CONDUCTING NON-INTERVENTIONAL STUDIES IN EUROPE
Attempts at Clarity Lead to Increased Complexity

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For years, industry stakeholders have been hoping for a clearer definition of non-interventional studies (NIS), which observe patients treated under real-life conditions to obtain information on a drug’s safety and effectiveness. NIS are the “untamed beast,” and each must be approached carefully in order to identify the complex regulatory and operational requirements that pertain to each European country.

Unfortunately, sometimes an attempt at clarity begets complexity. Such is the consequence of the new European Clinical Trials Regulation (EU CTR) EU Regulation No 536/2014, which was adopted in April 2014 and will become applicable no earlier than May 28, 2016. The EU CTR defines a low-interventional clinical trial—a new middle ground between the clinical trial and NIS—that, in practice, further complicates sponsors’ job of untangling requirements and making sense of country-level interpretations.

Here, we review the various definitions of NIS, explore the aspects of those definitions left open to interpretation, and offer recommendations to sponsors for dealing with the ambiguity.

TERMS & CONDITIONS

The classification of a given body of research as interventional or non-interventional has momentous consequences for sponsor companies’ budgets, timelines, and approaches to demonstrating the value of their products. The definitions of various study types thus bears scrutiny. The following definitions may at first seem basic, but readers will see that the complexity rises quickly. As management guru and author Tom Peters suggested, “If you’re not confused, you’re not paying attention.”

NIS Considerations for 2016

All prospective NIS will be affected by additional expedited safety reporting requirements. In addition to the 15-day reporting requirement for serious adverse reactions (SARs) related to marketed products; Directive 2010/84/EU (amended Directive 2001/83/EC) mandated the reporting of all non-serious suspected adverse reactions (SARs) within 90 days. That requirement was only partially implemented and postponed in the majority of EU countries because the functionality to capture the information did not exist within EudraVigilance. The expedited safety reporting of non-serious suspected adverse reactions will be obligated six months after the functionality is added to EudraVigilance, which is anticipated to be sometime in 2016:

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has, along with the regulatory bodies, implemented an EU version of the U.S. “Sunshine Act.” In reporting payments to physicians (“transfers of value”), companies in all 28 countries will be required to begin collecting data in 2015 and disclosing it by 2016. They must also secure the consent of physicians to disclose such data, which will present a “Catch 22” if physicians do not give their consent.
Clinical Trials

According to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), classical, experimental clinical trials involve fundamental interventions in treatment. These include strict criteria for inclusion and exclusion of subjects, allocating treatment a priori (i.e., by randomization), and enforcing a particular protocol. The term "trial" implies an element of experimentation and a prospective approach to data collection.

Observational/NIS Studies

Again, according to ENCePP, observational, epidemiological (including pharmacoepidemiological) studies involve no interventions and so are often also called NIS. Unlike in clinical trials, the patient is (usually) already taking the drug and the treatment is not determined or assigned by study procedures. What happens in the clinical setting is only observed, monitored, and recorded based on data collected from the provider’s notes. A study, as opposed to a trial, is a systematic assessment of events that unfold with no interference in their course.

This definition was reflected in the EU Clinical Trials Directive (2001/20/EC), specifying that a NIS is one in which:

…the medicinal product(s) is (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.2

The terms NIS, observational studies, and real-world data are often used interchangeably and broadly refer to studies that are not interventional and that are collected under real-life circumstances, post approval. (See the Sidebar: The Importance of NIS/Observational Studies.)
“Observational” Studies

But, what of studies that apply additional, yet very minor, low-risk, diagnostic or monitoring procedures? Need they be automatically classified as interventional trials? The answer is an unequivocal, “it depends.” The European Medicines Agency (EMA) provided guidance in the EMA GVP Module VIII which states:

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 these studies, interviews, questionnaires and blood samples may be performed as part of normal clinical practice.

This latter, highlighted short sentence added ambiguity to the definition of NIS, giving rise to the term “observational study” to describe observational studies that by design include low-risk, low-impact interventions such as study-specific blood sampling, interviews and/or questionnaires. Admittedly, the interviews or questionnaires may have a psychological impact, and the collection of biosamples could possibly be painful or lead to bruising, but the treatment regimen remains unchanged. While patients may not benefit directly from the additional information gained via these study-specific procedures, neither are they negatively impacted, assuming that the data are handled correctly. In essence, these are not truly non-interventional studies in the strictest sense, but neither are they clinical trials. They lie in a grey area.

The interpretation of what falls into this category has been left to individual countries according to their own definition of risk, with the result that the same study design can be classified as interventional or non-interventional, depending on the country. (See Table 1.)

Table 1 – What Makes a Study Interventional?

<table>
<thead>
<tr>
<th>Country</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| Netherlands | • Additional blood samples  
              • Highly personal, embarrassing, intimate or extensive questionnaires  
              • Patient has to be physically present during the study |
| Austria     | • Additional blood samples                                                     |
| Slovakia    | • NIS can only be conducted up to 2 years after the drug has been registered in Slovensko |

In four of the 28 EU countries, a study in which a blood sample was taken would automatically be classified as interventional. In the other 24 countries, the same study would be considered non-interventional in 21 and “potentially interventional” in three.

Consequently, when sponsors and other stakeholders ask about the requirements for NIS, the only accurate answer is simply stated: “It depends.” But the ramifications of that answer are uncertainty, inconsistency, and potential non-compliance. How a study is classified, directly and significantly impacts which regulations must be followed.

MOUNTING AMBIGUITY

The ENCePP has listed various types of studies that in its view should be considered observational, non-interventional studies and, therefore not be governed by Clinical Trials Directive 2001/20/EC, issued by the European Parliament.

Retrospective, observational studies:

- Purely observational database review and/or research.
- Retrospective review of records where all the events of interest have already happened (case-control, cross-sectional, and purely retrospective cohort studies).
- Studies in which the prescriber later becomes an investigator but prescribing has already occurred (e.g. retrospective data collection from individual medical records at the site of the investigator).

Prospective, observational studies:
Registries in which the data collected derive from routine clinical care.

Studies that evaluate patterns of the usage of medicines, including potential off-label use or measuring the effectiveness of risk management measures in current practice, such as collection of data on drug utilization and occurrence of health outcomes.

The following situations are, however, examples of studies that involve prospective data collection and that may—or may not—be considered non-interventional. They require careful consideration.

Prospective cohort studies that involve additional diagnostic or monitoring requirements, but in which the prescription of the medicine that is being investigated is independent from the inclusion of the patient in the study.

A retrospective study to which a prospective element is subsequently introduced (e.g. the researcher wants to evaluate further variables that are not in the existing dataset and, therefore, prospective additional research is undertaken. This might range from further analyses in linked databases to additional blood draws or other additional diagnostic or monitoring events).

Long-term extension studies in which patients that received treatment with a medicinal product in a completed randomized clinical trial are followed beyond the time specified by the clinical trial protocol for the observation and the active collection of data on safety or other outcomes (e.g., death, event-free survival, etc.) (See Figure 2.)

Figure 2: When Long-Term Extension Studies become Interventional Clinical Trials

<table>
<thead>
<tr>
<th>Country</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech Republic1</td>
<td>• The selection of patients must depend solely on the decision of the attending physician as a part of the current practice</td>
</tr>
</tbody>
</table>

Case Study
• Prospective non-interventional safety study
• Patients must have participated in a previous clinical trial in which they were administered the Sponsor’s drug
• Patients do not need to be taking the [now approved] drug to be eligible for the study

SUKL Decision
• Patients must have participated in a previous clinical trial in which they were administered a novel immunosuppressant
• Therefore, selection of patients does not depend on the decision of the attending physician
• Study was classified as INTERVENTIONAL

1 = As per SUKL Guidance PHV-3 [http://www.sukl.eu/medicines/phv-3-version-3]

A CRY FOR CLARITY

The need for clarification and simplification on the Clinical Trials Directive (2001/20/EC) was evident in a May 2011 public consultation paper issued by the European Confederation of Pharmaceutical Entrepreneurs.

A clinical trial conducted as phase IV study, i.e. within the authorized indication, population, dosage and treatment duration usually poses only “minimal risk” to the safety of the trial subject. It needs, however, to be more clearly defined what the Commission considers as “the interventions in the trial do not pose more than insignificant additional risk to the safety compared to normal clinical practice in a MS [Member State] concerned.” Usually, phase IV studies require not only randomization but at least also some additional blood samples. Is this considered as “insignificant additional risk”? It has to be defined who will decide on the classification of a study as a type A trial.5

Such variations by country and confusion around the classification of studies make it increasingly difficult to satisfy the first order of regulatory compliance: knowing what to be compliant with. It’s not a simple matter with NIS.

A NEW REGULATION, YET ANOTHER DEFINITION

In April 2012, the European Parliament and the Council of the European Union New European Clinical Trials adopted new clinical trial regulations with an expressed goal of helping the EU become more attractive for clinical research through simplifying and harmonizing the procedures for multinational trials.7 Regulation (EU CTR) EU Regulation No. 536/2014 will become available no earlier than May 28, 2016.3

Aware of the issues created through inconsistent interpretation of the Clinical Trials Directive (2001/20/EC), the European Medicines Agency (EMA) aimed for agreement on whether or not biosample collection is “interventional.” The solution was to create a new study category: a low-interventional clinical trial, in essence what the industry had been referring to as an observational study.

An early overview of the EU CTR explained that the new low-intervention clinical trials category resulted from the Regulation’s adopting a “risk-based approach” to acknowledge that not all clinical trials carry the same level of risk. These trials use authorized rather than investigational medicinal products. They will be subject to “less stringent rules, in particular with regard to insurance requirements, monitoring and reporting obligations, and traceability of investigational medicinal products.”9
The new Regulation defines a low-interventional clinical trial as a clinical trial that fulfills all of these conditions:

(a) the investigational medicinal products, excluding placebos, are authorized;
(b) according to the protocol of the clinical trial,
   (a) the investigational medicinal products are used in accordance with the terms of the marketing authorization; or
   (b) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

Based on the Regulation, all NIS involving biosampling will be considered low-interventional clinical trials. Unfortunately, the Regulation, stops short of clarifying the earlier Directive (2001/20/EC) by changing the definition of NIS. In effect, NIS—a non-interventional study—means “a clinical study other than a clinical trial.” The definition is an anti-definition with tremendous impact. Individual member states can still interpret as they see fit, so the confusion over conducting NIS at the country level remains without harmonization of requirements.

THE COMPLIANCE IMPERATIVE

Within the EU, regulations for clinical trials have been harmonized, while NIS regulations have not. A paradox is at play between the two.

Clinical trials are based on highly complex designs, but the regulations applying to them are harmonized and therefore relatively simple and straightforward. The sponsor registers the study on EudraCT, applies to the regulatory authority for approval to run the trial, and secures approval from the Research Ethics Committee (REC) and other applicable approval bodies. In contrast, NIS are based on simple research designs, but because regulations have not been harmonized, the approval process is complex. As they saying goes, “When you’ve done one non-interventional study…you’ve done one non-interventional study,” meaning that the regulatory requirements for each one are different. The requirements are driven by the study design (retrospective, prospective, or both), what data will be collected (existing data, patient-reported outcomes, genetic data, etc.), the patient population (minors, legally incompetent adults, etc.). This leads to each country having various categories of NIS and its own approval and notification requirements.

For example, in France, approval from both the data protection agency (CNIL) and physicians’ association (CNOM) is required, but approval from the ethics committee is not, unless biosamples are taken and/or additional monitoring procedures are applied. Also, the study need not be registered. But in Germany, ethics committee approval is required and the sponsor must notify all health insurance companies and competent authorities and must register the study. In Spain, where the study must be classified by the competent authority, there are five different types of post-approval studies (EPA), all with different approval requirements. In Austria, there is no legal requirement to obtain ethics committee approval, but it is strongly recommended by the competent authority. In the UK, sponsors must appoint a local legal representative, regardless of whether they have a legal presence elsewhere in Europe. This isn’t a requirement when conducting clinical trials in the UK. (See Figure 3.)

There are additional requirements for mandated non-interventional post-authorization safety studies (PASS)—a subject beyond the scope of this paper and worthy of its own discussion.
Figure 3: NIS Categories in EU 5 Countries

### France – NIS Categories

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Approvals</th>
<th>Notifications/Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandated PASS Multi-Country</td>
<td>PRAC CCTIRS, CNIL, CNOM</td>
<td>ANSM EMA PAS Register</td>
</tr>
<tr>
<td>Mandated PASS Single-Country</td>
<td>ANSM CCTIRS, CNIL, CNOM</td>
<td>EMA PAS Register</td>
</tr>
<tr>
<td>Other NIS</td>
<td>CCTIRS, CNIL, CNOM</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Other NIS + Biosampling</td>
<td>CPP, CCTIRS, CNIL, CNOM</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

### Germany – NIS Categories

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Approvals</th>
<th>Notifications/Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandated PASS Multi-Country</td>
<td>PRAC CEC</td>
<td>BfArM/PEI, GKV, KBV, PKV, EMA PAS Register</td>
</tr>
<tr>
<td>Mandated PASS Single-Country</td>
<td>BfArM/PEI CEC</td>
<td>GKV, KBV, PKV EMA PAS Register</td>
</tr>
<tr>
<td>Other NIS</td>
<td>CEC</td>
<td>BfArM/PEI, GKV, KBV, PKV, Vfa register</td>
</tr>
</tbody>
</table>
### Italy – NIS Categories

#### Retrospective NIS

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Approvals</th>
<th>Notifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandated PASS Multi-Country</td>
<td>AIFA</td>
<td>CEC/LEC</td>
</tr>
<tr>
<td>Mandated PASS Single Country</td>
<td>AIFA</td>
<td>CEC/LEC</td>
</tr>
<tr>
<td>Mandated PASS Single Country + Genetic Data</td>
<td>AIFA/ DPA</td>
<td>CEC/LEC</td>
</tr>
<tr>
<td>Mandated PASS Multi-Country</td>
<td>PRAC</td>
<td>AIFA/ CEC</td>
</tr>
<tr>
<td>Mandated PASS Multi-Country + Genetic Data</td>
<td>PRAC/DPA</td>
<td>AIFA/ CEC</td>
</tr>
<tr>
<td>Mandatory PASS Other</td>
<td>N/A</td>
<td>CEC/LEC</td>
</tr>
<tr>
<td>Mandatory PASS Other + Genetic Data</td>
<td>DPA</td>
<td>CEC/LEC</td>
</tr>
</tbody>
</table>

#### Prospective NIS

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Approvals</th>
<th>Notifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandated PASS Single Country</td>
<td>AIFA</td>
<td>N/A</td>
</tr>
<tr>
<td>Mandated PASS Single Country + Genetic Data</td>
<td>AIFA/ DPA</td>
<td>N/A</td>
</tr>
<tr>
<td>Mandatory PASS Multi-Country</td>
<td>PRAC</td>
<td>N/A</td>
</tr>
<tr>
<td>Mandatory PASS Multi-Country + Genetic Data</td>
<td>PRAC/DPA</td>
<td>N/A</td>
</tr>
<tr>
<td>Mandatory PASS Other</td>
<td>N/A</td>
<td>CEC/LEC</td>
</tr>
<tr>
<td>Mandatory PASS Other + Genetic Data</td>
<td>DPA</td>
<td>CEC/LEC</td>
</tr>
</tbody>
</table>

### Spain – NIS Categories

#### Study Type

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Approvals</th>
<th>Notifications/ Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandated PASS Multi-Country</td>
<td>PRAC</td>
<td>AEMPS EMA PAS Register, REEC</td>
</tr>
<tr>
<td>EPA-LA</td>
<td>AEMPS</td>
<td>EMA PAS Register, REEC</td>
</tr>
<tr>
<td>EPA-AS</td>
<td>CEC</td>
<td>AEMPS REEC</td>
</tr>
<tr>
<td>EPA-SP</td>
<td>CEC, Autonomous Communities</td>
<td>AEMPS REEC</td>
</tr>
<tr>
<td>EPA-OD</td>
<td>CEC</td>
<td>AEMPS REEC</td>
</tr>
<tr>
<td>Non-EPA</td>
<td>CEC</td>
<td>AEMPS REEC</td>
</tr>
</tbody>
</table>
The Triage: Classifying Research and Sorting Out the Action Steps

To determine regulatory requirements for a given NIS, the sponsor must answer a range of questions about what needs to be collected and why:

- Is this a mandated or voluntary study?
- Is it a prospective or retrospective study, or both?
- Is the drug reimbursed?
- What is the patient population?
- Are the patients legally competent?
- Are the patients deceased?
- Does the study involve quality of life (QoL) and patient-reported outcome (PRO) assessments?

Next, the sponsor should consider in which countries the study should run to determine which local regulations and guidelines will apply.

A best-practice approach is to work from a study synopsis to create a late-stage submission plan that takes into account the scope of the study. The plan should include a summary of the regulatory risks based on the protocol, country-specific regulatory maps, and a list of country-specific requirements (see Figure 4).
When a classification is wrong

Incorrectly classifying an interventional study as a NIS when it should be a clinical trial has grave consequences: it could jeopardize the data and endanger patients. Key good clinical practice (GCP) elements would be missing, patients put at risk, study data invalidated, and time and resources wasted. (See Figure 5.)

Conversely, incorrectly classifying a NIS as a clinical trial could result in waste in the tens of millions. A study that should cost $1-$3M would instead cost between $10-60M, while the resulting data would be the same. Being highly conservative, pharmaceutical companies tend to err on this side rather than risk endangering patients or invalidating a study. (See Figure 6.)
FUTURE OUTLOOK AND RECOMMENDED NEXT STEPS

EMA is not likely to sort out the complexity around conducting non-interventional studies for several years, as the main focus in the short term will be on the change in clinical trial legislation. All 28 countries will have to change their legislation to accommodate the new EU regulation. It could easily be 2018 until EMA can assess the impact on NIS.

A few action items may prepare the forward-thinking company for dealing with the uncertainty in the short-term while planning for a less ambiguous future:

• Talk to payers about their requirements.
• Become as familiar as possible with the NIS requirements so as not to confuse the two types of studies. A correct classification is essential. (Keep in mind that regulators are more familiar with clinical trials, which are mandated, rather than with NIS, which typically need only Ethics Committee or IRB approval. While FDA and EMA have some understanding of NIS, the sponsor needs advice at the level of each individual country.)
• Work closely with Regulatory Affairs staff and with trusted advisors.
• Continue to lobby for harmonization.

Clinical trials legislation has not been changed for a decade, but globally, NIS legislation is changed about every six months. The companies that expect a regulatory environment in flux will be more likely to marshal their resources to transform promising ideas into reality. As George Bernard Shaw said, “Progress is impossible without change, and those who cannot change their minds cannot change anything.”

KEY TAKE-AWAY MESSAGES

• Non-interventional studies are simple by design, but are governed by complex and often confusing non-harmonized country-specific regulations.
• Non-interventional studies can be physically interventional and yet remain non-interventional at a regulatory level (observational studies)
• Regulators have defined a new hybrid: the low-interventional clinical trial that is, in essence, an observational study
• Sponsors should take great care to ensure that they classify their studies correctly, calling upon advice to prevent costly errors
• Non-interventional studies exist in a dynamic regulatory landscape, and further change is inevitable
REFERENCES

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11. Article 2(4) of Regulation EU.536/2014
15. As per Article 2(3) of Directive 2010/84/EU
17. http://www.hunton.com/files/News/777a6378-3b08-418d-a23e-0e2e6b3beab1/Presentation/NewsAttachment/9ae04029-df45-4e47-b031-12ad61b2a33f/Sunshine_in_Europe_for_Pharma.pdf

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