Non-interventional Post-Authorisation Safety Studies (NI-PASS): A different type of report

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Abstract

Although Post-Authorisation Safety Studies (PASS) have been around since 2001, most regulatory writers would have been unaware of their existence until the recent changes in European regulations, which include mention of these studies as part of general strengthening of pharmacovigilance procedures. Interventional PASS will largely adhere to International Conference on Harmonisation requirements, but non-interventional (NI) PASS should be reported according to a particular mandated format, which may appear strange to writers used to drafting clinical study reports for interventional trials. Given their novelty, there is no consensus as to how these reports should be drafted. This article addresses the structure of NI-PASS reports and provides an interpretation, albeit preliminary, of the corresponding European Medicines Agency guidance text.

Keywords: Post-authorisation safety studies (PASS), Non-interventional (NI), Pharmacovigilance Risk Assessment Committee (PRAC), Risk Management Plan

Background

A clinical development programme, however exhaustive, will always be subject to certain limitations. For example, the number of patients exposed may be insufficient to detect small but significant safety signals. In addition, the controlled setting of clinical trials may not adequately reflect clinical practice in that real-life patients may, for example, be multi-medicated or have more concurrent illnesses. In this context, the regulations in the European Union have recently been changed to enable more proactive assessments of approved drugs (see Sarah Richardson's article on p. 267 for a good overview of these changes). Notably, a body dedicated to post-authorisation assessment known as the Pharmacovigilance and Risk Assessment Committee (PRAC) has been set up.

Post-Authorisation Safety Studies (PASS) are one of the tools available to PRAC for monitoring approved drugs.[1] However, the concept of a PASS predates the PRAC by more than a decade. 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).

PASS can be divided into interventional and non-interventional studies. Interventional PASS will, by and large, be conducted and reported in accordance with familiar International Conference on Harmonisation (ICH) guidance and are not discussed further here. In non-interventional observational studies, treatment is assigned by decisions guided entirely by clinical practice and administered according to approved labelling, with no additional protocol-mandated procedures or tests. Non-interventional (NI) PASS studies can include, for example, literature reviews or retrospective analysis of registry data, in addition to observational studies, and cohort studies. The rest of this article will focus on non-interventional observational studies, as these are the ones that regulatory writers will most likely encounter. A NI PASS should, like an interventional

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study, also be conducted largely in the general spirit of ICH and Good Clinical Practice, but certain aspects may differ. In particular, a final study report for an NI-PASS (note the guidance refers to 'final study report' rather than clinical study report [CSR]) should be based on the guidance issued by the European Medicines Agency[3] and differs in many features from a typical 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 registry

Methodological details of all PASS studies should be posted to the EU PAS registry, 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, and this analogous requirement for NI-PASS is presumably a further effort to increase transparency and strengthen pharmacovigilance procedures. The study results should also be posted to the website within 2 weeks of submission of the final study report (usually submitted within 1 year of completion of data collection). Some companies post the entire report (with redactions and stripped of the appendices) while others opt for posting the report abstract.

Guidance for posting to this registry is available.[3] Nowadays, most pharmaceutical companies have groups dedicated to posting details of interventional trials on sites such as clinicaltrials.gov. Observational studies, however, may have slipped under the radar and when drafting a report it is worth checking early on that the study has been registered on the ENCePP website and hence has an EU PAS registration number. Note that a final study report for an NI-PASS cannot be completed without this registration number.

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 Table 1). If this table of contents is not used directly, it would still seem advisable to stick as closely as possible to the structure provided by the guidance. A sensible approach might be to keep the headings of the structure given in the guidance with 'not applicable' if appropriate, and add extra headings and subheadings if necessary. By analogy with ICH-based CSRs, sections covered by the guidance 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.

Table 1: Suggested structure of NI-PASS according to the EMA guidance[4]

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

Cover page and EU PAS registry

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

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 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 should not exceed 3 pages, but is subject to some flexibility). 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 is to be used for disclosure of the 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 sensitivity analysis may be addressed in protocol sections such as 'Data analysis' and 'Limitations of the research methods'. With a view to facilitating drafting of the NI-PASS report further down the line, it might be helpful to have the guidance for final study reports to hand as well as the protocol guidance when writing an NI-PASS protocol.

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 (or it might be redacted during disclosure). In general, the methods section of an NI-PASS report should perhaps be more stand-alone than an ICH-based CSR counterpart. 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 and it will not have been submitted PRAC. In some cases, studies intended largely as marketing exercises may have subsequently been designated as an NI-PASS. The original protocol of these studies may therefore not resemble the mandated protocol format and the methods section will require more thought and work. The writer will have to refer to the guidance text to ensure that the content is appropriate, especially as some sections will be unfamiliar to someone used to writing ICH-based CSRs.

The report structure also includes a section entitled '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 brief guidance text for this section, the 'numbers of subjects across categories of main outcomes'. In some of the few examples of NI-PASS reports available, these have been interpreted as referring to outcomes such as pregnancies. However, when the guidance text says 'numbers of subjects' this perhaps suggests that patient results *per se* should not be included here (contrary to what the heading implies). Moreover, there are other sections where outcome results can be included (e.g., 'Main results' and 'Other analyses'). So another interpretation would be that this subsection could be used as the 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. A clear, well-structured subsection here will, for example, enable ready incorporation of data into a Periodic Safety Update Report. This section will likely closely resemble the adverse-event-reporting section of an ICH-based CSR.

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. However, an NI-PASS report does not form part of a clinical development programme and so may be more likely to be read in isolation. Moreover, in the case of NI-PASS reports, the discussion section is structured into four subsections (key results, limitations, interpretation, and generalisability). It is thus more difficult to avoid involved discussion.

As with the results section, this part of the final study report will 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, embellished with *post hoc* knowledge and understanding gleaned from the results. Most observational studies will be subject to similar limitations (e.g., bias) 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 (e.g., listings) while Annex 2 is for any additional information.

NI-PASS: past, present, and future

When the PRAC was established, NI-PASS were plucked from relative obscurity and given a much more prominent role. At present, the reporting of these studies according to the mandated format is still a relatively new undertaking for many companies. The guidance is also evolving, so it is advisable to check the EMA website occasionally (Home>Human regulatory>Pharmacovigilance>Post-authorisation safety studies at http://www.ema.europea.eu) for new developments. With time, a consensus will likely emerge as to how to approach NI-PASS reports, although the wide range of possible study types may slow this process down. I emphasise that my interpretation for the particular case of observational studies here is just that, an early take on how to best follow the guidance when reporting an NI-PASS. For the most part, common sense, along with drawing on analogies from ICH-based CSRs, should be sufficient to produce a report that is fit for purpose.

Author information

Greg Morley A chemist by training, but starved of career opportunities in Spain, Greg Morley made the switch first to translation and editing, and then 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.

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