Non-Interventional Studies: Europe (Part 1)

Considerations when Managing and Conducting Non-Interventional Studies in Europe

Belgium • Czech Republic • France • Germany • Greece • Netherlands • Poland • Portugal • Spain • Sweden • Switzerland
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Publisher</td>
<td>24</td>
</tr>
<tr>
<td>PUBLISHER</td>
<td>24</td>
</tr>
<tr>
<td>COPYRIGHT</td>
<td>24</td>
</tr>
<tr>
<td>Disclaimer</td>
<td>25</td>
</tr>
<tr>
<td>NIS Definitions</td>
<td>26</td>
</tr>
<tr>
<td>EUROPEAN NIS DEFINITIONS</td>
<td>26</td>
</tr>
<tr>
<td>NIS DEFINITIONS</td>
<td>26</td>
</tr>
<tr>
<td>Non-interventional Study (NIS)</td>
<td>26</td>
</tr>
<tr>
<td>Post-authorisation Safety Study (PASS)</td>
<td>27</td>
</tr>
<tr>
<td>Post-authorisation Efficacy Studies (PAES)</td>
<td>27</td>
</tr>
<tr>
<td>Common NIS Terminology</td>
<td>28</td>
</tr>
<tr>
<td>COMMONLY USED NIS TERMS</td>
<td>28</td>
</tr>
<tr>
<td>COMMON NIS TERMINOLOGY</td>
<td>28</td>
</tr>
<tr>
<td>Introduction</td>
<td>31</td>
</tr>
<tr>
<td>NIS REGULATIONS &amp; GUIDELINES</td>
<td>31</td>
</tr>
<tr>
<td>EUROPE - GENERAL CONSIDERATIONS</td>
<td>31</td>
</tr>
<tr>
<td>Figure 1 - NIS Regulatory Road Map</td>
<td>33</td>
</tr>
<tr>
<td>ETHICAL CONSIDERATIONS</td>
<td>34</td>
</tr>
<tr>
<td>DATA PRIVACY</td>
<td>36</td>
</tr>
<tr>
<td>EFPIA CODE OF PRACTICE</td>
<td>36</td>
</tr>
</tbody>
</table>

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NIS-Considerations - Europe (Part 1) - 3rd Edition - September 2012
COUNTRY-SPECIFIC CONSIDERATIONS

Country-Specific Considerations for Conducting and Managing NIS

NON-INTERVENTIONAL STUDIES - USEFUL LINKS

Study Classification

GENERAL CONSIDERATIONS WHEN PLANNING NIS

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

Is your Study Interventional?

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

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

STEP 2 - DETERMINE THE COUNTRY-SPECIFIC REQUIREMENTS

STUDY CLASSIFICATION - USEFUL LINKS

NIS Summary

SUMMARY OF THE COUNTRY-SPECIFIC CONSIDERATIONS WHEN CONDUCTING NON-INTERVENTIONAL STUDIES

SUMMARY TABLE

Belgium

COUNTRY-SPECIFIC CONSIDERATIONS

SUMMARY OF CHANGES SINCE PREVIOUS VERSION

DEFINITIONS

Non-Interventional Study

"non-interventional trial"

Clarification

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS

REGULATORY BODIES

Competent Authority

Competent Authority Approval

Research Ethics Committees (RECs)

Ethical Approval
REGULATORY FRAMEWORK

Applicable Legislation and Guidance

REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES

Purpose

Prohibition of Promotion

Quality Framework

Contract

Declaration of Conflicts of Interest/ Financial Support

Market Research

Remuneration

Study Protocol

Procedures for the Supply of Medicines

Justification for the Number of Patients and Number of Investigators

Future Use of Data

Study Design and Follow-up

Limited Involvement of Medical Reps

Competent Authority Approval

Favourable Ethics Opinion

Procedure for Submission to Ethics Committees

Approval of Substantial Amendments

Attendance at Scientific Events

Advance Visa Procedure

End of Study Notification

Analysis and Retention of Study Results

Dissemination of Study Results
Further Information and/or Free Demonstration

Czech Republic - USEFUL LINKS

France

COUNTRY-SPECIFIC CONSIDERATIONS

SUMMARY OF CHANGES SINCE PREVIOUS VERSION

DEFINITIONS

“Non-interventional Studies”

Non-Interventional Study

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS

REGULATORY BODIES

Competent Authority

Competent Authority Approval

Research Ethics Committees (CPPs)

Ethical Approval

Pharmaceutical Self-regulation Body (LEEM)

Data Protection Agency (CCTIRS & CNIL)

CCTIRS & CNIL Approvals

National Medical Council (CNOM)

CNOM Approval

REGULATORY FRAMEWORK

Applicable Legislation and Guidance

REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES

Purpose

Prohibition of Promotion

Limited Involvement of Medical Reps

Study Protocol

Company Oversight

Remuneration
Competent Authority 137
Competent Authority Notification 138
Research Ethics Committees (RECs) 138
Ethical Approval 138
Pharmaceutical Self-regulation Body (vfa) 139
Data Protection Agency (BFDI) 139
Notification 140
Other Notification Requirements 140
REGULATORY FRAMEWORK 141
Applicable Legislation and Guidance 141
BFARM GUIDANCE ON NIS 142

How are clinical trials using investigational medicinal products distinguished from open post-marketing observations? 142

Which documents are necessary for the submission of a non-interventional trial pursuant to Section 67 sub-section 6 of the German Medicines Act? 142

Is there an official form for notification of non-interventional studies? 143

When does a non-interventional trial in accordance with Section 67 sub-section 6 of the German Medicines Act have to be notified? 143

Is the non-interventional trial limited to a particular number of patients per doctor or to a particular number of doctors? 143

Is the Announcement on the Authorisation and Registration of Medicinal Products - Recommendations for Design and Conduct of Observational Post-authorisation Safety Studies dated 12 November 1998) still up-to-date? 143

REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES 144

Purpose 144
Prohibition of Promotion 144

Head of Medical Department/ Scientific Service (Body Responsible for Approval & Supervision of NIS) 144

Limited Involvement of Medical Reps 145
Guidelines for Medical Reps 145
Internal Procedures 148
Competent Authority 167
Competent Authority Approval 168
Research Ethics Committees (RECs) 168
Ethical Approval 169
Pharmaceutical Self-regulation Body (Pharma.be) 169
Data Protection Agency (CPP) 169
Notification 170
REGULATORY FRAMEWORK 171
Applicable Legislation and Guidance 171
REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES 172
Purpose 172
Prohibition of Promotion 172
Scientific Service (Body Responsible for Approval and Supervision of NIS) 172
Involvement of Medical Reps 172
Authorisation by the Competent Authority (EOF) 172
Favourable Ethics Opinion 173
Contract 173
Provision of Counseling Services or similar collaborations by Healthcare Professionals to the Pharmaceutical Industry 173
Declaration of Conflicts of Interest 175
Financial Compensation/ Remuneration 175
Compliance with Data Protection Legislation 175
Registration of NIS 176
Scientific Events 176
Scientific Content Conferences (Type A events) 176
Provisions for the organization of ‘Type A’ scientific events 176
Scientific Information Events (Type B events) 178
Scientific Information Events on medicinal or other products (Type C events) 178
Legality of doctors’ participation 178

Provisions for the organization of Type B and Type C scientific events 178

Determination of ceilings for hospitality expenses of physicians for scientific events in Greece and abroad 180

Scientific Advisory Boards 180

Analysis and Retention of Study Results 181

Dissemination of Study Results 181

Notification of Important Risk-Benefit Information 181

‘Other’ Studies 181

Market Research 182

ADDITIONAL RESOURCES 183

Country-specific eLearning Module 183

Course Format 183

Who Would Benefit from the Course? 184

Further Information and/or Free Demonstration 184

GREECE - USEFUL LINKS 185

The Netherlands 187

COUNTRY-SPECIFIC CONSIDERATIONS 187

SUMMARY OF CHANGES SINCE PREVIOUS VERSION 188

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS 189

REGULATORY BODIES 190

Competent Authority 190

Competent Authority Approval 191

Research Ethics Committees (METC) 191

Ethical Approval 191

Pharmaceutical Self-regulation Body (Nefarma) 192

CGR Approved Review Process for Non-WMO Research 192

Data Protection Agency (DPA) 192
Notification

REGULATORY FRAMEWORK

Applicable Legislation and Guidance

IN INVOLVEMENT OF HUMAN SUBJECTS IN SCIENTIFIC RESEARCH

WMO RESEARCH

Is the study Medical/scientific research?

Does the research involve subjecting people to treatment/ procedures or will it require them to follow specific rules of behaviour?

APPROVAL REQUIREMENTS FOR WMO RESEARCH

Protocol

Protocol Amendments

Patient Information

Consent Form

Independent Physician

Insurance for Research Subjects

Notification of Study Start

Progress Reports

End of Study Notification

Final Report

SCIENTIFIC RESEARCH USING PERSONAL DATA (NON-WMO)

SEPARATE REVIEW OF STUDIES NOT SUBJECT TO THE WMO (NON-WMO)

CGR Review Process for non-WMO Research Studies

IF IN DOUBT ABOUT THE STUDY CLASSIFICATION...

We are currently setting up a phase IV drugs trial. The drug is already registered. Does the trial still have to be reviewed?

Our research consists simply of a questionnaire that the subjects have to complete. Is it covered by the WMO?

What about clinical drugs trials that are not covered by the WMO, surely they have to undergo some kind of review?

SEPARATE REVIEW OF DRUG TRIALS NOT SUBJECT TO THE WMO
DEFINITIONS

Non-interventional Studies

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS

REGULATORY BODIES

Competent Authority

Competent Authority Approval

Research Ethics Committees (RECs)

Ethical Approval

Pharmaceutical Self-regulation Body (INFARMA)

Data Protection Agency (GIODO)

Notification

REGULATORY FRAMEWORK

Applicable Legislation and Guidance

REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES

Scientific Objective

NIS Criteria

TRANSPARENCY OF STUDIES

Prohibition of Promotion

Prohibition of Using NIS to Compare Medicinal Products

NIS TO BE CONDUCTED IN LINE WITH THE PROTOCOL

PRIOR ETHICS APPROVAL

RESPONSIBILITIES OF THE MEDICAL DEPARTMENT

CONTRACTS

The obligation to conclude a contract for financing a trial/study

Remuneration

Services Rendered by Health Care Centres

Employing Consultants
What rules govern the offering of hospitality to health professionals? Does it make a difference if the hospitality offered to those health professionals will take place in another country?

Is it possible to pay for a doctor in connection with attending a scientific meeting? If so, what may be paid for? Is it possible to pay for his expenses (travel, accommodation, enrolment fees)? Is it possible to pay him for his time?

To what extent will a pharmaceutical company be held responsible by the regulatory authorities for the contents of and the hospitality arrangements for scientific meetings, either meetings directly sponsored or organised by the company or independent meetings in respect of which a pharmaceutical company may provide sponsorship to individual doctors to attend?

Is it possible to pay doctors to provide expert services (e.g. participating in focus groups)? If so, what restrictions apply?

Is it possible to pay doctors to take part in post marketing surveillance studies?

What rules govern such studies?

Is it possible to pay doctors to take part in market research involving promotional materials?

Is there a requirement in law and/or self-regulatory code for companies to make publicly available information about donations, grants, benefits in kind or any other support provided by them to health professionals, patient groups or other institutions? If so, what information should be disclosed, from what date and how?
Communication to the Competent Authority of Results Significant for the Assessment of the Product

241

Archiving

242

CONDITIONS FOR CONDUCTING OTHER STUDIES

242

Epidemiological Trials, Registers and Health Economic Studies

242

Market Research

242

ADDITIONAL RESOURCES

243

Country-specific eLearning Module

243

Course Format

243

Who Would Benefit from the Course?

244

Further Information and/or Free Demonstration

244

POLAND - USEFUL LINKS

245

Portugal

247

COUNTRY-SPECIFIC CONSIDERATIONS

247

SUMMARY OF CHANGES SINCE PREVIOUS VERSION

248

DEFINITIONS

249

Non-interventional Studies (NIS)

249

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS

250

REGULATORY BODIES

251

Competent Authority

251

Competent Authority Approval

251

Research Ethics Committees (RECs)

252

Ethical Approval

252

Pharmaceutical Self-regulation Body (Pharma.be)

252

Data Protection Agency (CNPD)

252

CNPD Notification

253

CNPD Approval

253

REGULATORY FRAMEWORK

254
REGULATORY SUBMISSION ROADMAPS

Post-Authorisation Studies (EPA) 267

Prospective Observational Studies (EPA-SP) 268

Retrospective Observational Studies (EPA-OD) and Disease Registries (Non-EPA) 269

Post-Approval Commitments (EPA-LA) 270

Publicly Funded Prospective Observational Studies (EPA-AS) 271

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS 272

REGULATORY BODIES 274

Competent Authority 274

Competent Authority Approval 275

Competent Authority Classification 275

Research Ethics Committees (RECs) 275

Ethical Approval 276

Pharmaceutical Self-regulation Body (Pharma.be) 276

Data Protection Agency (CPP) 276

Notification 276

REGULATORY FRAMEWORK 278

Applicable Legislation and Guidance 278

NIS OBJECTIVES 279

ETHICAL CONSIDERATIONS 279

STUDY PROTOCOL 281

Identification of those Responsible for the study 281

Sponsor 281

Monitor 282

Researchers 282

Research Coordinator 282

Key Elements of the Study Protocol 283
<table>
<thead>
<tr>
<th>Study Identification</th>
<th>285</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Amendments</td>
<td>286</td>
</tr>
<tr>
<td><strong>OPERATIONAL REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES</strong></td>
<td>287</td>
</tr>
<tr>
<td>Ethical Considerations</td>
<td>287</td>
</tr>
<tr>
<td>Notification of Start Date</td>
<td>287</td>
</tr>
<tr>
<td>Progress Reports</td>
<td>287</td>
</tr>
<tr>
<td>Monitoring</td>
<td>287</td>
</tr>
<tr>
<td>Study Protocol</td>
<td>287</td>
</tr>
<tr>
<td>Study Identification</td>
<td>288</td>
</tr>
<tr>
<td>CEIC Approval of Substantial Amendments</td>
<td>288</td>
</tr>
<tr>
<td>Notification of Related Serious Adverse Events</td>
<td>289</td>
</tr>
<tr>
<td>Inspections</td>
<td>289</td>
</tr>
<tr>
<td>Final Report</td>
<td>289</td>
</tr>
<tr>
<td>Archiving</td>
<td>289</td>
</tr>
<tr>
<td><strong>BEST PRACTICE REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES</strong></td>
<td>290</td>
</tr>
<tr>
<td>Purpose</td>
<td>290</td>
</tr>
<tr>
<td>Prohibition of Promotion</td>
<td>290</td>
</tr>
<tr>
<td>Registration of the Study with the AEMPS</td>
<td>290</td>
</tr>
<tr>
<td>Contract</td>
<td>290</td>
</tr>
<tr>
<td>Services Provided by Healthcare Professional</td>
<td>291</td>
</tr>
<tr>
<td>Remuneration</td>
<td>293</td>
</tr>
<tr>
<td>Competent Authority Approval (AEMPS)</td>
<td>293</td>
</tr>
<tr>
<td>Classification of the Study by the AEMPS</td>
<td>293</td>
</tr>
<tr>
<td>Autonomous Community Approval</td>
<td>293</td>
</tr>
<tr>
<td>Favourable Ethics Opinion</td>
<td>294</td>
</tr>
<tr>
<td>Insurance</td>
<td>294</td>
</tr>
<tr>
<td>Protocol Amendments</td>
<td>294</td>
</tr>
<tr>
<td>Notification &amp; Reporting</td>
<td>294</td>
</tr>
</tbody>
</table>
Archiving of Study Documents 295
Appointment of an Archivist 295
Dissemination of Summary Reports 295
Notification of Important Benefit-Risk Information 296
Safety Reporting 296
ADDITIONAL RESOURCES 297
Country-specific eLearning Module 297
Course Format 297
Who Would Benefit from the Course? 298
Further Information and/or Free Demonstration 298
Spain - USEFUL LINKS 299

Sweden 302

COUNTRY-SPECIFIC CONSIDERATIONS 302

SUMMARY OF CHANGES SINCE PREVIOUS VERSION 303

DEFINITIONS 304

Non-Interventional Study 304

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS 305

REGULATORY BODIES 307

Competent Authority 307

Competent Authority Approval 307

Research Ethics Committees (RECs) 307

Ethical Approval 308

Pharmaceutical Self-regulation Body (LIF) 308

Data Protection Agency (Data Inspection Board) 308

Notification 309

Notification need not be made if there is a Personal Data Representative 309

Personal Data that are Handled within the Scope of Clinical Trials 309

REGULATORY FRAMEWORK 311
Applicable Legislation and Guidance 311

REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES 312

THE DIFFERENCE BETWEEN CLINICAL TRIALS & NON-INTERVENTIONAL STUDIES 313

WHEN ARE NON-INTERVENTIONAL STUDIES PERFORMED? 314

CRITERIA FOR NON-INTERVENTIONAL STUDIES 315

Standard Healthcare Provision 315

Purpose 316

Prohibition of Promotion 316

Limited Involvement of Medical Reps 316

Considerations when Engaging Healthcare Personnel in Research 317

Limited Market Research Studies 318

Contracts and Agreements 319

Ownership of data 319

Conditions for clinical trials/non-interventional studies that has been initiated by a pharmaceutical company 319

Financial Compensation/ Remuneration 322

Ethics Approval 322

The Swedish Medical Products Agency 322

Study Plan/ Protocol 322

The Company's Internal Process 323

Company Approval and Monitoring of Non-Interventional Studies 323

Quality Assurance 324

The Swedish Data Protection Act (PUL) 324

Notification Duty 324

Notification need not be made if there is a Personal Data Representative 324

Reports 325

Industry Self-Regulation 325

Reporting of Results Likely to have an Impact on the Drugs Risk Profile 325
COUNTRY-SPECIFIC CONSIDERATIONS

SUMMARY OF CHANGES SINCE PREVIOUS VERSION

DEFINITIONS

Non-interventional Studies using Authorized Medicinal Products

VKlin or Non-VKlin Studies

SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS

REGULATORY BODIES

Competent Authority

Competent Authority Approval

Research Ethics Committees (RECs)

Ethical Approval

Pharmaceutical Self-regulation Body (SGCI)

Data Protection Agency (CPP)

Notification/Registration

REGULATORY FRAMEWORK

Applicable Legislation and Guidance

REGULATION OF RESEARCH INVOLVING HUMAN SUBJECTS

Regulations at the Swiss Federal Level

The Federal Law on Research on Humans

Chronology and Status of the Federal Law on Research on Humans
Cantonal Regulations 342
Human Research Requirements 342
Cantonal Ethics Commissions (CECs) 343
Cantonal Ethics Commission Submission Guidelines (Zurich CEC Example) 343
REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES 343
SGCI Code of Practice 343
PROSPECTIVE NON-INTERVENTIONAL STUDIES 343
Prohibition of Promotion 344
Scientific Service (Body Responsible for Approval & Supervision of NIS) 344
Limited Involvement of Medical Reps 345
Competent Authority Approval 345
Favourable Ethics Opinion 346
Ethics Approval Process - Multi-Centre Studies 346
Contract 346
Compliance with Data Protection Legislation 347
Compliance with Data Protection Legislation/ Need for Informed Consent 347
Insurance 347
Evidence of GCP Training 348
Safety Reporting 348
Dissemination of Study Reports 348
ADDITIONAL RESOURCES 349
Country-specific eLearning Module 349
Course Format 349
Who Would Benefit from the Course? 350
Further Information and/or Free Demonstration 350
switzerland - USEFUL LINKS 351
Disclaimer

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

It Depends!
STEP 1 - DETERMINE WHAT TYPE OF STUDY YOU INTEND TO CONDUCT

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

**Study Classification**

- **Interventional?**
  - Is your study an interventional clinical trial?
    - **Yes**
      - Refer to the Clinical Trials Directive (2001/20/EC)
    - **No**
      - **PASS?**
        - Is your study a post-authorization safety study (PASS)?
          - **Yes**
            - Refer to the Pharmacovigilance Directive (2010/84/EU)
          - **No**
            - **Other NIS?**
              - Is your study a non-safety related non-interventional study?
                - **Yes**
                  - Refer to the Country Specific!

**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 standardised and you will need to determine the country-specific considerations.

STEP 2 - DETERMINE THE COUNTRY-SPECIFIC REQUIREMENTS
The regulatory requirements for ‘Other’ NIS are very much dependent on a number of factors (see below), which is why there isn’t generally a single answer to the question, “what are the regulatory requirements for my non-interventional study?”

There are no short cuts. You will need to verify the country-specific regulations and considerations for each of the countries where you intend to conduct your non-interventional study.
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

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NIS-Considerations - Europe (Part 1) - 3rd Edition - September 2012
45
<table>
<thead>
<tr>
<th>Useful Links</th>
<th>Accessed From</th>
</tr>
</thead>
</table>
NIS Summary

SUMMARY OF THE COUNTRY-SPECIFIC CONSIDERATIONS WHEN CONDUCTING NON-INTERVENTIONAL STUDIES

SUMMARY TABLE

The following table summarises the country-specific considerations when conducting non-interventional studies in Europe.

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>CA Approval? (Competent Authority)</th>
<th>REC Approval? (Research Ethics Committee)</th>
<th>DPA Approval? (Data Protection Agency)</th>
<th>Other Considerations</th>
</tr>
</thead>
</table>
| Belgium | No                                | Yes                                      | Notification                          | • Pharma.be visa required for studies outside scope of LEHP e.g., retrospective studies  
|         |                                   |                                          |                                       | • Invitation of health professionals to and the defrayment of the costs of participating in a scientific event that involves at least one overnight stay is subject to an advance visa procedure. Obliged to obtain the visa from the Visas Bureau of the non-profit association Mdeon  
|         |                                   |                                          |                                       | • Register study with Pharma.be before study starts |
### SUMMARY OF CHANGES SINCE PREVIOUS VERSION

Summary of country-specific changes implemented since the publication of the 2nd Edition of Non-Interventional Studies: Europe Part 1 in August 2010

<table>
<thead>
<tr>
<th>Area Impacted</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legislation</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Competent Authority Requirements</td>
<td>Not applicable</td>
</tr>
<tr>
<td>REC Requirements</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Data Privacy Requirements</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Pharmaceutical Association Requirements</td>
<td>• Pharma.be Code of Deontology has been updated from the 2008 version to the 2012 version</td>
</tr>
<tr>
<td></td>
<td>- There is no significant difference and therefore impact on the NIS requirements listed in the updated version of the Pharma.be Code of Deontology</td>
</tr>
<tr>
<td></td>
<td>• This now includes details of the Mdeon visa requirements</td>
</tr>
</tbody>
</table>
DEFINITIONS

Non-Interventional Study

A non-interventional study is understood to mean a study in which the medicinal products are 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 medical practice and the decision to prescribe the medicinal product is clearly separated from the decision to include a patient in the study. The patient in question must not be subject to additional diagnostic or monitoring procedures and epidemiological methods shall be used for the analysis of collected data (as per Article 43 of the Pharma.be Code of Deontology, 2012).

"non-interventional trial"

A study where the medicinal products are prescribed in the usual manner in accordance with the terms of the marketing authorization. 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. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data (as per Article 2.8 of the Law Concerning Experiments on the Human Person (LEHP) of 7th May 2004).

Clarification

For a non-interventional trial to come within the scope of application of the legislation, it also must be a prospective study. The notification relating to the safety required for clinical trials is not applicable and only the normal post-marketing drug monitoring system is applicable (as per Annex 1 of Circular 455 of 28/11/2004).
SUMMARY OF THE REGULATORY & OPERATIONAL REQUIREMENTS

The following table provides an overview of the approval and notification requirements when planning to conduct non-interventional studies in Belgium.

Note: This table is not intended to be exhaustive.

<table>
<thead>
<tr>
<th>Study Tasks</th>
<th>NIS Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competent Authority (FAMHP)</td>
<td>✔</td>
</tr>
<tr>
<td>Notification</td>
<td>✔</td>
</tr>
<tr>
<td>Approval</td>
<td>✔</td>
</tr>
<tr>
<td>Research Ethics Committee (REC)</td>
<td>✔</td>
</tr>
<tr>
<td>Approval</td>
<td>✔</td>
</tr>
<tr>
<td>Data Protection Agency (CPP)</td>
<td>✔</td>
</tr>
<tr>
<td>Notification/ Registration</td>
<td>✔</td>
</tr>
<tr>
<td>Approval</td>
<td>✔</td>
</tr>
<tr>
<td>Institutional Approval</td>
<td></td>
</tr>
<tr>
<td>Contractual agreement between study Sponsor and Investigator/Institution</td>
<td>✔</td>
</tr>
<tr>
<td>where the study will be conducted</td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical Self-Regulation Body (Pharma.be)</td>
<td></td>
</tr>
<tr>
<td>Pharma.be visa required for studies outside scope of LEHP e.g., retrospective studies</td>
<td>✔</td>
</tr>
<tr>
<td>Invitation of health professionals to and the defrayment of the costs of</td>
<td>✔</td>
</tr>
<tr>
<td>participating in a scientific event that involves at least one overnight</td>
<td></td>
</tr>
<tr>
<td>stay is subject to an advance visa procedure. Obliged to obtain the visa</td>
<td></td>
</tr>
<tr>
<td>from the Visas Bureau of the non-profit association Mdeon</td>
<td></td>
</tr>
<tr>
<td>Register study with Pharma.be before study starts</td>
<td>✔</td>
</tr>
</tbody>
</table>

✔ = not required; ✗ = required

* The following types of studies that fall outside the scope of the LEHP:
  - Retrospective studies in which the past is examined using already available data and based on existing records and/or databases (electronic or other), in which the data subjects do not participate directly.
  - Studies on surplus biological material collected as part of a diagnosis (blood sample, biopsy material, etc...) of which a surplus was kept.
  - Experiments on corpses (studies of the Anatomy Laboratory of the Faculty of Medicine).
Psychological studies: Psychologists are not mentioned in the Royal Decree n° 78 on the Practice of Healthcare Professions and the law of May 2004 only applies to “any trial, study or investigation carried out on a human being in order to gain knowledge to further the practice of healthcare professions as set out in Royal Decree n° 78 of 10 November 1967” as specified in Article 2, point 11. However, any psychological study that is based on medical examinations (EEG, brain scan, etc.) falls within the scope of the law through the intervention of the physician responsible for the medical examinations.

Source: http://www.erasme.ulb.ac.be/page.asp?id=11373&langue=EN
### Competent Authority

The Belgian Federal Agency for Medicines and Health Products (FAMHP) was officially created on the 1st January 2007. The FAMHP has completely taken over the role and fields of competency of the Directorate-General for Medicinal Products (DG Medicinal Products) of the Federal Public Service (FPS) Public Health (FAMP Annual Report 2007).

### Competent Authority Approval

There is currently no legal requirement to seek FAMHP approval for non-interventional studies or notify the FAMHP of an intention to perform a non-interventional study.

### Research Ethics Committees (RECs)

The Royal Decree of 12th August 1994 (RD 12/08/1994) made RECs compulsory for every hospital or group of hospitals. This law also defined the RECs aims, composition & function, closely following the code of deontology of the Order of Doctors.

---

| **Competent Authority** | Federal Agency for Medicines and Health Products (FAMHP)  
(Agence Fédérale pour les Médicaments et les Produits de Santé - AFMPS) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research Ethics Committees</strong></td>
<td>Ethical approval of “Experiments on Human Persons” is provided by the Leading Ethics Committees (LECs)</td>
</tr>
<tr>
<td><strong>Data Protection Agency</strong></td>
<td>Commission for the Protection of Privacy (CPP)</td>
</tr>
<tr>
<td><strong>Pharmaceutical Self-Regulation Body</strong></td>
<td>Association Générale de l’Industrie du Médicament (Pharma.be)</td>
</tr>
<tr>
<td><strong>Pharmaceutical Code of Practice</strong></td>
<td>Pharma.be Code of Deontology (March 2012)</td>
</tr>
</tbody>
</table>
There are currently about 215 research ethics committees. The majority are associated with hospitals and some are associated with non-hospital institutions. Until the 31st of March 2012, only 38 of these research ethics committees (see link) have full recognition to give a single opinion (EFGCP Report, Belgium - 2011).

There is a central Consultative Committee for Bioethics, officially installed in 1996, which formulates opinion & informs the public; however this is only a consultative body (EFGCP Report, Belgium - 2011).

On 7 May 2004 the Law relating to Experimentation on Humans (LEHP) came into force, which for the first time endowed Belgian RECs with a legal status. It covers all types of medical experimentation, including prospective non-interventional studies.

**Ethical Approval**

Sponsors are legally required to obtain ethical approval prior to starting a prospective non-interventional study.

**Pharmaceutical Self-regulation Body (Pharma.be)**

The ‘Association Générale de l’Industrie du Médicament’, otherwise known as “Pharma.be” is the Belgian self-regulation Pharmaceutical body affiliated with EFPIA.

The website and most of the resources are currently only available in Dutch and French. However, an English translation of the Pharma.be Code of Practice on the Promotion of Medicines (Pharma.be Code of Deontology - 2012) is available through the Pharma.be website.

**Data Protection Agency (CPP)**

The Commission for the Protection of Privacy (CPP), better known as the Privacy Commission, is an independent authority ensuring the protection of privacy during the processing of personal data.
The Commission was established by the Belgian Federal House of Representatives with the Act of 8 December 1992.

**Notification**

According to Article 17 of the Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data (Privacy Act or Data Protection Act - as amended), prior to any wholly or partly automatic operation or set of operations intended to serve a single purpose or several related purposes, the controller or his representative, if any, must notify the Commission for the Protection of Privacy (CPP).
**Applicable Legislation and Guidance**

The laws and guidelines which are applicable to the management and conduct of non-interventional studies in Belgium include (but are not limited to):

<table>
<thead>
<tr>
<th>Regulations Applicable to NIS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Law Concerning Experiments on the Human Person (LEHP) of 7th May 2004</td>
<td>Royal Decree of August 12th 1994 - Local Hospital Ethics Committee (RD 12/08/1994)</td>
</tr>
<tr>
<td>The Patient Rights Act (August 2002)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data Protection Regulations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data (LVLP)</td>
<td>Royal Decree of 13/2/2001</td>
</tr>
<tr>
<td>Royal Decree of 17/12/2003</td>
<td></td>
</tr>
<tr>
<td>CPP Guidance - How to apply the Privacy Act in biomedical research (2011)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethical Standards</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH GCP</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>NIS best Practice Considerations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharma.be Code of Deontology (March 2012)</td>
<td></td>
</tr>
</tbody>
</table>
REQUIREMENTS FOR NON-INTERVENTIONAL STUDIES

**Purpose**

The study should be conducted with a clear scientific purpose (as per Article 44 of the Pharma.be Code of Deontology, 2012).

**Prohibition of Promotion**

The study must not constitute an inducement to recommend, prescribe, purchase or sell, supply or administer medicinal products (as per Article 44 of the Pharma.be Code of Deontology, 2012).

**Quality Framework**

Non-interventional studies shall be conducted within a quality framework (as per Article 43 of the Pharma.be Code of Deontology, 2012).

**Contract**

A written contract shall provide a detailed description of the services expected from the investigators as well as of the amount and the procedures for remunerating the investigators (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Notwithstanding article 40 of this Code and notwithstanding the legal provisions, contracts between pharmaceutical companies and institutions, organisations or associations of healthcare professionals by the terms of which such institutions, organisations or associations provide services to companies, are only allowed if such services:

1) support healthcare or research,

2) do not constitute an inducement to recommend, prescribe, purchase, sell, supply or administer medicinal products.

(as per Article 41 of the Pharma.be Code of Deontology, 2012).
Notwithstanding article 40 of this Code and notwithstanding the legal provisions, a pharmaceutical company may use one or more healthcare professionals as consultants or advisors for services such as speaking at or chairing scientific meetings, involvement in medical/scientific studies, clinical trials or training courses, participation in advisory board meetings or participation in market research, in which the healthcare professionals concerned receive a remuneration and/or are expected to travel (as per Article 42 of the Pharma.be Code of Deontology, 2012).

The arrangements made in this respect, if relevant to this subject, must satisfy the following conditions:

(a) a legitimate need for the services is clearly identified before retaining the healthcare professionals and making arrangements in this respect;

(b) the criteria for selecting consultants are directly related to the identified legitimate need as referred to in clause a and the persons responsible for selecting the consultants have the expertise necessary to evaluate whether the contacted healthcare professionals meet those criteria;

(c) the number of healthcare professionals retained is not greater than the number reasonably necessary to achieve the identified need;

(d) a written contract must be drawn up before the commencement of the services which specifies the nature of the services to be provided by the healthcare professionals as well as the basis for payment for their services notwithstanding what is cited in clause g. hereafter;

(e) the pharmaceutical company maintains records concerning the services provided and makes appropriate use of them;

(f) the hiring of the healthcare professionals to provide the services is not an inducement to recommend, prescribe, purchase, sell, supply or administer medicinal products and

(g) the compensation for the services is reasonable and reflects the usual market value of the services provided.

(as per Article 42.1 of the Pharma.be Code of Deontology, 2012).
Declaration of Conflicts of Interest/ Financial Support

For the purposes of transparency, pharmaceutical companies are strongly encouraged to include in the written contract as mentioned above in paragraph 1.d. a provision regarding the obligation of the healthcare professional in question to declare that he/she is fulfilling a consultancy or advisory mission for the company whenever he/she speaks in public or publishes on matters that are the subject of the agreement or any other issue relating to that company (as per Article 42.2 of the Pharma.be Code of Deontology, 2012).

Similarly, pharmaceutical companies that employ healthcare professionals on a part-time basis who are still practising their profession are strongly encouraged to impose on such persons the obligation to declare their employment arrangement with the company whenever they speak in public or publish on matters that are the subject of their employment arrangement or any other issue relating to that company (as per Article 42.2 of the Pharma.be Code of Deontology, 2012).

Market Research

The provisions mentioned under paragraph 1.d. do not apply to limited market research, such as one-off phone interviews or surveys by post, e-mail or internet, provided that the healthcare professionals concerned are not consulted repeatedly, whether in the context of the same or another survey, and that the remuneration for their collaboration is of token value (as per Article 42.3 of the Pharma.be Code of Deontology, 2012).

Remuneration

The remuneration is commensurate with the services requested and reflects the market value thereof (as per Article 44 of the Pharma.be Code of Deontology, 2012).
Study Protocol

A written scientific protocol shall provide a detailed description of the purpose sought and methodology implemented; the aforementioned purpose and methodology shall always be coherent with one another (as per Article 44 of the Pharma.be Code of Deontology, 2012).

The scientific protocol must be approved in advance by the company’s scientific service as referred to under article 6 of this Code and this service has to supervise the conduct of the study (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Procedures for the Supply of Medicines

The procedures for supplying the medicines studied shall be described in detail in the protocol; they shall be coherent in regard to the stated purpose and methodology (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Justification for the Number of Patients and Number of Investigators

The number of patients requested for inclusion as well as the number of investigators included shall be justified in a scientific manner in the protocol, for example by means of a biostatistical calculation (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Future Use of Data

The future use of the data collected shall be stated clearly in the protocol (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Study Design and Follow-up

The holder of the marketing authorisation shall establish a permanent connection with a scientific service charged with providing information on the medicinal products that it markets and which is responsible for the approval and the supervision of non-interventional studies which are carried out by or with the support of the holder of the authorisation (as per Article 6 of the Pharma.be Code of Deontology, 2012).
Regardless of the way the scientific service is organised, this service should include a medical doctor or a pharmacist who will approve any promotional material before release (as per Article 6 of the *Pharma.be Code of Deontology, 2012*).

In addition, the scientific service must include a medical doctor or a pharmacist who will be responsible for the supervision of all non-interventional studies which are carried out or sponsored by the company (as per Article 6 of the *Pharma.be Code of Deontology, 2012*).

**Limited Involvement of Medical Reps**

Medical informants (Medical or Sales Representatives) may only intervene in a study to perform administrative tasks under the supervision of the Company’s Scientific Service; this service will ensure that the medical informants are adequately trained for this purpose; their involvement in scientific studies must not be linked to the promotion of medicinal products (as per Article 44 of the *Pharma.be Code of Deontology, 2012*).

**Competent Authority Approval**

Not required.

**Favourable Ethics Opinion**

This type of study must be carried out in respect of the requirements set out by applicable legislation – among others, the favourable opinion of an accredited Lead Ethics Committee (LEC) must be granted before the study can start (Article 10 of the *LEHP*).

**Procedure for Submission to Ethics Committees**

The procedure for submission to the Ethics Committees of the sites concerned should be in accordance with strict rules.

- The sponsor designates a principal investigator (PI) for Belgium and an ethics committee that has to issue a single opinion (CAISO = Committee authorised to issue a
single opinion or LEC = Leading Ethics Committee) as per Articles 11.2 and 11.3 of LEHP.

The CAISO communicates with the local ethics committees of the different sites involved in the research project and summarises the received opinions (as per Articles 11.7 & 11.8 of LEHP) to formulate:

- a first temporary opinion intended to obtain amendments of the protocol / patient information leaflet and the informed consent form;
- a final opinion or approval, which applies to all the sites that participated in the review process.

According to Article 11.5 of LEHP, the ethics committee has a maximum of 15 days to provide an opinion for single centre Phase 1 studies and a maximum of 28 days for all other experiments.

Further detailed information on the LEC submission requirements can be found via the website of the Ethics Committee at the Erasmus Hospital in Brussels. This includes:

- **Remuneration for examining an application** – Lists the fees which must be paid in advance to the Ethics Committee.

- **Definitions and types of clinical research** – Explains which types of studies fall within the scope of the LEHP (e.g., prospective NIS) and further explains the process for submitting applications to ethics committees.

- **Non-interventional clinical trial sponsored by the industry** – Lists which documents must be submitted to the ethics committee when applying for favourable opinion to conduct an NIS.

- **Submitting an amendment** – Explains the procedure to follow when submitting an amendment to the ethics committee.

- **Information about the completion, premature discontinuation, temporary discontinuation and restart of a trial.**

- **Insurance and Clinical Investigation on Human Subjects** – Explains the liability and insurance requirements as laid down by Article 29 of LEHP.
Data Privacy and the Processing of Medical Data – Provides a summary of the applicable data privacy laws as applicable to processing medical data.

Approval of Substantial Amendments
Belgian law (Chapter X of LEHP) requires ethical approval (favourable opinion) of substantial amendments to the NIS protocol.

Attendance at Scientific Events
Scientific events that are directly or indirectly supported or organised by pharmaceutical companies and that are attended by health professionals shall take place within a framework of quality, as required by articles 31 to 35. When a scientific event does not take place in Belgium, it must also, in accordance with article 3, § 3 of this Code, comply with the criteria laid down by the Code of Deontology that applies in the country where the event takes place (as per Article 30 of the Pharma.be Code of Deontology, 2012).

This applies, for example, to events of an exclusively professional and scientific nature, events to promote medicinal products, symposiums, international scientific congresses, advisory board meetings, visits to research or manufacturing facilities, investigator meetings for clinical or other scientific studies and any other form of scientific meeting held in Belgium or abroad (as per Article 30 of the Pharma.be Code of Deontology, 2012).

When a healthcare professional attends a scientific event in the capacity of consultant or advisor, the articles 30 to 35 of this Code apply (as per Article 42.3 of the Pharma.be Code of Deontology, 2012).

Advance Visa Procedure
The invitation of health professionals to and the defrayment of the costs of participating in a scientific event as referred to under article 30 that involves at least one overnight stay are subject to an advance visa procedure (as per Article 72 of the Pharma.be Code of Deontology, 2012).
In which case, pharmaceutical companies are obliged to obtain the visa from the Visas Bureau of the non-profit association Mdeon (as per Article 72 of the Pharma.be Code of Deontology, 2012).

End of Study Notification
Within 90 days of the end of an experiment, the sponsor shall notify the ethics committee that the experiment has ended. If the experiment must be terminated early, this term shall be reduced to 15 days. The notification shall clearly explain the reasons for the early termination (Article 21 of LEHP).

Analysis and Retention of Study Results
The study results must be analysed and reports thereof must be submitted within a reasonable period of time to the company’s scientific service which shall maintain these reports for a reasonable period of time (as per Article 44 of the Pharma.be Code of Deontology, 2012).

The study results should also be kept at the disposal of the bodies of pharma.be as referred to under article 52, paragraph 1 of this Code and must be submitted following a request on their part (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Dissemination of Study Results
The company must send the study results to all healthcare professionals who participated in the study (as per Article 44 of the Pharma.be Code of Deontology, 2012).

Notification of Important Risk-Benefit Information
If the study shows results that are important for the assessment of the benefit–risk ratio of the studied medicinal product(s), these results should be immediately forwarded to the competent authority (as per Article 44 of the Pharma.be Code of Deontology, 2012).
Retrospective & ‘Other’ Non-Interventional Studies

The non-interventional studies referred to under article 43 of this Code, with the exception of the experiments referred to in the law of 7 May 2004 concerning experiments on human persons (LEHP) and that are subject to the advice of an ethics committee, are subject to an advance visa procedure (as per Article 73 of the Pharma.be Code of Deontology, 2012).

Visa Application

To this end, pharmaceutical companies are bound to obtain the visa from the Visas Bureau of pharma.be prior to the inclusion of the first investigator (as per Article 73 of the Pharma.be Code of Deontology, 2012).

Only the studies cited in the first paragraph and that cumulatively meet the following conditions are submitted to the visa procedure:

- they are carried out or supported directly or indirectly by a pharmaceutical company;
- they relate to one or more of the characteristics of the medicinal product(s) studied;
- they involve one or more persons from outside the company.

Proceedings in regard to the Visas Bureau are conducted in writing only (as per Article 73 of the Pharma.be Code of Deontology, 2012).

Dossier Requirements for a Visa Application

Companies introduce an application for visa by submitting the duly completed model dossier as drawn up by the Secretariat, together with all information and documents attesting to compliance with article 43 and 44 of the Code (as per Article 74 of the Pharma.be Code of Deontology, 2012).

The model dossier drawn up by the Secretariat includes the following elements:

- general identification data,
- the starting and closing dates of the study,
the detailed scientific protocol including the following elements: the objective, methodology, possible approval by the company’s scientific service referred to under article 6 of this Code and added value,

the detailed financial protocol including the following elements: the amount and methods of remuneration for the investigators, the detailed description of the services requested of the investigators who receive the remuneration and the model contract concluded with the investigators,

the methods for the supply and distribution of the medicinal products studied,

the description of the future use of the data collected,

the scientific justification, biostatistical if applicable, for the number of patients and investigators included as well as their geographical distribution,

any other information deemed to be useful by the applicant company.

On pain of being declared inadmissible, five copies of the application file must be submitted by post (as per Article 74 of the Pharma.be Code of Deontology, 2012).

The Secretariat acknowledges reception of each dossier received and at the same time issues a dossier number to the applicant company. This dossier number may only be used by the applicant company in accordance with the conditions laid down under article 75, para. 2 and article 76, para. 2 (as per Article 74 of the Pharma.be Code of Deontology, 2012).

Visa Approval Timeframe

The Visas Bureau notifies the applicant company of its decision no later than the tenth working day following that on which the Secretariat receives the application (as per Article 76 of the Pharma.be Code of Deontology, 2012).

If, at the end of the tenth working day following that on which the Secretariat receives the application, the Visas Bureau has not notified the applicant company of its decision, the visa is deemed to have been granted. In which case, the applicant company is bound to indicate the dossier number referred to under article 74, last paragraph, of this Code, known as the “visa number”, on all documents concerning the project in question drawn up after the expiry of the aforementioned term (as per Article 76 of the Pharma.be Code of Deontology, 2012).
Ethical Review of Retrospective NIS & Applicability of the LEHP

If, during a retrospective study, the patient is contacted specifically in the context of the study, this study is interventional and falls well within the law experiments (as per Section 1.4.2 of the FAMHP Guide for the Evaluation of Non-interventional Studies - May 2008).

Under general ethical principles, it is advisable to submit all non-interventional studies, including those not falling within the scope of the law, for the opinion of a medical ethics committee (as per Section 1.4.2 of the FAMHP Guide for the Evaluation of Non-interventional Studies - May 2008).

Informed Consent in the Context of Retrospective Non-interventional Studies

Studies of records, studies based on questionnaires, etc., do not fall within the scope of the law concerning experiments on humans (LEHP). * The treatment team has a right of direct access to uncoded data extracted from medical records of patients and this right is not open to discussion. In this regard, it should be noted that when the therapeutic team consults and processes data for its own use, the patient’s informed consent is not required provided that the rules of confidentiality are respected.

[* Therapeutic teams acting under the direct responsibility of the attending physician: personnel (para-) medical external - prosthetic intervention, for example - must also be included in the therapeutic team. It does not however apply to hospital pharmacists, for example, who have partial knowledge of pharmaceutical personal data, but are bound by professional secrecy. ]

Communication of data outside of the therapeutic team must be in compliance with the LPVP and RD-LPVP (Chapter 2):

- Where anonymised data are made available to third parties not part of the therapeutic team, the patient’s consent is not necessary.
- When the encoded data are made available to third parties not part of the therapeutic team, the obligation to inform the patient (or his legal representative in the case of a minor or an incompetent patient) applies, except in exceptional cases for which
arrangements specific statement to the Commission for the Protection of life are provided.

When uncoded data are made available to third parties not part of the therapeutic team, the principle of informed consent (or its legal representative in the case of a minor or an incompetent patient) applies, except in exceptional cases for which specific arrangements for reporting to the Commission for the Protection of Privacy Act are provided.
ADDITIONAL RESOURCES

Country-specific eLearning Module

CHCUK now offer an eLearning Module for Belgium that explores the country-specific requirements when conducting non-interventional studies in Belgium and looks specifically at:

- Regulatory classification
- Regulatory framework/applicable legislation and guidelines
- Approval requirements and timeframes
- Submission documents
- Who is responsible for what?
- Practical considerations when conducting non-interventional studies
- Requirements for non-interventional studies that intend to collect, store and/or analyse human tissue samples
- Industry best practice

Course Format

The course:

- Includes reminders at the end of each module
- Has an audio commentary
- Includes PDFs of all the training materials
- Includes a comprehensive tools and resources report that is an ideal reference guide for anyone involved in the oversight or operations aspects of non-interventional studies

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77
Includes a certificate of completion that is automatically issued to all participants who complete the course.

**Who Would Benefit from the Course?**

The course is intended for anyone involved in the oversight or operations aspects of non-interventional studies, such as:

- Medical Affairs groups/ Company Affiliates
- Project Managers
- CRAs
- Quality Assurance personnel
- Regulatory Affairs personnel

**Further Information and/or Free Demonstration**

If you would like further details, or would like to request a free demo then please contact us at:

Email: info@chcuk.co.uk

Phone: +44 1997 42 33 11

website: www.chcuk.co.uk
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