CAPSULAS
Boletín de información jurídica

Special Edition | Faus & Moliner Abogados | February 2021

New rules for conducting observational studies with medicines in Spain: less complexity and more transparency

Royal Decree 957/2020, of 3 November, which regulates observational studies with medicines for human use

On 2 January 2021, Royal Decree 957/2020 (RD 957/2020) entered into force and replaced the Ministerial Order SAS/3470/2009 which had governed observational studies (OS) in Spain until then. After more than a decade with the 2009 Ministerial Order, it became clear that such Order was too complex, involved too much bureaucracy and needed and update considering the new EU and national rules in the field.

Concept of "observational study"

According to RD 957/2020 an OS is (i) an investigation with medicines, (ii) that implies gathering individual health data from patients, (iii) that does not qualify as a clinical trial, and (iv) that has at least one of the following purposes: to determine the beneficial effects of medicines (including patients perspective) and the resources necessary to achieve them or to identify adverse reactions and other risks to the security of patients and to measure the effectiveness of risk control measures, or to obtain information about patterns of medicines use.

Regulatory requirements

Under Order SAS/3470/2009, before carrying out an OS, sponsors had to obtain the prior classification (and sometimes prior green light) of the AEMPS. RD 957/2020 eliminates these requirements. However, RD 957/2020 does maintain the obligation for OS to get the favorable opinion of an Ethics Committee (CEIm) which evaluates the protocol and the methodological, ethical and legal aspects of the OS. Upon submission of the protocol by the sponsor (which may be in English provided that a summary in Spanish is also provided), the CEIm has 40 calendar days to issue an opinion; which is unique, binding, and valid for the whole Spanish territory.

Prospective OS may be subject to further requirements imposed by the Health Authorities of the Autonomous Regions.

As per the informed consent of patients, RD 957/2020 states that if an OS includes interviews with patients, their informed consent is required unless the CEIm approves a waiver. The CEIm may approve such waiver if: (i) the OS would not be feasible or practicable to carry out without such waiver, (ii) the OS has important social value; or (iii) the research poses no more than minimal risks to participants.

Personal data

If the OS involves the processing of personal data, then the provisions of the General Data Protection Regulation (GDPR) and the Spanish Organic Law 3/2018 shall apply. As per such regulations, the explicit consent of the patient must be obtained for the processing of its personal data unless such processing can rely on an alternative legal basis (e.g. "public interest" ex art. 6(1)(e) GDPR, a legal ground broadly used in the context of the Covid-19 pandemic).

Further, RD 957/2020 also contemplates (i) that the sponsor must evaluate the risk inherent in the processing of personal data derived from the OS and implement measures to mitigate those risks; and (ii) that the protocol must laid down the terms of the processing of patients' personal data, including, if applicable, the terms of envisaged transfers of such data outside the European Economic Area and the proceeding followed to apply pseudonymization / anonymization to such data.

Transparency & results

RD 957/2020 enhances transparency requirements regarding funding sources of OS, payments made by sponsors and results of the studies.

Funding sources must be included in the documentation to be submitted to the CEIm as well as in the contract to be executed with the center where the study will be carried out.

As per the payments made by the sponsors, RD 957/2020 requires, on the one hand, the remuneration of the research team to be in accordance with the time invested and the expenses incurred and, on the other hand, patients' compensations to be in a form and quantity that does not influence their decision to participate in the OS.

Regarding the results, RD 957/2020 obliges sponsors of prospective OS to, upon finalization of the study, provide the AEMPS with the results (whether positive or negative) for publication in the Spanish Registry of Clinical Studies. For not prospective OS, this communication is not compulsory but highly recommended. Further, sponsors of any type of OS must always notify the OS' results to the AEMPS if such results may entail a modification of the risk-benefit balance of the medicine under study.

Patient support programs

"Patient support program" (PSP) is a term used to refer to a wide variety of programmes and with no unique definition. In Spain, prior to RD 957/2020, the term had no legal basis at all; and, apart from some references in regional guidelines on advertising of medicines, only the EU Guideline on good pharmacovigilance practices (GVP) defined it. As per such GVP, a PSP is "an organised system where a marketing authorization holder receives and collects information relating to the use of its medicinal products". Be that as it may, the truth is that PSPs are widely run and sponsored by marketing authorization holders, and that this has sometimes been a matter of concern by the authorities because of the risk of such PSPs being used as an undue promotional tool.

RD 957/2020 aims to tackle this problem. For this, it starts by laying down a general rule: it is forbidden to run or sponsor OS with the objective to promote medicines. Then, it adds that PSPs (understood as "organized systems by virtue of which marketing authorization holders receive and gather data from patients related to the use of its medicines") under which information is gathered through "planned contacts with patients" can only be carried out in Spain under a protocol that contemplates any of the purposes identified in the definition of OS (see above Concept of OS, ap. IV).

The interpretation of this rule is somehow tricky: what exactly sponsors of such type of PSP has to do? Is it enough for them to merely adjust the protocol of the study to include one

of the mentioned purposes? Or they have to, on top of that, seek the prior approval of a CEIm as any other OS? A systematic read of RD 957/2020 does not offer a clear answer. However, the AEMPS published a Q&A (20 January 2021) which seems to choose the latter (PSP to be approved by the CEIm). To have a definitive answer on this matter, we will have to wait and see how this rule is applied in practice and how the Courts interpret it. For the time being, we would only like to note that Q&As aim to clarify the interpretation of rules, they should not (and, indeed, they cannot) alter the rule they are clarifying or create new obligations.

Monitoring of studies

The protocol of an OS submitted to the CEIm may be altered during the execution of the study. In this respect, RD 957/2020 contemplates that while for substantial amendments of the protocol the approval of the CEIm is needed, for not substantial ones it is not (although such amendments must be recorded in the master file of the study).

As per the management of suspected adverse reactions, RD 957/2020 imposes reporting obligations to both healthcare professionals and sponsors. With respect the sponsors, RD 957/2020 provides that sponsors that, in turn, are the marketing authorization holders of the medicine under study must report suspected adverse reactions to *Eudravigilance* in accordance with the GVP. Other sponsors must report before the Spanish System of Pharmacovigilance (accessible through the AEMPS's website).

Implementing provisions

Implementing provisions of RD 957/2020 will have to be approved and published by both the Ministry of Health and the AEMPS. We expect CEIMs across Spain and healthcare regional authorities to approve their guidelines as well. For the time being, only the AEMPS has approved and published a Q&A.