guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/). See also, Section V, Communication. The Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/statement/revisedstatement.htm) refers to randomized studies, but provides useful guidance applicable to nonrandomized studies as well.

K. Resources required to conduct the study;
i. Describe time, personnel, services (e.g. database access), and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.

L. Bibliographic references;

M. Dated amendments to the protocol.

i. Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, along with the rationale, should be documented in writing. Any changes made after data analysis has begun should be documented as such and the rationale provided.

(as per Section II of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

RESPONSIBILITIES

The organization(s) and individual(s) conducting and sponsoring the research shall be fully responsible for the research. The relationship, roles, and responsibilities of the organizations and/or individuals conducting and sponsoring the study should be described (as per Section III.A of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

For safety studies sponsored and conducted by a pharmaceutical company, the individuals responsible for pharmacoepidemiological research, along with the type of expertise and autonomy in conducting the research, should be stated clearly. For projects sponsored by one organization (such as a pharmaceutical company or, government agency) but implemented by another (e.g., an academic institution or a contract research organization-CRO), responsibility for scientific integrity is shared by the collaborating institutions (e.g, sponsor, the principal investigator conducting the study, the senior qualified epidemiology staff within the CRO and the organization that employs the principal investigator). In such situations of shared responsibility, contractual arrangements should include a timeline for study completion and contingency plans if the timeline cannot be met. In particular, the contract should delineate the roles and responsibilities to be assumed by the study sponsor and the contractor(s) in communicating various aspects of the study as well as data access, ownership and archiving (as per Section III.A of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
PERSONNEL

Personnel engaged in epidemiological research and related activities should have the education, training, or experience necessary to perform the assigned functions competently. The organization should maintain a current summary of training and experience of these personnel. A list of individuals engaged in or supervising activities should be maintained and updated periodically with current job titles (as per Section III.B of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

FACILITIES

Adequate physical facilities shall be provided to all those engaged in epidemiological research and related activities. Sufficient resources, e.g., office space, relevant equipment, and office/professional supplies, shall be available to ensure timely and proper completion of all studies. Suitable storage facilities shall be available to maintain technical records in a secure and confidential environment in compliance with local regulations (as per Section III.C of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

RESOURCE COMMITMENT

Sufficient commitment shall be made at the beginning of each study to ensure its timely and proper completion (as per Section III.D of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

CONTRACTS

For studies that are funded by a marketing authorisation holder, including studies developed, conducted or analysed fully or partially by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the marketing authorisation holder and investigators should ensure that the study meets its regulatory obligations while permitting their scientific
expertise to be exercised throughout the research process. In the research contract, the marketing authorisation holder should consider the provisions of the ENCePP Code of Conduct and address the following aspects:

- rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
- rights and obligations of the investigator(s) and marketing authorisation holder;
- clear assignment of tasks and responsibilities;
- procedure for achieving agreement on the study protocol;
- provisions for meeting the marketing authorisation holder’s pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;
- intellectual property rights arising from the study and access to study data;
- storage and availability of analytical dataset and statistical programmes for audit and inspection;
- communication strategy for the scheduled progress and final reports;
- publication strategy of interim and final results.

(as per Section VIII.B.3 of EMA GVP Module VIII)

**CONTRACTORS**

For the purposes of ensuring and documenting the contractor’s conformance with the GPP, it is recommended that the study sponsor have the right during the course of the study, and for a reasonable period following completion of the study, to inspect the contractor’s facilities, including equipment, technical record, and records relating to the work conducted under the sponsor’s contract. The nature of the audit, including procedures that ensure patient confidentiality, should be agreed upon at the outset of any contract (as per Section III.E of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
STUDY CONDUCT

The principal investigator shall be responsible for the overall content of the individual research project, including the day-to-day conduct of the study, interpretation of the study data, and preparation and publication of the final report. These responsibilities extend to all aspects of the study, including periodic reporting of study progress as well as quality assurance (as per Section IV of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

The unusual decision to terminate a study prematurely should be taken with great caution, and should be based on good scientific and ethical reasons and documented in writing. There may be rare instances in which administrative reasons require study termination. Such decisions should be independent of any study results. Investigators and sponsors should specify and agree in advance about the circumstances under which the study could be terminated early. Included should be a mechanism for resolution of any disagreement (as per Section IV of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

PROTECTION OF HUMAN SUBJECTS

Approval by an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or other appropriate body, should be obtained for all research involving human subjects. Informed consent will be needed when the research imposes a risk for patients. Informed consent also is normally required if the study requires data containing personal identifiers. Studies conducted entirely using administrative databases or records that do not contain any personal identifiers, or which meet certain other criteria, may require only abbreviated review or may not require formal review, at the discretion of the IRB/IEC (as per Section IV.A of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Investigators shall ensure that personal identifiers will be removed from any study files that are accessible to non-study personnel in accordance with applicable laws and regulations. Whenever feasible, study files should be coded and stripped of personal identifiers, and code keys stored separate from study files. All personnel with access to data containing personal identifiers will sign a pledge to maintain the confidentiality of study subjects, and will maintain an ability to verify the origin and integrity of data sets from which personal identifiers will have been removed. For additional information, please consult the ISPE guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of
Public Health (http://www.pharmacoepi.org/resources/privacy.cfm). Blood and serum sample collections stored after completion of clinical studies are a valuable resource. However, protecting confidentiality in such data requires special consideration and investigators are encouraged to consult guidelines developed by the NHLBI (as per Section IV.A of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

DATA COLLECTION, MANAGEMENT AND VERIFICATION

All data collected for the study should be recorded accurately, promptly, and legibly. The individual(s) responsible for the integrity of the data, computerized and hard copy, shall be identified, and shall have the education, training, and experience to perform the assigned tasks (as per Section IV.B of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

All procedures used to obtain, verify and promote the quality and integrity of the data should be recorded in sufficient detail so that others can replicate them. A historical file of these procedures shall be maintained, including all revisions and the dates of such revisions. Any changes in data entries shall be documented (as per Section IV.B of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Security of the data should be maintained at all times. Access should be limited to authorized individuals. Control systems, such as document encryption, should be used to ensure the authenticity, integrity and confidentiality of electronic records when transmitted over open networks (e.g., the internet). Adequate back up of the data should be maintained throughout the course of the study (as per Section IV.B of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Data Privacy Requirements in Europe

In Europe, European Union (EU) and national laws are the keys to what may and may not be done with regard to data access, data linkage and consent issues, including such domains as human rights and duty of confidentiality. While differing data custodians currently have differing requirements related to what approvals are needed before data can be released, the requirements will fit within the overall need to meet all applicable EU and national laws and guidelines for the actual study. This includes situations where multi-country studies are being
conducted and there may be transfer of data or information. In addition to meeting legislative requirements, studies also need to adhere to a set of principles that meet with the requirements of scientific and ethical reviews (ENCePP Guide on Methodological Standards in Pharmacoepidemiology, EMA/95098/2010).

**MONITORING**

Monitoring is key to ensure patient safety and data quality and is a legal requirement for interventional clinical trials and is described in detail in Section 5.18 of ICH GCP.

The differences in the study design, potential risks to patients, study duration, number of patients and global footprint of non-interventional studies means that the monitoring approaches adopted for interventional clinical trials are generally not feasible, or required for non-interventional studies.

Monitoring of NIS therefore needs to be tailored to accommodate a range of NIS considerations including the study design, regulatory requirements, study duration, number of sites and patients and study outcomes.

**Why are non-interventional studies different from interventional clinical trials?**

- Drug commercially available and used according to marketing authorisation
- Not protocol driven
- Retrospective and prospective designs
- Country-specific requirements
- Breach of data privacy is greatest study risk to patient, not IMP-related SARs

**Considerations when Designing a Monitoring Plan for Non-interventional**

When designing an NIS monitoring plan, need to consider:

- Regulatory requirements
e.g., monitoring of NIS is a legal requirement in Spain

Study design and purpose/endpoints

Study size, duration and global footprint

Therapeutic area

Business policy - The degree of risk the business is willing to accept e.g., a 0% monitoring policy significantly increases the risk that any data generated will not be credible or submissable (e.g., RMP) or publishable

Types of Monitoring

1. On-site monitoring

2. On-site & remote monitoring (Hybrid)

3. Remote monitoring
   - Phone calls, emails, eCRF etc

4. No monitoring

<table>
<thead>
<tr>
<th>Type of Monitoring</th>
<th>Opportunities</th>
<th>Challenges</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>On-Site Monitoring</td>
<td>Can be used for short-term prospective NIS such as PASS where data credibility is paramount</td>
<td>• Impractical for large, long-term prospective studies</td>
<td>• Classic gold standard</td>
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<td></td>
<td></td>
<td>• High cost and resource implications</td>
<td>• On-site monitoring every 4 to 8 weeks</td>
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<tr>
<td></td>
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<td></td>
<td>• 100% SDV of X% of CRFs</td>
</tr>
<tr>
<td>Type of Monitoring</td>
<td>Opportunities</td>
<td>Challenges</td>
<td>Comments</td>
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</tbody>
</table>
| Hybrid Monitoring  | • Allows for frequent contact with sites to provide support and reinforce appropriate performance  
• Reduced resource and cost requirements  
• Can be used to trigger on-site monitoring  
• Schedule periodic site visits to address site needs and assess data quality | • Needs to be conducted by an experienced CRA for it to be effective  
• Sponsor-site relationship is more effective when a single point of contact is maintained (may be impacted by staff turnover)  
• Need to clearly define ‘triggers’ for on-site monitoring prior to study start e.g.,  
• Suspected fraud  
• Rate of enrollment  
• Missing CRFs  
• Number of data queries | |
Overview of NIS Monitoring Approaches

100% on-site monitoring  
100% remote monitoring  
0% monitoring  
Hybrid monitoring  
Short-term Prospective NIS PASS  
First choice for most NIS  
Retrospective data mining

ANALYSIS

A clearly defined statistical analysis plan with statistical procedures should be presented (as per Section IV.C of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

All data management and statistical analysis programs and packages used in the analyses should be documented and archived. Reasonable effort should be made to document and validate interim steps in the analysis (as per Section IV.C of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

The analysis should be directed toward the unbiased estimation of the epidemiological parameters of interest (e.g., risk or rate differences, risk or rate ratios). The precision of effect estimates should be quantified separately using confidence intervals. Interpretation of statistical measures, including confidence intervals, should be tempered with appropriate judgment and acknowledgements of potential sources of error and limitations of the analysis, and should never be taken as the sole or rigid basis for concluding that there is or is not a relation between an exposure and outcome. Sensitivity analyses should be conducted to examine the effect of varying the study population inclusion/exclusion criteria, the assumptions regarding exposure, potential effects of misclassification, unmeasured confounders, and the definitions of potential confounders and outcomes on the association between the a priori exposure of interest and the outcome(s) (as per Section IV.C of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
STUDY REPORTS

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative has developed recommendations on what should be included in an accurate and complete report of an observational study (von Elm et al., 2008).

Research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn. The credibility of research depends on a critical assessment by others of the strengths and weaknesses in study design, conduct, and analysis. Transparent reporting is also needed to judge whether and how results can be included in systematic reviews. However, in published observational research important information is often missing or unclear. An analysis of epidemiological studies published in general medical and specialist journals found that the rationale behind the choice of potential confounding variables was often not reported. Only few reports of case control studies in psychiatry explained the methods used to identify cases and controls. In a survey of longitudinal studies in stroke research, 17 of 49 articles (35%) did not specify the eligibility criteria. Others have argued that without sufficient clarity of reporting, the benefits of research might be achieved more slowly, and that there is a need for guidance in reporting observational studies (von Elm et al., 2008).

ISPE Guidance on NIS Study Reports

The study protocol should describe the need and purpose of interim reports, when applicable. If required, the issuance of such reports must be pre-specified in the study protocol (as per Section IV.D of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Completed studies shall be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings (as per Section IV.D of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

The final report shall include at minimum:
1. A descriptive title;

2. An abstract;

3. Purpose (objectives) of the research, as stated in the protocol;

4. The names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators;

5. Name and address of each sponsor;

6. Dates on which the study was initiated and completed;

7. Introduction with background, purpose, and specific aims of the study;

8. A description of the research methods, including:

   (a) source population and selection of study subjects;

   (b) data collection methods and, if questionnaires or surveys are involved, complete copies (including skip patterns);

   (c) transformations, calculations, or operations on the data;

   (d) statistical methods used in data analyses.

9. A description of circumstances that may have affected the quality or integrity of the data; Describe the limitations of study approach and the methods used to address them (e.g., response rates, missing or incomplete data)

10. Analysis of the data; Include sufficient tables, graphs, and illustrations to present the pertinent data and to reflect the analyses performed. Epidemiological parameters (e.g., risks, rates, risk or rate differences, risk or rate ratios) are the most typical epidemiological measures to report. Both unadjusted and adjusted results should be presented. Effect measures should not be described as ”significant” or ”not significant.” Precision of estimates should be quantified using confidence intervals. Estimation is preferable to tests of statistical significance. Confidence intervals communicate both the strength of the relationship and the precision of the measure and are therefore more informative than point estimates accompanied by p-values.

11. A statement of the conclusions drawn from the analyses of the data;
12. A discussion of the implication of study results; Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research. Inferences about causal effects should be based on a variety of factors that should be explored in the discussion section. These factors include strength of relationship, temporal relationship, biological mechanism, plausibility of alternative theories, biases, confounding, precision, and others.

13. References.

(as per Section IV.D of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

STROBE Checklist for Cohort, Case-Control, and Cross-Sectional Study Reports

Much of biomedical research is observational. The reporting of such research is often inadequate, which hampers the assessment of its strengths and weaknesses and of a study’s generalizability. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative developed recommendations on what should be included in an accurate and complete report of an observational study (von Elm et al., 2008).

The study report should be traceable, transparent and objective

Follow STROBE statement for a checklist of items that should be addressed in articles reporting on cohort, case-control and cross-sectional observational studies

22 items essential for good reporting of observational studies:

- Article’s title (item 1)
- The introduction (item 2 and 3)
- Methods (item 4-12)
- Results (item 13-17)
- Discussion (item 18-21)
- Other information (item 22)

8 items are common to all 3 designs, 4 items (6,12,14, 15) are design-specific


<table>
<thead>
<tr>
<th>Items that should be included in reports of observational studies</th>
<th>Item No</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>TITLE AND ABSTRACT</td>
<td>1</td>
<td>(a) Indicate the study's design with a commonly used term in the title or the abstract</td>
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<tr>
<td></td>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
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<tr>
<td>INTRODUCTION</td>
<td></td>
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</tr>
<tr>
<td>Background/rationale</td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
<td>State specific objectives, including any pre-specified hypotheses</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
</tr>
<tr>
<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
</tr>
<tr>
<td>Items that should be included in reports of observational studies</td>
<td>Item No</td>
<td>Recommendation</td>
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<td>---------------------------------------------------------------</td>
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</table>
| Participants                                                 | 6      | (a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  
Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants  
(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed  
Case-control study—For matched studies, give matching criteria and the number of controls per case |
| Variables                                                    | 7      | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement                                    | 8*     | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias                                                         | 9      | Describe any efforts to address potential sources of bias |
| Study size                                                   | 10     | Explain how the study size was arrived at |
| Quantitative variables                                       | 11     | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods                                          | 12     | (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed |
<table>
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<th>Items that should be included in reports of observational studies</th>
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<tr>
<td></td>
<td></td>
<td>(d) Cohort study—If applicable, explain how loss to follow-up was addressed</td>
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<tr>
<td>Case-control study—If applicable, explain how matching of cases and controls was addressed</td>
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<tr>
<td>Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy</td>
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<td></td>
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<tr>
<td>(e) Describe any sensitivity analyses</td>
<td></td>
<td></td>
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<tr>
<td>RESULTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>13*</td>
<td>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</td>
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<tr>
<td></td>
<td></td>
<td>(b) Give reasons for non-participation at each stage</td>
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<td></td>
<td>(c) Consider use of a flow diagram</td>
</tr>
<tr>
<td><strong>Descriptive data</strong></td>
<td>14*</td>
<td>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Indicate number of participants with missing data for each variable of interest</td>
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<tr>
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<td>(c) Cohort study—Summarise follow-up time (eg, average and total amount)</td>
</tr>
<tr>
<td><strong>Outcome data</strong></td>
<td>15*</td>
<td>Cohort study—Report numbers of outcome events or summary measures over time</td>
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<tr>
<td></td>
<td></td>
<td>Case-control study—Report numbers in each exposure category, or summary measures of exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-sectional study—Report numbers of outcome events or summary measures</td>
</tr>
<tr>
<td>Items that should be included in reports of observational studies</td>
<td>Item No</td>
<td>Recommendation</td>
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<tr>
<td><strong>Main results</strong></td>
<td>16</td>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included</td>
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<tr>
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<td>(b) Report category boundaries when continuous variables were categorized</td>
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<td>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</td>
</tr>
<tr>
<td><strong>Other analyses</strong></td>
<td>17</td>
<td>Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses</td>
</tr>
<tr>
<td><strong>DISCUSSIONS</strong></td>
<td></td>
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<tr>
<td><strong>Key results</strong></td>
<td>18</td>
<td>Summarise key results with reference to study objectives</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>19</td>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
</tr>
<tr>
<td><strong>Interpretation</strong></td>
<td>20</td>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
</tr>
<tr>
<td><strong>Generalisability</strong></td>
<td>21</td>
<td>Discuss the generalisability (external validity) of the study results</td>
</tr>
<tr>
<td><strong>OTHER INFORMATION</strong></td>
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<tr>
<td><strong>Funding</strong></td>
<td>22</td>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
</tr>
</tbody>
</table>

**COMMUNICATION**

Each organization and its advisory board, if there is one, shall predetermine procedures under which communications of the intent, conduct, results, and interpretation of an epidemiologic study will occur, including what function individuals associated with the research must fulfill.
These individuals should include the principal investigator, study director, and/or the sponsor. This procedure may be documented in the form of a company standard operating procedure, in the study protocol, or through contractual agreement (as per Section V of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

ISPE encourages communicating estimates of epidemiologic measures quantitatively in the results section, generally by using point estimates and confidence intervals, either directly or graphically. It is useful in reporting results of safety studies to include both the relative and absolute risk estimates. Inferences about causal effects should be based on a variety of factors that should be explored in the discussion section. These factors include strength of relationship, temporal relationship, biological mechanism, plausibility of alternative theories, biases, confounding, precision, and others. Investigators should not make inferences about causation based solely on the outcome of a test of significance (e.g., a p-value or a statement about the confidence interval including or not including the null value). See also: Guidelines established by the International Committee of Medical Journal Editors, http://www.icmje.org/, section IV, and CONSORT Statement, http://www.consort-statement.org/Statement/examples20.htm (as per Section V of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

There is an ethical obligation to disseminate findings of potential scientific or public health importance. Scientific peers shall be informed of study results in a timely fashion by publication in the scientific literature and presentations at scientific conferences, workshops, or symposia. Presentations at meetings should not be considered as a substitute for publication in the peer-reviewed literature. Authorship of study reports should follow the guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/). All authors should meet the criteria for authorship, and all people who meet the criteria should be authors. Potential conflicts of interest, financial and non-financial, should be disclosed. Agreement to adhere to these guidelines should be described in the protocol (as per Section V of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Finally, research sponsors (government agencies, private sector, etc.) shall be informed of study results in a manner that complies with local regulatory requirements. Sources of research funding should always be acknowledged, whether results are presented orally or in writing (as per Section V of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
ADVERSE EVENT REPORTING

The findings of epidemiologic studies of health risks associated with healthcare products must be reported by pharmaceutical sponsors to regulatory agencies according to local and international requirements. Depending on the nature of the result and the regulations in effect, the result may need to be reported in an expedited manner (e.g. as ”new relevant safety information”). In any case, results of all epidemiologic studies of healthcare product safety should be included by companies in their periodic aggregated regulatory reports, such as Periodic Safety Update Reports (PSUR) and similar regulatory documents. Relevant regulatory guidance documents should be consulted (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

It is useful to distinguish reporting of aggregate results from epidemiologic studies (i.e., study reports) from the reporting of individual adverse drug events (ADEs). Pharmacoepidemiologic studies are usually designed to assess the relation between certain exposures and health outcomes based on aggregate analyses. In such studies, particularly in case-control studies and others that may be based on retrospectively collected data, it is generally not possible or appropriate for companies to assess the causality of individual cases, although aggregate analysis of a series of study cases might identify a newly recognized adverse effect. In studies where there is no assessment of causality for individual cases, sponsors should report aggregate findings as study reports, not as individual spontaneous reports (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

In prospective clinical trials where clinicians are systematically asked to report adverse events and to indicate whether each event could have been related to treatment, serious events indicated by the investigator to be at least possibly related are reportable (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Individual case reporting may be appropriate in prospective cohort studies aimed at elucidating information about a specific ADE (e.g., a drug safety registry). It is appropriate, therefore, to consider the potential value of, and necessity for, collecting such data when designing the study, taking into account existing safety experience with the drug being studied and the objectives of the study (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
The principal aim of expedited reporting of individual ADEs from studies to regulatory authorities is to contribute to recognition of unexpected effects (e.g., "signal detection"). In general, an individual study case should be reported on an expedited basis by pharmaceutical sponsors when, after an evaluation of the circumstances of the individual patient, the adverse event is considered serious and unexpected (unlabeled) and there is a reasonable possibility that a healthcare product may have contributed to the occurrence of the adverse event. Expedited individual case reporting is generally required when all of the following conditions obtain: 1) the study prospectively gathers data on individual patients, 2) the study involves direct contact with patients, 3) study personnel are trained on gathering and reporting adverse events and determining whether events might be considered “expected” for a specific product, 4) a serious event is identified by someone who has direct contact with the patient, 5) the event is considered unexpected, and 6) the reporter believes there is a causal association with the product or that causality cannot be ruled out. The suspicion that a drug is responsible for an event will usually be that of the study investigator or other clinical personnel with direct contact with the patient, although the pharmaceutical company may report on the basis of its own suspicion even if the study personnel do not infer a causal relation (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Occasionally information on suspected adverse events may be identified during the course of a study, but not as a formal part of the protocol-defined data collection. Procedures for follow-up and reporting of such information should be defined by the sponsor and research team at the time of protocol development (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

Increasingly, automated databases are being used by universities, pharmaceutical companies, and other commercial enterprises to evaluate the relationship between exposure to a healthcare product and adverse events. Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines. Aggregate analysis should not be confused with the automated search for signal detection using algorithms to detect disproportionate reporting rates in data sets of spontaneous reports (data mining), which should always be considered as hypothesis generating or refinement techniques. Results obtained from these techniques should always be accompanied by the caveats regarding reporting rates and biases.
ARCHIVING

Secure archives must be maintained for the orderly storage and expedient retrieval of all study related material. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any materials that by their general nature are not retained in the study archive. Access to the archives shall be controlled and limited to authorized personnel only. Special procedures may be necessary to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected (see, II. Protocol Development, Section I) (as per Section VII of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).

The archive should be maintained for at least five years after final report or first publication of study results, whichever comes later. At minimum, the study archive should contain, or refer to, the following:

1. Study protocol and all approved modifications;

2. A final report of the study;

3. All source data and, where feasible, any biologic specimens. A printed sample of the master computer data file(s), if feasible, with reference to the location of the machine-readable master. All "source data" should comprise the raw data that provided the basis for the final analysis of the study. The archival material should be sufficiently detailed to permit re-editing and re-analysis;

4. Documentation adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate (see section IV(C): Study Conduct);

5. Copies of electronic versions of analytic data sets and programs, computer printouts, if feasible, including relevant execution code, which form the basis of any tables, graphs, discussions, or interpretations in the final report. Any manually developed calculations shall be documented on a work sheet and similarly retained;

inherent in the collection of spontaneous reports (as per Section VI of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
6. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits. Communication of study results to the sponsor, regulators, and scientific community should be documented; Include, for example, questionnaires, name, make and model numbers of relevant measurement instruments, calibration information and procedures.

7. Documentation relating to the collection and processing of study data, including laboratory/research notebooks, training and reference documents for abstracts, interviews, and coders.

(as per Section VII of the ISPE: Guidelines for Good Pharmacoepidemiology Practices (2007)).
## Useful Links

<table>
<thead>
<tr>
<th><strong>Useful Links</strong></th>
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<td>Politis and Delgra, 2012</td>
<td>Politis H and Delgra CJ. Industry Perspective on Quality Management Systems and Outsourcing - Challenges and Expectations. Quasar, October 2012</td>
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Study Classification

The first step when assessing the specific requirements for a study is to determine what type of study it is that you intend to conduct. The following section uses the European clinical research regulatory framework as an example of why it’s imperative that you correctly classify your study during the early planning stages.

STEP 1 - DETERMINE THE TYPE OF STUDY YOU INTEND TO CONDUCT

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

**Study Classification**

<table>
<thead>
<tr>
<th>Interventional?</th>
<th>Is your study an interventional clinical trial?</th>
<th>Regulatory Framework</th>
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<td><img src="image" alt="Decision tree" /></td>
<td>Clinical Trials Directive (2001/20/EC)</td>
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<td>PASS?</td>
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<td>Pharmacovigilance Directive (2010/84/EU)</td>
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<tr>
<td>Other NIS?</td>
<td><img src="image" alt="Decision tree" /></td>
<td>Country Specific!</td>
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Is your Study Interventional?

Is your study an interventional clinical trial?

➡ Refer to the Decision tree
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)

Furthermore, 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.

Is your study a Non-Safety Related Non-Interventional Study?

If so, the requirements are not standardized and you will need to determine the country-specific considerations.
Regulatory Requirements for Post-Authorisation Safety Studies (PASS)

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)

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

**Regulatory Requirements for Non-safety Related NIS**

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.

---

**NIS Considerations**

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

- Notifications
- Approvals
- Submissions procedures
- Registration
- Classification
- Insurance requirements

**'Other' NIS**

Need to verify requirements for each country
<table>
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<th>Useful Links</th>
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<tr>
<td>Decision Tree: Is your study a clinical trial of a medicinal product or a non-interventional clinical trial?</td>
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Types of Non-Interventional Study

POST-AUTHORISATION SAFETY STUDY (PASS)

Definition
Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures (Article 1(c)(15) of 2001/83/EC as amended by Directive 2010/84/EU)

PASS Classification
A post-authorisation study should be classified as a PASS when the study includes any of the following objectives:

- to quantify potential or identified risks, e.g. to characterise the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another drug or class of drugs, and investigate risk factors and effect modifiers;
- to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment);
- to provide evidence about the absence of risks;
- to assess patterns of drug utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
- to measure the effectiveness of a risk minimisation activity.
(as per Section VIII.B.3 of the EMA Guideline on good pharmacovigilance practices (GVP), 2012)

PASS STUDY DESIGNS

Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the main types of studies, as well as the types of data resources available, is provided hereafter. However, this Appendix is not intended to be exhaustive and should be complemented with other information sources, such as the ENCePP Guide for Methodological Standards (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organised process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system. Automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may also provide an efficient active surveillance system (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Intensive Monitoring Schemes

Intensive monitoring is a system of record collation in designated areas, e.g. hospital units or by specific healthcare professionals in community practice. In such cases, the data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be causally related to the medication. Monitoring may also be focused on certain major events that tend to be drug-related such as jaundice, renal failure, haematological disorders, bleeding. The major strength of such systems is that the monitors may document important
information about the events and exposure to medicinal products. The major limitation is the need to maintain a trained monitoring team over time (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Intensive monitoring may be achieved by reviewing medical records or interviewing patients and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Intensive monitoring with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and haemodialysis centres. Institutional settings may have a greater frequency of use for certain products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerised laboratory reports in certain clinical settings may provide an efficient active surveillance system (as per Appendix 1 of EMA GVP Module VIII - July 2012).

**Prescription Event Monitoring**

In prescription event monitoring, patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire [VIII.App 1. References 6-7]. Limitations of prescription event monitoring include incomplete physician response and limited scope to study products which are used exclusively in hospitals. More detailed information on adverse events from a large number of physicians and/or patients may be collected (as per Appendix 1 of EMA GVP Module VIII - July 2012).
POST-AUTHORISATION EFFICACY STUDY (PAES)

Any study conducted where concerns relating to some aspects of the efficacy of the medicinal product are identified and can only be resolved after the medicinal product has been marketed (Article 21(a) of 2001/83/EC as amended by Directive 2010/84/EU).

Definitions

Efficacy

Pre-authorisation term used when determining whether an investigational medicinal product will work.

Effectiveness

Post-authorisation term used when determining whether a drug or treatment works in real-world terms.

Data Sources

Pharmacoepidemiological studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research. There are two main types of automated databases, those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. They may not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a...
random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmacoepidemiological studies or in their validation phase (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Marketing authorisation holders should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results). External validity should also be taken into account. As far as feasible the data source chosen to perform the study should include the population in which the safety concern has been raised. In case another population is involved, the marketing authorisation holder should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored (as per Appendix 1 of EMA GVP Module VIII - July 2012).

With any data source used, the privacy and confidentiality regulations that apply to personal data should be followed (as per Appendix 1 of EMA GVP Module VIII - July 2012).

**Summary of Product Characteristics (SmPC)**

Part of the marketing authorisation of a medicinal product setting out the agreed position of the product as distilled during the course of the assessment process which includes the information described in Article 11 of Directive 2001/83/EC. It is the basis of information for healthcare professionals on how to use the product safely and effectively. The package leaflet is drawn in accordance with the summary of product characteristics (based on A Guideline on Summary of Product Characteristics, Volume 2C of the Rules Governing Medicinal Products in the EU) (as per Annex I of the EMA Guideline on Good Pharmacovigilance Practices (GVP) - July 2012).

**REGISTRY STUDY DESIGNS**

**European (EMA) Definition**

An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure (as per Annex I of the EMA Guideline on Good Pharmacovigilance Practices (GVP) - July 2012)
**Disease/Outcome Registries**

Disease/outcome registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations may help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition or from outside the registry, or for a case-only design (as per Appendix 1 of [EMA GVP Module VIII - July 2012](#)).

**Exposure Registries**

Exposure registries address populations exposed to medicinal products of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicinal product has a special impact on this group of patients. Some exposure registries address exposures to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Simple cohort studies may measure incidence, but, without a comparison group, cannot evaluate any association between exposures and outcomes. Nonetheless, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan drug indicated for a specific condition (as per Appendix 1 of [EMA GVP Module VIII - July 2012](#)).

**US (FDA) Definition**

An organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects. Whenever possible, a control group or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or exposed to medical interventions other than the intervention of interest) (as per Section V.B

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of the *FDA Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment - March 2005*).

**Registry Protocols**

Sponsors electing to initiate a registry should develop written protocols that provide:

- Objectives of the registry
- A review of the literature, and
- A summary of relevant animal and human data

FDA suggest that protocols also contain detailed descriptions of:

- Plans for systematic patient recruitment and follow-up
- Methods for data collection, management and analysis, and
- Conditions under which the registry will be terminated

**Monitoring of Registries**

A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with healthcare providers.

**Design of Registries**

FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and encourage sponsors to discuss their registry development plans with FDA.
DESIGN OF OBSERVATIONAL STUDIES

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports, active surveillance programmes or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies, based on primary data collection or secondary use of existing data (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Cross-Sectional Study (Survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. A drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for etiologic research unless the exposures do not change over time. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for serial time-points can be captured. These studies may also be used to examine the crude association between exposure and outcome in ecologic analyses (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Cohort Study

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the basis of medication use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events may also be investigated using the same data source in a cohort study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan drug) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from
data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Case-Control Study

In a case-control study, cases of disease (or events) are identified and patients without the disease or event of interest at the time of selection, are then selected as controls from the source population that gave rise to the cases. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared to the non-exposed. Patients may be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (the elderly, children, pregnant women, etc.). Existing large population-based databases are a useful and efficient means of providing needed exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product (or products) and one specific rare adverse event, as well as to identify risk factors for adverse events (or actually, effect-modifiers). Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study may also provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated (as per Appendix 1 of EMA GVP Module VIII - July 2012).

When the source population for the case-control study is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The name “nested case-control study” has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on those persons who make up the source population regardless of the duration of
time they may have contributed to it (as per Appendix 1 of EMA GVP Module VIII - July 2012).

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant aetiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Other Designs
Other designs have been proposed to assess the association between intermittent exposures and short-term events, including the self-controlled case-series, the case-crossover and the case-time-control studies. In these designs, only cases are used and the control information is obtained from past person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change within individuals are automatically matched (as per Appendix 1 of EMA GVP Module VIII - July 2012).

Drug Utilisation Studies (DUS)
Drug utilisation studies (DUS) describe how a medicinal product is, prescribed and used in routine clinical practice in large populations, including elderly patients, children, pregnant women or patients with hepatic or renal dysfunction, who are often excluded by randomized clinical trials. Stratification by age, gender, concomitant medication and other characteristics allows a comprehensive characterization of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes. From these studies, denominator data may be derived for use in determining rates of adverse reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS may be used to examine the relationship between recommended and actual clinical practice. These studies may help to monitor use in everyday medical practice and medication error and to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence
of inappropriate repeat prescribing (as per Appendix 1 of EMA CVP Module VIII – July 2012 ).
### TYPES OF NIS - USEFUL LINKS

<table>
<thead>
<tr>
<th>Useful Links</th>
<th>Accessed From</th>
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NIS Standards, Guidelines and Resources

There are 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.

NON-INTERVENTIONAL STUDY STANDARDS, GUIDELINES AND RESOURCES

Bioethics

- The Mengele Twins and Human Experimentation: A Personal Account by Eva Mozes-Kor
- The Tuskegee Syphilis Study
- A History of Non-Consensual Human Medical Experiments

Ethical Standards and Guidelines

- Declaration of Helsinki (1964, 2000, 2008)
- ICH E2E
- ICH E6 (ICH GCP)
- ISPE: Guidelines for Good Pharmacoepidemiology Practices (GPP)
- CIOMS International Ethical Guidelines for Epidemiological Studies, 2008

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Data Privacy Standards and Guidelines

- ISPE: Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health

NIS Study Conduct Standards and 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 Code of Conduct
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology (2011)
- ENCePP Standards and Guidelines

European Post-Authorisation Safety Study (PASS) Regulations, Standards and Guidelines

- EMA Guidance on the 2010 Pharmacovigilance Legislation
- EMA Regulatory and 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

Study Protocol Guidelines and Checklists

ISPE: Guidelines for Good Pharmacoepidemiology Practices (GPP)

ENCePP Checklist for Study Protocols (2011)

ENCePP Guide on Methodological Standards in Pharmacoepidemiology (2011)

Monitoring Guidelines and Resources for Observational Studies


NIS Considerations – Monitoring Guidelines (2012)

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


STROBE Initiative.
<table>
<thead>
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<th>Useful Links</th>
<th>Accessed From</th>
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<tr>
<td>A History of Non-Consensual Human Medical Experiments</td>
<td><a href="http://www.bibliotecapleyades.net/sociopolitica/esp_sociopol_depopu28.htm">http://www.bibliotecapleyades.net/sociopolitica/esp_sociopol_depopu28.htm</a></td>
</tr>
<tr>
<td>Decision Tree: Is your study a clinical trial of a medicinal product or a non-interventional clinical trial?</td>
<td><a href="http://www.mhra.gov.uk/home/groups/l-unti/documents/websiteresources/con009394.pdf">http://www.mhra.gov.uk/home/groups/l-unti/documents/websiteresources/con009394.pdf</a></td>
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<tr>
<td>ISPE: Guidelines for Good Pharmacoepidemiology Practices (GPP)</td>
<td><a href="http://www.pharmacoepi.org/resources/guidelines_o8o27.cfm">http://www.pharmacoepi.org/resources/guidelines_o8o27.cfm</a></td>
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<td>The Mengele Twins and Human Experimentation: A Personal Account by Eva Mozes-Kor</td>
<td><a href="http://www.chcuk.co.uk/mengeletwins.html">http://www.chcuk.co.uk/mengeletwins.html</a></td>
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<tr>
<td>The Tuskegee Syphilis Study</td>
<td><a href="http://www.cdc.gov/tuskegee/timeline.htm">http://www.cdc.gov/tuskegee/timeline.htm</a></td>
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QUALITY ASSURANCE IN NON-INTERVENTIONAL STUDIES

Nowadays, drug research and surveillance after authorisation becomes more and more important for several reasons. Non-interventional studies (NIS) investigate various aspects of drug use including efficacy and safety under real life conditions. Such kind of health services research should be on a high scientific, methodological and organisational level. Therefore accompanying measures to improve or to keep the quality are highly recommended. The aim of quality management is: first to avoid bias of results by using an appropriate study design and an adequate data analysis, second to assure authenticity, completeness and validity of the data and third to identify and resolve deficiencies at an early stage. Basic principles are laid down in corresponding guidelines and recommendations of authorities, institutes and societies. Various guidelines for good epidemiological practice (GEP) were published by the U.S. Food and Drug Administration (FDA) and international and regional societies for epidemiology (Theobold et al., 2009).

Key points are the advanced publishing of information about the project, developing of a study plan/protocol containing the scientific objectives, a sample size justification and a description of the planned analyses and the publishing of a summary of the results timely after completion of the study. The quality of the data can be improved by using standardized case report forms (CRF) and the CRF should be reviewed and tested before start of study by some participants. A source data verification (SDV) should be performed in randomly selected centres – in between 2% and 5% of the centres depending on the number of participating centres. Before start of statistical analysis a statistical analysis plan (SAP) should be created. The use of standardized tables and figures is highly recommended. The basis of the report writing should be the STROBE-statement “Strengthening the Reporting of Observational studies in Epidemiology Initiative” containing a checklist of 22 points to be covered in the report. The development of own standard operating procedures (SOP) describing the processes during planning, conduct and evaluation of a non-interventional study as well as the
quality management and the regular training of all involved people is also highly recommended (Theobold et al., 2009).

All accompanying measures to improve or to keep the quality of the NIS should not violate the concept of non-intervention (Theobold et al., 2009).

**Quality Standard for Epidemiological Research**

Basic principles for this kind of research are laid down in guidelines and recommendations for assurance of good epidemiological practice (GEP) and other additional international guidelines. The aim of GEP is to establish a quality standard for epidemiological research. The guidelines contain partially detailed recommendations regarding the topics ethic, research questions (e.g. a priori defined hypothesis), study plan, biological sample databases, quality assurance, data storing and data documentation, analysis, data protection, contractual provisions and interpretation of research results (Theobold et al., 2009).

**Quality Assurance in Non-Interventional Studies**

The aim of quality assurance is to make valid, scientific statements based on the results in NIS, meaning to avoid possible bias of results by using an appropriate study design and an adequate data analysis, assure authenticity, completeness and validity of the data and to identify and resolve deficiencies at an early stage (Theobold et al., 2009).

Laws, guidelines and recommendations relating to NIS are very helpful to implement quality assurance measures (Theobold et al., 2009).

General quality assurance measures include:

- Employ SOPs specifically designed for managing the planning, operational, and evaluation processes involved in non-interventional studies (NIS);
- Keep the study staff/project management team apprised of legal and regulatory requirements and recommendations for NIS;
- Ensure that the protocol and study-related management processes do not interfere with the non-interventional premise of NIS;
Implement a quality plan that describes which quality control and quality assurance activities must be conducted.

(Source: Theobold et al., 2009).

INDUSTRY PERSPECTIVE ON QUALITY MANAGEMENT SYSTEMS AND OUTSOURCING

In the light of the recent financial turmoil, companies are increasingly outsourcing processes and activities to external vendors. There is an ever increasing loss of expertise within organisations due to downsizing, mergers and acquisitions. Furthermore, vendors have the capacity and bandwidth to provide increasingly diverse services in response to the current financial and regulatory climate. They have the ability to provide quick start-up services by utilising either internal or client systems, processes and procedures (Politis and Delgra, 2012).

Furthermore, the ever changing regulatory landscape requires industry to ensure that oversight and quality of deliverables are maintained in all instances and in particular when significant processes have been outsourced. As the ultimate accountability for compliance rests with the company, assessment of vendors’ quality management systems (QMS) are becoming more common as a means to identify potential risks for consideration and remediation (Politis and Delgra, 2012).

The principles of an adequate QMS can be summarised as follows:

- Defines customer requirements
- Ensure products are processes are developed and verified to meet requirements
- Measures performance
- Addresses quality issues and improves quality
- Improves productivity
- Ensures that acceptable product is delivered to the customer
Even though the principles of QMS are universally defined, the implementation at vendors may differ depending on interpretation, QMS maturity (see table below), commitment to QMS principles and size of the organisation. However, there is the general expectation from companies that vendors’ QMSs are quality driven, promote the ‘right first time’ culture and match the customers’, industry, requirements and expectations (Politis and Delgra, 2012).

The advantages for vendors to establish a mature QMS are multiple. Firstly, there is the financial reward through their diversification of services and value proposition to potential clients. Secondly, there is opportunity for process development and improvement which ultimately results in increased efficiency and decrease in costs/overheads. Lastly, they may gain insight into regulatory intelligence through additional activities such as inspection readiness (Politis and Delgra, 2012).

Examples of QMS Maturity:

<table>
<thead>
<tr>
<th>Immature QMS</th>
<th>Developing QMS</th>
<th>Mature QMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Little or no QMS elements in place</td>
<td>• Some or many QMS elements in place</td>
<td>• Most or all QMS elements in place</td>
</tr>
<tr>
<td>• Institutional knowledge but little documentation</td>
<td>• Partially documented processes</td>
<td>• Well controlled process improvements</td>
</tr>
<tr>
<td>• Uncontrolled process improvements</td>
<td>• Some metrics developed helping drive process</td>
<td>• Metrics monitoring</td>
</tr>
<tr>
<td>• No incident management or CAPA process</td>
<td>• Incident/ non-conformance tracking</td>
<td>• Incident/ non-conformance tracking and trending</td>
</tr>
<tr>
<td>• Training gaps</td>
<td>• Some training methods visible</td>
<td>• Role-based curricula training</td>
</tr>
<tr>
<td>• Lack of business continuity/ disaster recovery plan</td>
<td>• Some business continuity/ disaster recovery elements in place</td>
<td>• Business continuity/ disaster recovery plan in place and tested on a regular basis</td>
</tr>
<tr>
<td>• No audit/ inspection methodology or plan</td>
<td>• Some self audit plans in place</td>
<td>• Self audit program, inspection readiness training</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Senior management oversight</td>
</tr>
</tbody>
</table>

Source: Politis and Delgra, 2012
Key Elements of Quality Management Systems

- Organisational structure - Understanding of business functions, responsibilities and senior management oversight
- Procedural documentation - Description of controlled document hierarchy and management
- Training program - Assurance vendors associates are properly trained to perform duties
- Information system - Description of system development life cycle and system validation
- Senior management oversight - Awareness of business activities and accountability
- Metrics and process monitoring - Key indicators to assess processes and compliance
- Audit and inspection management - Demonstrates vendors internal review of processes, procedures and hosting of regulatory inspections
- Incident/non-conformance (NC) and corrective action/preventative action (CAPA) management - An understanding of how process breakdowns are monitored and remediated
- Risk management - Ensure business continuity plan and disaster recovery plans are in place
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<tr>
<th><strong>Useful Links</strong></th>
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<tbody>
<tr>
<td>Politis and Delgra, 2012</td>
<td>Politis H and Delgra CJ. Industry Perspective on Quality Management Systems and Outsourcing - Challenges and Expectations. Quasar, October 2012</td>
</tr>
</tbody>
</table>
NIS Definitions
Considerations when providing access to unapproved drugs

EUROPEAN NIS DEFINITIONS

NIS DEFINITIONS

Non-interventional Study (NIS)

A non-interventional study is a study fulfilling cumulatively the following requirements:

- The medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;

- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study; and

- No additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for the analysis of collected data.

Non-interventional studies are defined by the methodological approach used and not by the scientific objectives. Non-interventional studies include database research or review of records where all the events of interest have already happened (e.g. case-control, cross-sectional and cohort studies). Non-interventional studies also include those involving primary data collection (e.g. prospective observational studies and registries in which the data collected derive from routine clinical care), provided that the conditions set out above are met.
In this context, interviews, questionnaires and blood samples may be performed as normal clinical practice.

(as per Annex I of the EMA Guideline on good pharmacovigilance practices (GVP), 2012)

**Post-authorisation Safety Study (PASS)**

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures (Article 1(c)(15) as 2001/83/EC as amended by Directive 2010/84/EU)

**Post-authorisation Efficacy Studies (PAES)**

Any study conducted where concerns relating to some aspects of the efficacy of the medicinal product are identified and can only be resolved after the medicinal product has been marketed (Article 21(a) as 2001/83/EC as amended by Directive 2010/84/EU)
# Common NIS Terminology

## Commonly Used NIS Terms

### Common NIS Terminology

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Term</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>AR</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>CA</td>
<td>Competent Authority (e.g., MHRA)</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>CTD</td>
<td>Clinical Trials Directive (2001/20/EC)</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>DPA</td>
<td>Data Protection Agency</td>
</tr>
<tr>
<td>EFPIA</td>
<td>European Federation of Pharmaceutical Industries and Associations</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>ENCePP</td>
<td>The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GEP</td>
<td>Good Epidemiological Practice</td>
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<tr>
<td>CPP</td>
<td>Good Pharmacoepidemiology Practice</td>
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<td>Acronym</td>
<td>Term</td>
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<tr>
<td>GVP</td>
<td>Good Pharmacovigilance Practice</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
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<tr>
<td>ICH GCP</td>
<td>ICH Good Clinical Practice Guidelines</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>ISF</td>
<td>Investigator Site File</td>
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<tr>
<td>ISPE</td>
<td>International Society of Pharmacoepidemiology</td>
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<tr>
<td>MA</td>
<td>Marketing Authorisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>NCA</td>
<td>National Competent Authority</td>
</tr>
<tr>
<td>NIS</td>
<td>Non-interventional Study</td>
</tr>
<tr>
<td>NTF</td>
<td>Note to the File</td>
</tr>
<tr>
<td>PAS</td>
<td>Post-authorisation Study</td>
</tr>
<tr>
<td>PAES</td>
<td>Post-authorisation Efficacy Study</td>
</tr>
<tr>
<td>PASS</td>
<td>Post-authorisation Safety Study</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>PIL</td>
<td>Patient Information Leaflet</td>
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<tr>
<td>PV</td>
<td>Pharmacovigilance</td>
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<tr>
<td>QA</td>
<td>Quality Assurance</td>
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<tr>
<td>QC</td>
<td>Quality Control</td>
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<tr>
<td>QMS</td>
<td>Quality Management System</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
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<td>QP</td>
<td>Qualified Person</td>
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<td>REC</td>
<td>Research Ethics Committee</td>
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<td>Term</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
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<tr>
<td>SDV</td>
<td>Source Data Verification</td>
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<tr>
<td>SIF</td>
<td>Subject Information Form</td>
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<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
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<tr>
<td>WMA</td>
<td>World Medical Association</td>
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