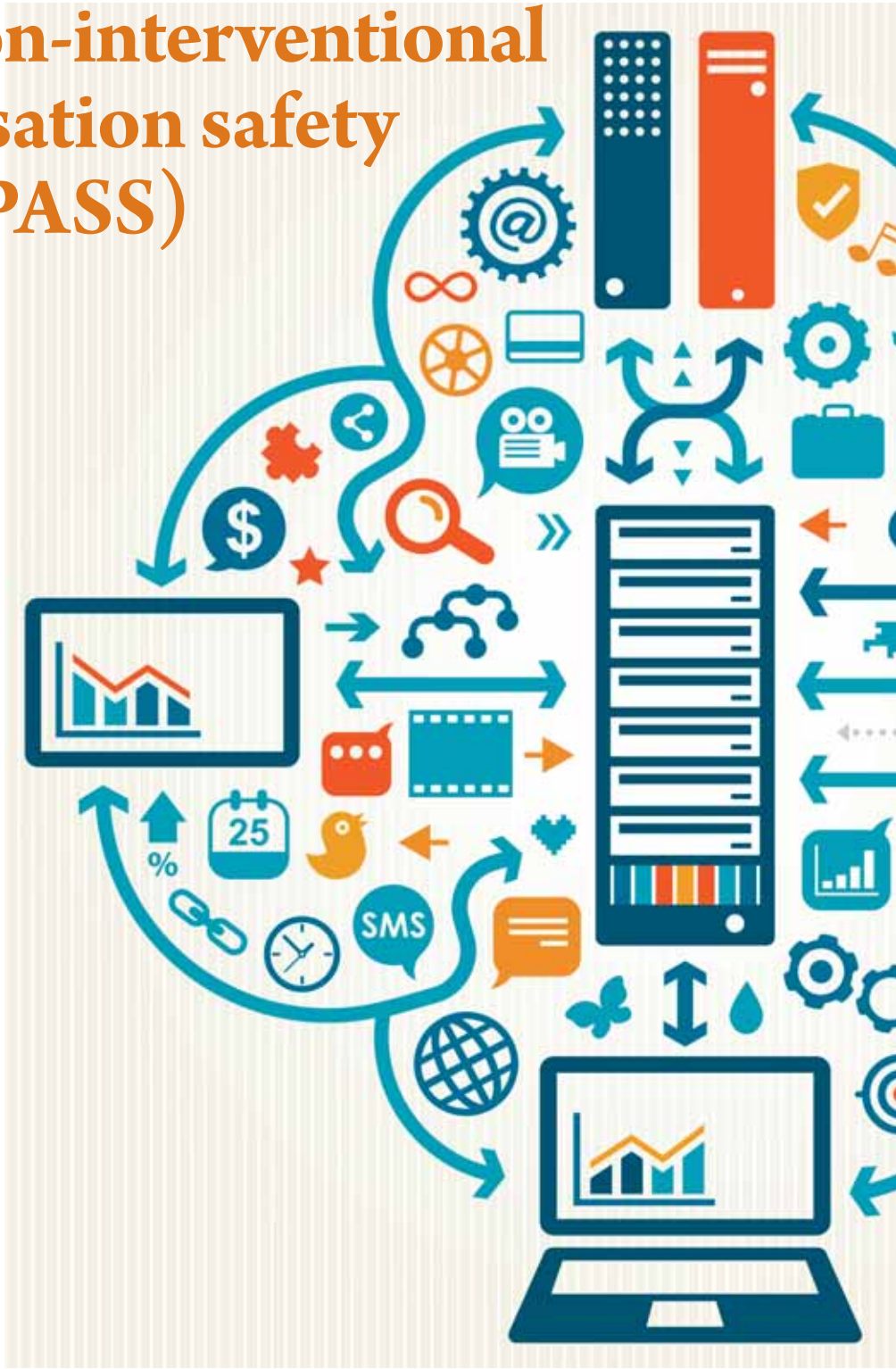
Reporting non-interventional post-authorisation safety studies (NI-PASS)



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Abstract
Post-authorisation safety studies (PASS), whether interventional or, more commonly, non-interventional (NI), can be used by entities such as the European Medicine Agency´s Pharmacovigilance and Risk Assessment Committee to oblige drug companies to collect data on approved products. NI PASS study reports should be drafted according to a particular mandated format, which may not be intuitive for writers more familiar with clinical study reports for interventional trials. This article addresses the structure of NI-PASS reports, comparing and contrasting with the clinical study reports of interventional trials.

This article is an update of "Non-interventional Post-Authorisation Safety Studies (NI-PASS): A different type of report," first published in Medical Writing, Volume 23, 2014 – Issue 4.

Background
Randomised clinical trials are considered to sit atop the hierarchy of clinical evidence and form the basis for most drug approvals. In contrast, non-interventional studies and observational studies are considered a weaker form of evidence and have, until recently, received little attention from regulatory agencies. There is a growing recognition, however, that randomised clinical trials may not adequately reflect clinical practice; for example, multiple concurrent medications and illnesses may affect benefit-risk. Furthermore, the number of patients exposed to a drug or the duration of exposure in a clinical development programme may not be sufficient to detect a rare but important safety signal. The Pharmacovigilance and Risk Assessment Committee (PRAC) was set up within the European Medicines Agency in response to this greater emphasis on pharmacovigilance and real-world data. Specifically, the PRAC´s mandate covers:

> *All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies (PASS)*

and pharmacovigilance audit. (REGULATION [EU] No 1235/ 2010 OF THE EUROPEAN PARLIAMENT)

PASS are therefore an important tool at the disposal of the PRAC for assessing how a medicine behaves outside the confines of clinical trials.[1] According to Directive 2001/83/EC (DIR) Art 1(15),[2] a PASS is defined as "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." In particular, these studies are conducted to quantify potential or identified risks, fill gaps in existing safety data, further define risks (or absence thereof), for example after long-term use, or assess the effectiveness of a risk minimisation activity. As such, they may form part of a Risk Management Plan (RMP).

Although a PASS can in principle be an interventional study (which is conducted and reported in accordance with familiar International Conference on Harmonisation [ICH] guidance), the majority are non-interventional studies. In such studies, treatment is assigned according to clinical practice and administered according to approved labeling. Non-interventional PASS studies can include, for example, literature reviews or retrospective analyses of registry data, but non-interventional observational studies are the most common. Like an interventional study, an NI-PASS is also conducted largely in the general spirit of ICH and Good Clinical Practice, but certain aspects may differ. For example, the final study report for an NI-PASS, if submission to the PRAC is required, should be based on the guidance issued by the European Medicines Agency[3] and will differ in many features from a typical clinical study report (CSR) for interventional trials (hereafter referred to as "ICH-based CSRs"). The following sections discuss various aspects of NI-PASS reports, with reference where appropriate to familiar ICH-based CSRs.

EU PAS Register

Methodological details of all PASS should be posted to the EU PAS Register, which is run by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, see http://www.encepp.eu/). Much has been made about the need to disclose interventional trial protocols and results in the interests of transparency, and this is the analogous requirement for NI-PASS. The study results, once available, should be posted to the website within 2 weeks of submission of the final study report (in turn usually submitted within 1 year of completion of data collection).[3] Some companies post the entire report (with redactions and stripped of the appendices) while others opt for posting the report abstract.

Most pharmaceutical companies now scrupulously post details of interventional trials on sites such as clinicaltrials.gov, but observational studies – particularly the older ones – may have been overlooked. It is worth checking early on in the drafting procedure whether the study has been registered on the ENCePP website and assigned an EU PAS registration number necessary for completion of the final study report.

Structure of NI-PASS reports

A guidance document covering the format and content of the final study report of NI-PASS was issued in 2013.[4] The guidance document suggests that the table of contents of the guidance document itself can be used to build a template for the NI-PASS report (see Figure 1). As noted above, the type of PASS can vary widely, and a single template might not always cover the reporting needs. Often there will be section headings without any content. In these cases, a sensible approach would be to keep the headings of the structure given in the guidance with "not applicable" if appropriate. Extra headings and subheadings can be added if necessary. By analogy with ICH-based CSRs, guidance-mandated sections do not have to be considered as separate numbered sections in the report. Thus, the abstract does not necessarily need to be numbered as Section 1.

Cover page

The format of the cover page is mandated by the guidance and should be fairly self-explanatory. As described above, the EU PAS Register number is required information.

Abstract

Unlike the synopsis of an ICH-based CSR, an NI-PASS report has a structured abstract, in some ways similar to a journal abstract but with more subheadings. The structure of the abstract is defined by the guidance and, in addition to the title and key words, includes rationale and background, research question and objectives, study design, setting, subjects and study size, variables and data sources, results, and discussion. The guidance actually states that the word count (excluding the title and certain other administrative details) should not exceed 500 words. With so many subheadings, and for a

1.	Abstract
2.	List of abbreviations
3.	Investigators
4.	Other responsible parties
5.	Milestones
6.	Rationale and background
7.	Research question and objectives
8.	Amendments and updates
9.	Research methods
	9.1. Study design
	9.2. Setting
	9.3. Subjects
	9.4. Variables
	9.5. Data sources and measurement
	9.6. Bias
	9.7. Study size
	9.8. Data transformation
	9.9. Statistical methods
	9.9.1. Main summary measures
	9.9.2. Main statistical methods
	9.9.3. Missing values
	9.9.4. Sensitivity analyses
	9.9.5. Amendments to the statistical analysis plan
	9.10. Quality control
10.	Results
	10.1. Participants
	10.2. Descriptive data
	10.3. Outcome data
	10.4. Main results
	10.5. Other analyses
	10.6. Adverse events/adverse reactions
11.	Discussion
	11.1. Key results
	11.2. Limitations
	11.3. Interpretation
	11.4. Generalisability

Figure 1. Suggested structure of NI-PASS according to the EMA guidance (4).

study of any complexity, this will be challenging. As far as I am aware, this word count can be exceeded (in the same way that the synopsis of an ICH-based synopsis may if needed exceed 3 pages). Sensible advice here would be to keep as close to 500 words as possible without omitting any important features, results, or conclusions of the study, particularly if the abstract rather than the entire report is to be used when disclosing results.

Administrative sections and methodology

As with an ICH-based CSR, the first part of an NI-PASS report has sections covering administrative aspects (investigators, other responsible parties, milestones) and research methods. In the case of protocols written according to the latest NI-PASS guidance,[5] the methodology sections can be adapted from the corresponding sections in the protocol. The correspondence is not exact; report subsections such as "Bias", "Subjects", and "Sensitivity analyses" do not have an exact counterpart in the protocol, although issues such as bias and the need for sensitivity analyses may be addressed in protocol sections such as "Data analysis" and "Limitations of the research methods". When writing an NI-PASS protocol, it might be helpful to have the guidance for final study reports in hand as this may facilitate subsequent drafting of the NI-PASS report. If the NI-PASS study was initiated prior to 2012 (when the PRAC became operational), then it is unlikely that the study was conducted with a protocol drafted according to the latest guidance or has been submitted to PRAC. The study protocol may therefore not follow the mandated protocol format and the methods section will require more thought and work to map out content. The writer will have to refer to the guidance text to ensure that the content is appropriate, especially as some section headings are not intuitive for someone used to writing ICH-based CSRs.

For an ICH-based CSR, it is generally considered good practice to extensively cross-reference the protocol. In the case of an NI-PASS report, however, the protocol may not necessarily be appended to the CSR, although details of the methods should of course be available on the register website. To enhance readability, the methods section of an NI-PASS report should perhaps be more stand-alone than an ICH-based CSR counterpart.

The report structure also includes a section titled "Amendments and updates", which unlike the equivalent section in an ICH-based CSR, refers only to amendments to the protocol. Changes to the statistical analysis are presented as part of the results.

Results

The structure of the report as presented in the guidance has six sections. The "Participants" section is self-explanatory. The next section "Descriptive data", according to the guidance text, refers largely to patient characteristics. As NI-PASS are by definition non-randomised studies, it is important to have a good understanding of the baseline characteristics of different patient groups in order to assess potential biases when making group comparisons. The "Outcome data" section should include, according to the single line of guidance text for this section, the "numbers of subjects across categories of main outcomes". This section is likely intended to reflect that there are often considerable amounts of missing data in observational studies. As there are other sections where outcome results can be included (for example, "Main results" and "Other analyses") one interpretation is that this subsection could be considered as roughly equivalent of the Section "Analysis populations" in an ICH-based CSR.

The last subsection of the Results section is "Adverse events/adverse reactions". Detailed guidance is given for this particular subsection, which will likely closely resemble the adverse event–reporting section of an ICH-based CSR. If applicable, a clear, well-structured subsection here will enable ready incorporation of data into other documents such as a Periodic Benefit Risk Evaluation Report.

Discussion

For many ICH-based CSRs, the standard advice is to keep the discussion section brief and fairly non-committal, the argument being that higher-level documents such as the clinical overview are more appropriate places to relate the study findings to the rest of the clinical development programme and the literature. The template for an NI-PASS, however, with four separate subsections (key results, limitations, interpretation, and generalisability), invites an involved discussion.

This part of the final study report will also be

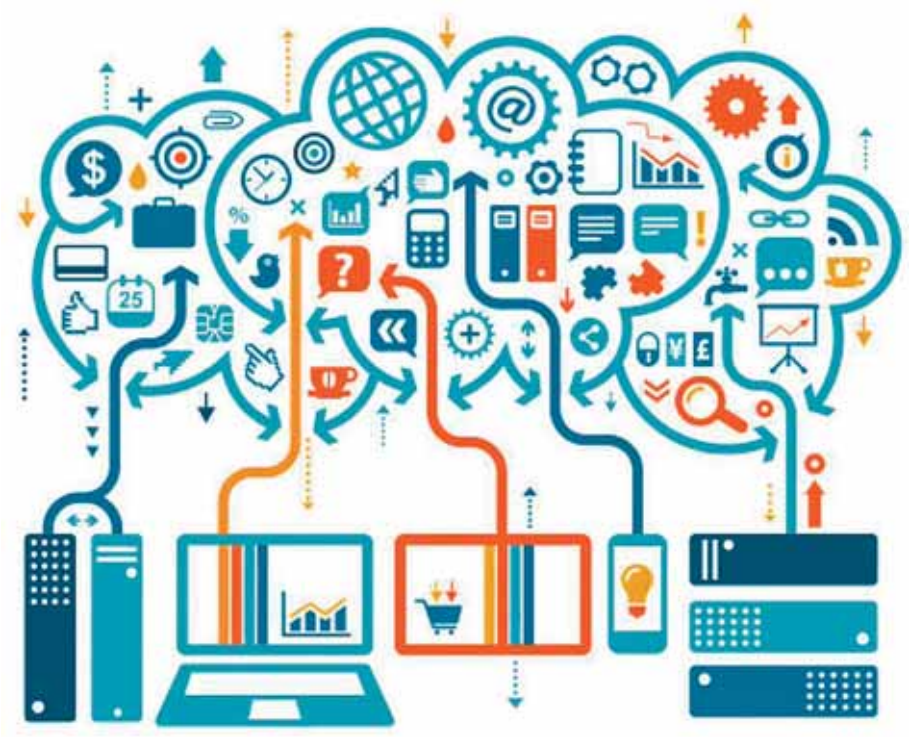
easier to write if the protocol has been written in the NI-PASS template. For example, the "Limitations" subsection can largely be based on the "Limitations of the research methods" in the protocol, enhanced with post-hoc knowledge and understanding gleaned from the results. Most observational studies will be subject to similar limitations (bias, for example) and similar strengths as well (greater applicability to clinical practice, a point that is specifically addressed in the "Generalisability" subsection).

Appendices and annexes

The template has the option of including appendices. These would likely include certain key study documentation such as the protocol and selected summary tables not included in the report body. No details are given as to how to structure this information, so it is probably reasonable to follow the approach used by the company for ICH-based CSRs. Annex 1 (mandatory) is a list of documents available on request (for example, listings) while Annex 2 is for any additional information.

NI-PASS: Past, present, and future

When I first wrote about NI-PASS reports in 2014, these types of report were relatively new, and my advice then was check the EMA website occasionally for updated guidance. For this update, I took my own advice but could not find anything new of significance for actual report drafting (although detailed procedural guidance is now available). However, given that some companies include the full (but appropriately redacted) report on the ENCePP website, an increasing number of examples are becoming available. Unfortunately, the search functionality of the ENCePP website does not allow filtering of results by availability of a final report, so you will need to look one by one. Nevertheless, with patience, it should be possible to retrieve some relevant examples of the approach of other writers and their interpretation of the guidelines.



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A chemist by training, but starved of career opportunities in Spain, **Greg Morley** made the switch first to translation and editing and then to medical writing. He now has more than 15 years of experience as a medical writer. He is currently working as an embedded contractor with a major pharmaceutical company.