Requests for post-registration studies (PRS), patients follow-up in actual practice: Changes in the role of databases

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Summary Early market access of health products is associated with a larger number of requests for information by the health authorities. Compared with these expectations, the growing expansion of health databases represents an opportunity for responding to questions raised by the authorities. The computerised nature of the health system provides numerous sources of data, and first and foremost medical/administrative databases such as the French National Inter-Scheme Health Insurance Information System (SNII/RAM) database. These databases, although developed for other purposes, have already been used for many years with regard to post-registration studies (PRS). The use thereof will continue to increase with the recent creation of the French National Health Data System (SNDS [2016 health system reform law]). At the same time, other databases are available in France, offering an illustration of “product use under actual practice conditions” by patients and health professionals (cohorts, specific registries, data warehouses, etc.). Based on a preliminary analysis of requests for PRS, approximately two-thirds appeared to have found at least a partial response in existing databases. Using these databases has a number of disadvantages, but also numerous advantages, which are listed. In order to facilitate access and optimise their use, it seemed important to draw up recommendations aiming to facilitate these developments and guarantee the conditions for their technical validity. The recommendations drawn up notably include the need for measures aiming to promote the visibility of research conducted on databases in the field of PRS. Moreover, it seemed worthwhile to promote the interoperability of health data warehouses, to make it possible to match information originating from field studies with information originating from databases, and to develop and share algorithms aiming to identify criteria of interest (proxies). Methodological documents, such as the French National Authority for Health (HAS) recommendations on “Les études post-inscription sur les technologies de santé (médicaments, dispositifs médicaux et actes). Principes et méthodes” [Post-registration studies on health technologies (medicinal products, medical devices and procedures). Principles and methods] should be updated to incorporate these developments.

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Abbreviations
ASA/IEB improvement in expected benefit
CEPS French Economic Committee for Healthcare Products (Comité économique des produits de santé)
CNEDimTS French National Medical Device and Health Technologies Evaluation Committee (Commission nationale d’évaluation des dispositifs médicaux et des technologies de santé)
CNIL French Data Protection Authority (Commission nationale de l’informatique et des libertés)
CPRD clinical practice research datalink
EGB French database on a sample of the French National Health Data System SNDS (échantillon généraliste des bénéficiaires)
EMA European Medicines Agency

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Introduction

The provision of medicinal products and medical devices leads to requests for additional data by the health authorities, notably under actual conditions of use once on the market. This requirement is even more important when these products are made available early, particularly in the context of rapid access to innovation, and involves additional knowledge as soon as these products are used in standard medical practice. Although these medicinal products and medical devices have previously undergone evaluation processes to establish their potential safety and efficacy profile in specific clinical indications, residual uncertainty related to the benefits and risks observed beyond clinical trials may necessitate additional data under actual conditions of use [1,2]. This requirement is increased when the marketing authorisation process is accelerated for certain health products [3,4].

In this context, the competent authorities may request the collection of data when new health products (medicinal products, medical devices) are made available to prescribers and patients [5] so as to respond to questions relating to efficacy under actual conditions of use (effectiveness), safety in use, relative medical value, impact on public health or even on the practical methods of use.

In France, reimbursement by the national health insurance scheme and the determination of the price of health products by the French Economic Committee for Healthcare Products (CEPS) first require evaluation of clinical or, indeed, health-economic data by the French National Authority for Health (HAS).

The clinical data are submitted to the Transparency Committee (TC) for medicinal products and to the National Medical Device and Health Technologies Evaluation Committee (CNEDiMTS) for medical devices. Under certain conditions stipulated by the regulations, health-economic data are submitted to HAS Commission for Economic Evaluation and Public Health (CEESP). Lastly, CEPS, a committee under the auspices of the Ministry for Health, Social Security and the Economy, like the above three HAS committees, may request additional data relating to the actual conditions of use of the health products. These data may be collected in the context of studies classified as post-registration studies (PRS) described as such due to being conducted after these health products have been included on the list of reimbursed products. At present, these studies mainly consist of systematic data collection from prescribers and patients (PRS known as ad hoc or field studies).

The increasingly computerised nature of healthcare activities is accompanied by the extensive development of databases containing information on the prescribing and use of medicinal products and medical devices. With the management instruments which have long been used by the national health insurance scheme for reimbursement of health expenses, new opportunities are emerging with regard to making data available: medical records in electronic format, electronic prescriptions and dispensing, hospital data warehouses ¹, etc. Although developed for purposes other than for conducting post-registration studies, these instruments contain useful information for responding to the questions raised by the health authorities.

Objective

The primary objective of the research conducted by the round table "Requests for post-registration studies, patients follow-up in actual practice and databases: reconciliation based on new methodologies" during the 2017 Ateliers de Giens was to evaluate the potential for replacing field post-registration studies by database PRS. For this purpose, and prior to discussion in the Atelier setting, an assessment was carried out on the implementation method used for the PRS conducted to date and on the ability of these medical/administrative databases to respond to this request.

¹ A hospital data warehouse consists of a collection data in various formats bringing together administrative and medical information collected during appointments and hospital stays for patients treated in a hospital setting. It is used, in particular, for carrying out non-interventional research on data, clinical trial feasibility studies or studies on the management of hospital activities (as per https://recherche.aphp.fr/eds/definition/ accessed on 30 October 2017).
Method

Medicinal products

Twenty opinions issued by the Transparency Committee, dating from 2011 to 2016 (published on HAS website) and containing a request for a PRS, were randomly selected. The following information was extracted from these opinions with a view to conducting a descriptive analysis:

- name of the medicinal product and clinical indications concerned;
- date of HAS opinion requesting the PRS;
- text of the PRS request;
- primary objective of the PRS if identifiable;
- all post-registration data expected, with the following clarifications:
  - list of expected data available in the existing databases;
  - existing databases containing at least part of the expected data, currently accessible;
  - existing databases which could contain at least part of the expected data, currently inaccessible;
- studies proposed, planned or conducted in response to the request by HAS (if known, with an extended search particularly on clinicaltrials.gov, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) EU PAS Register® and databases of publications for completed and published PRS);
- type(s) of studies proposed or planned: field or database studies;
- PRS results, if available.

For medicinal products, the results were supplemented by a systematic search for new opinions (updates) issued by the Transparency Committee on HAS website. As the first opinions examined dated from 2011, it seemed necessary to identify new opinions [renewals, updates for the same medicinal product in the same indication(s)] available as of closure of the research (September 2017) in order to complete the analysis.

Medical devices

The round table benefited from the research conducted by the Syndicat national de l’industrie des technologies médicales [National Medical Technologies Union (SNITEM)] based on the 408 opinions issued by the CNEDiMTS since 2014. The data collected and used comprised the following information:

- name of the medical device;
- identity of the pharmaceutical company or manufacturer;
- date of the opinion issued by the CNEDiMTS;
- improvement in expected benefit (ASA/IEB) obtained;
- request for PRS or not;
- type of PRS request;
- if the request was issued by the CNEDiMTS:
  - the possibility as to whether or not the requested PRS could be performed fully or partly using databases (incorporated in the SNDS),
  - the exhaustive or non-exhaustive nature of the expected PRS. The following were considered to be "exhaustive": studies mentioning the terms or phrases "registry", "all patients undergoing implantation", "exhaustive" or "all treated patients". In other cases, the request was qualified as "non-exhaustive".

Results

Medicinal products

When a primary objective of the PRS can be identified in the request issued by the Transparency Committee, it first and foremost aims to confirm the efficacy and safety-in-use data on the medicinal product in an actual practice context, followed by data on the use of the medicinal product and, thirdly, a description of the treated population (Table 1).

When all objectives are taken into account (primary and secondary objectives), this type of evaluation endpoint is confirmed (Fig. 1) with the appearance of criteria to measure quality of life (8%) and impact on healthcare consumption (use of other preventive, diagnostic or therapeutic methods).

After evaluation of the 12 opinions in which a primary objective for the PRS can be identified, it appeared that the information in existing databases (including the SNDS) would have enabled a full response to the request for studies in nearly a third of cases, and a partial response in another third of cases (Fig. 2). Certain databases mentioned as potential information sources (e.g. data warehouses, registries) are nonetheless not currently fully functional or always accessible.

Out of the 20 opinions initially evaluated, 7 (35%) were the subject of a subsequent opinion available on HAS website, and mentioning the studies conducted further to the initial requests for PRS (see Section Method). Investigations beyond HAS website (including the EU PAS Register®) enabled 12 studies in total related to these opinions to be identified. Studies for which partial results were obtained mainly correspond to database studies: 5 database studies and 2 field studies. Only one of the studies identified appeared to fulfill all of the objectives of the expected PRS, according to the initial opinion issued by the Transparency Committee.

Medical devices

Out of the 408 opinions issued by the CNEDiMTS selected, 157 mention a request for a PRS in the conditions for renewal (38%). It should be noted that HAS activity report only lists 20 new requests in 2015 and 8 in 2014. This is explained by the fact that, according to our methodology, we evaluated all of the opinions without making any distinction as to whether they concerned a change in the range or a

Table 1  Distribution of primary objectives.

| Efficacy and safety in an actual practice context | 3 |
| Efficacy in an actual practice context | 2 |
| Efficacy in an actual practice and long-term context | 1 |
| Safety in an actual practice context | 1 |
| Evaluation of use | 2 |
| Conditions for prescription or use | 1 |
| Description of patients and their risk factors | 2 |
Requests for post-registration studies (PRS), patients follow-up in actual practice

Figure 1. Distribution of all measurement criteria shown in the post-registration studies (PRS) requests.

Figure 2. Availability of expected data in existing databases for medicinal products. CépicDC: Epidemiology centre on the medical causes of death (Centre d’épidémiologie sur les causes médicales du décès); PMSI: French National Computerized Medical Information System (programme de médicalisation des systèmes d’information); SNDS: French National Health Data System (Système national des données de santé); SNIIRAM: French National Inter-Scheme Health Insurance Information System (Système national d’information inter-régimes de l’Assurance maladie).

product in a category having already been the subject of a PRS request.

According to this methodology, 41% of requests asked for exhaustive data collection (i.e. notably in “all patients having undergone implantation” or in “all treated patients”, see Section Method).

In the majority of cases examined (61%), the PRS was able to be carried out, at least partly, using a medical/administrative database (Fig. 3).

The requests for data described as not being able to be extracted from medical/administrative databases include the measurement of quality of life or certain clinical information (e.g. number of falls, measurement of intraocular pressure).

In the 39% (62/157) of cases unable to be supported by information recorded in medical/administrative databases, the solution was notably supported by the use of registries set in place further to the PRS request. In contrast to the preexisting registries used for medicinal products, the registries relating to the use of medical devices are usually created at the request of the health authorities, at the time of or after market access, further to a favourable opinion for reimbursement by the French national health insurance scheme.

Figure 3. Post-registration studies able to be conducted using a medical/administrative database for medical devices.
In the 61% (70+25=95/157) of remaining cases, the detailed analysis is able to distinguish between the results according to whether the request for information collection is exhaustive or non-exhaustive in nature (Fig. 4). Irrespective of the degree of the exhaustive or non-exhaustive nature of the request (see Section Method), the use of medical/administrative databases alone seemed to provide a response in 16% of cases (25/157). When exhaustive collection of data on use was requested, medical/administrative data would have been sufficient to respond to the PRS request in 22% of cases (14/65).

This analysis of opinions issued by HAS on medicinal products and medical devices, conducted according to slightly different but nonetheless comparable methodologies, enabled the working group to draw up a situational analysis concerning the PRS requests.

Firstly, a key difference was observed in the way in which PRS requests are worded between the TC and the CNEDiMTS, the former having made an effort to define the objectives having led to more explicit requests for the firms.

It was then noted that, for both committees, approximately two-thirds of PRS could have obtained a full or partial response by using database studies.

The methods for critical analysis, recommendations and validation of the protocols for the PRS differ between the two committees. As regards medical devices, tripartite discussions relating to these PRS, between CEPS, HAS and the firm, take place before the finalised PRS request, hence possibly amended after these multi-party discussions, is incorporated into the agreement signed between CEPS and the firm. This procedure for early and systematic exchanges between HAS, CEPS and firms is usually considered as progress in the PRS process for medical devices. As regards medicinal products, the drafting of the protocol is the subject of two exchanges at the most between the firm and HAS, before validation. If arbitration is necessary, a hearing may take place in the monitoring committee for studies in actual practice [6] bringing together CEPS and HAS. However, this committee does not have a scientific vocation.

**Discussion**

Approximately 10% of medicinal products and a third of medical devices subjected to evaluation procedures by the French National Authority for Health (HAS) and price fixing by the French Economic Committee for Healthcare Products (CEPS) access the market further to an opinion issued by these authorities, accompanied by a request for additional data. As regards medical devices, an exhaustive study on the population of interest is requested in 41% of cases, specifically focusing on restricted populations requiring the creation of specific monitoring registries.

HAS recently conducted an assessment of PRS (concerning 172 PRS requests for medicinal products between 2006 and 2015), showing that 51% of the studies conducted are made up of prospective, non-comparative and descriptive cohorts ("field or ad hoc" PRS). The time frames for obtaining results were six years on average, longer for field studies compared to those conducted using databases, since the latter are predominantly based on the use of data derived from the French National Inter-Scheme Health Insurance Information System (SNIIRAM) database [7–9].

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2 For medical devices, requests for studies often cover several devices (in the same category or same range).
In this context, it seemed relevant, during the 2017 Ateliers de Giens, to examine the conditions that could favour the use of existing and future databases, so as to fulfill the need for additional data, notably expressed by HAS and its competent committees, and by CEPS for certain dossiers submitted to it. Furthermore, these studies are sometimes related to questions raised previously during the MA application (for medicinal products) and may be combined with special provisions for monitoring the products concerned included in their risk management plan (RMP).

Database studies have various advantages compared to field studies (Table 2), generally including a shorter implementation time, but also less stringent regulatory obligations (outside the scope of human research defined by French Law No. 2012-300 of 5 March 2012, known as the Jardé law).

Beyond the technical advantages of the database studies relative to the field studies, the recent developments in the creation of medical and medical/administrative databases and the rules for access and use of these databases constitute substantial progress offering new solutions in terms of responding to PRS requests.

One of the main examples resides in the application of Article 193 of the health system reform law of 26 January 2016, having led, in particular, to the creation of the French National Health Data Institute (INDS) and French National Health Data System (SNDS) [10].

Provided that certain conditions are met, access to SNDS health data is thus facilitated, offering various advantages such as the possibility of establishing links between data originating from different information sources, including both hospital data and outpatient healthcare data (Fig. 5). The possibility of having access to medical follow-up data will shortly be facilitated by the possibility of matching data by using the registration number in the national identification index (NIR) as the national health identifier (by a technical third party), which will link individual information collected in the SNDS to data originating from field studies (decree pending publication).

At the same time, the development of a specific reference methodology applicable to this type of study will facilitate the regulatory formalities relating to the protection of personal and medical data having undergone processing. A new reference methodology (RM-00x) is currently in discussion [11], in the same way as those already applicable to data managed in the context of human research. This new reference methodology would make it possible to obtain a compliance commitment declaration instead of a French Data Protection Authority (CNIL) authorisation procedure for each study. This would have noteworthy advantages by reducing the implementation time frame for these studies, and consequently making the results available more quickly. At the same time, easier access to the French database on a sample of the French National Health Data System (EGB) database, a 1/97th sample taken from the SNIRAM database, will also represent a major advantage.

Beyond the structuring of the SNDS, the computerisation of healthcare activities is accompanied by the development of new data sources and, in particular, the emergence of hospital data warehouses. These warehouses (premises) compile numerous hospital information system (SIH) sources, making it possible to avoid slowing database operation in production. Their optimised architecture and data processing before loading allow rapid querying which would often be impossible on all source data as a whole. They may be combined with instruments enabling de-identification of data, access traceability and automatic processing of text data notably to extract the concepts of interest. Hence, these data warehouses contain infinitely more clinical data than the SNDS and thus enable access to highly detailed medical information (including laboratory test data), inaccessible in the medical/administrative databases. They, however, have the disadvantage of having the same structuring level as the source databases, and having very variable formats, potentially very different for a given item of information if appropriate data processing is not performed. Furthermore, considerable heterogeneity may exist between different establishments. Hence, in addition to the difficulty in constructing these data warehouses (Fig. 6), particular care should be given to drawing up harmonisation rules to promote data pooling between establishments and warehouses, particularly by semantically describing each data item inserted into the warehouse.

Furthermore, certain healthcare establishment networks have united their efforts to share their data for various purposes. From this perspective, the Health-Economic Epidemiological Strategy (ESME) programme initiative [12,13] developed by UNICANCER (French centers against cancer) aims to create an oncology database with a view to conducting studies in actual practice to have a better understanding of the use of the different medicinal products and the determining factors for the therapeutic strategies in standard medical practice (Fig. 7).

Beyond the healthcare establishments, the future aggregation of data originating from software programs used in outpatient practice (electronic medical records, prescribing software, etc.) may contribute to these efforts to obtain a better understanding of the impact of health actions and, in particular, of medicinal products and medical devices in an "actual practice" context, compared with the results of clinical trials, which are essential but for which the external validity (extrapolation) has a number of limitations relative to data collected during the use of products on the scale of the entire population concerned and in a standard treatment context.

All of these electronic data are only of interest if they meet quality criteria essential to their intended use, and if the PRS are conducted in compliance with the applicable good practice guidelines [14–16]. Hence, it is essential to ensure that the required data for all patients concerned by a post-registration study are available, along with other metrological quality criteria, such as the accuracy of the measurement performed, together with its reliability over time. In certain cases, the simultaneous implementation of a field study and database study (combined studies) will make it possible to ensure the validity of the information extracted from the database. Future matching of field data with database data (hybrid studies) for a given individual will make it possible to further adjust the precision of the expected results. This is where the importance of using the NIR comes into play, its conditions of use now being governed by Article 193 of the health system reform law.

Hence, regardless of the PRS envisaged, verification of the following points in the early stages could avoid
Table 2 A few examples of the advantages and limitations of the two major categories of post-registration studies (PRS) implemented.

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<tr>
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<th>Advantages</th>
<th>Limitations</th>
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<tr>
<td><strong>Field studies</strong></td>
<td>Primary data: greater choice of variables and if needed specific requirement (e.g., quality of life)</td>
<td>Duration</td>
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<td></td>
<td>Direct measurement of criteria of interest</td>
<td>Implementation constraints (screening and enrolment of participants)</td>
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<td></td>
<td>Data contemporary with the launch of the product onto the market</td>
<td>High cost</td>
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<td>Implementation time frame</td>
<td>Mostly non-exhaustive</td>
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<td></td>
<td>Rapid accessibility to data of interest</td>
<td>Collected data defined prior to and independently of the PRS</td>
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<td></td>
<td>Lower cost</td>
<td>Development of proxies (substitution criteria) sometimes necessary and</td>
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<td></td>
<td>Patients included may be exhaustive in nature</td>
<td>limitations specific to these proxies (incl. validity)</td>
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<tr>
<td></td>
<td>Reliable data on healthcare consumption</td>
<td>Variability of the validity of available data</td>
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<tr>
<td></td>
<td>Secondary data (not &quot;protocolised&quot; in keeping with use in standard practice)</td>
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Figure 5. The French National Health Data System (SNDS) and its development.

subsequent difficulties, when conducting the study or submitting results to the authorities.

**Is the data source compatible with the objective of the PRS?**

As mentioned above, not all requests for PRS can be resolved by using medical/administrative databases or other hospital or study databases. Some required clinical information may be missing (e.g. precise identification of the disease, measurement of quality of life). In other cases, the development of these databases may enable new information of interest to be incorporated; however, this would be a prospective undertaking, which would necessitate sufficient hindsight to allow the new data to be used.

**Are the data of interest present in the database? Are they accessible?**

According to the data required, different sources may be involved. The development of hospital data warehouses could open up access to new areas of investigation (e.g. intra-hospital medication prescriptions not limited to medicinal products invoiced in addition to the hospital stay-related group [HSRG]). Access to these data may, however, vary according to the media chosen by the establishments (e.g. X-ray reports or discharge letters in text format, easier to use from an electronic perspective compared to image or sound formats). Accessibility will depend on variable legal conditions according to the chosen priority in terms of database operation by the hospitals concerned.

**Do proxies need to be used, and, if so, have they been validated?**

This is an area of development essential to operating medical/administrative databases designed with other objectives in mind than PRS. If the data of interest (e.g. diagnosis) are not directly made available, this does not, however, rule out using other information to approach the desired data (e.g. identification of insulin-dependent diabetic patients via reimbursement data for prescribed and dispensed insulin).
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Figure 6. Example of the overall architecture of the Assistance Publique des Hôpitaux de Paris (AP—HP) data warehouse.

Figure 7. Medical-Economic Epidemiological Strategy program (ESME) project, Research and Development (R&D), French centers against cancer (UNICANCER).
The substitution criteria used should then undergo strict validation, a research undertaking in itself, and therefore be the subject of scientific publications with a view to being shared [17,18].

**Are the accessible data of sufficient quality [19]?**

The collected data should be evaluated in terms of their quality, including metrological criteria, such as their accuracy, but also involving the evaluation of entry processes (for what initial purpose in particular?), standardisation of their values or not (including reference systems, dictionaries and successive versions), the processes for control (on raw file formats and prepared files with a view to analysis for PRS), correction, reclassification, processing of missing data, deduplication, etc.

**Are exhaustive data of interest provided for the population studied? If not, is the representativeness of the data guaranteed?**

Non-exhaustive data collection gives rise to a major bias related to the possible causes of missing data. The availability of the measurement for the criterion of interest may, in certain cases, be influenced by the intervention the impact of which is to be measured. This risk is very limited in the SNIIRAM database (unlike clinical practice research datalink [CPRD] data, for example [20]).

**Is the time frame for exposure to the health product and collection of the data of interest compatible with the time frame of the PRS?**

In order to be relevant, information collection sometimes requires a stabilisation period for the prescription and/or use of the health product so as to reflect conditions of use in the medium- and long-term. In other cases, the time frame chosen for the PRS should exclude one or more intervals affected by intercurrent events (epidemic, seasonal, etc.) causing transient disturbances of the measurement. Where appropriate, the time between the onset of the events evaluated and the presence of information relating to these events in the databases used should also be taken into account (lag time related to the entry process, then availability of data).

**Is the feasibility of the study guaranteed? Have the regulatory aspects and cost of the study been specified and accepted?**

Like all studies, the evaluation of the resources relative to the objectives will be carried out taking into account scheduling constraints (acceptable time until results become available, possible risk of the results being obsolete when they are expected to become available) and the available resources (financial resources notably covering the requirements in terms of internal and external human skills and essential material resources). Legal feasibility should also be carefully examined (legal framework, whether or not patients should be contacted to obtain consent or the absence of objection, management of confidentiality, implementation of contractual partnerships, need for validation by various public authorities — e.g. CNIL — or parent companies or other corporate structures involved — comarketing, evaluation of health product classes, etc.).

**Conclusion**

Taking into account the information shared during the round table, all participants decided on the following nine recommendations, grouped into three themes.

**A. Methodological recommendations**

1. **Structure health data warehouses to ensure their interoperability and to promote the quality of information saved therein.**

   Large-scale clinical data aggregation can only improve the conditions for conducting PRS. The semantic description of all coded information will facilitate the use of all pooled data and the sharing of development, maintenance and operating tools (together with database quality control).

2. **Enable the implementation of hybrid studies by matching information originating both from field studies and database studies.**

   A draft decree is currently being drawn up pursuant to the provisions of Article 193 of French Law No. 2016-46 of 26 January 2016 on the health system reform and decree No. 2017-412 of 27 March 2017 consecutive to this law and relating to the use of the registration number in the national identification index as a national health identifier (NIR). This decree would make it possible to envisage innovative methodologies and new PRS by matching the SNDS database with other external data sources (e.g. data collected directly from patients constituting a cohort).

3. **Develop and share quality algorithms intended to identify the criteria of interest (e.g. proxies for pathological conditions) within the databases (on the REDSIAM network model [21]).**

   As mentioned above, the development of substitution criteria is a research effort in itself and should meet all of the requirements of a scientific procedure, notably including the transparency of activities for developing proxies with appropriate validation and publication of the results.

4. **Promote information sharing and improve the visibility of work carried out in the field of PRS on databases by:**
   - harmonising the referencing of publications on this research, notably for the key words to be used [e.g. SNDS, SNIIRAM, EGB, French National Computerised Medical Information System (PMSI)] in the title or abstract;
   - approaching the INDS to have access to standard phrases (in French and English) on the technical description of the SNDS database for systematic and standardised use in publications.
The research published in the international scientific literature on the SNII RAM database uses highly variable English-language phrases for similar concepts and objects (PMSI, SNII RAM, etc.). The creation of a joint glossary with the INDS of all widely used terms has been proposed. Hence, this will facilitate the drafting of texts by authors and the visibility of their research (better results for literature search queries using standard key words).

B. Procedural recommendations

(5) Ensure that the committees concerned routinely define the data expected for the PRS (selection and prioritisation of endpoints in the study requests).

Defining the objectives of the PRS as accurately as possible will avoid any ambiguity on the expected results, and it is essential to define primary objectives so as to guarantee the methodological rigour applicable to all studies.

(6) Promote exchanges between HAS, CEPS and the firms prior to signing agreements between CEPS and firms once a request for PRS has been drawn up, and to stipulate the conditions for implementing these PRS prior to signature.

According to the sequence of the evaluation of medicinal products and medical devices by the competent authorities, the expression of the need for PRS generally precedes the signing of agreements between CEPS and the firms. Now, these agreements may cause the scope of the results expected from these PRS to be redefined. Hence, early exchanges between all interested parties were initiated in a satisfactory manner for everyone in the field of medical devices. This approach could be promoted in the field of medicinal products.

(7) Encourage the sharing of experience through early publication of the main aspects of the PRS protocols on HAS website (long before any publications, and including aspects of the methodology with the chosen evaluation endpoints, type of study, etc.). The information provided should specify whether the protocol has been validated (a priori) or not by HAS.

The experience of the firms in carrying out PRS varies considerably, particularly for manufacturers of medical devices. Early publication of the key aspects of the protocols (notably stating whether a database search was proposed), and mentioning possible validation thereof by the competent authorities, would help to anticipate the need for PRS before the authorities [European Medicines Agency (EMA), HAS, CEPS] are convened, and would help certain firms to optimise the PRS undertaken (methodology, implementation time).

C. Recommendations relating to the reference systems

(8) Develop and publish reference methodology applicable to database researches and of interest for PRS.

The development of such a reference methodology (RM) applicable to database researches (excluding researches applicable to human person) will make it possible to simplify the procedures relating to personal data protection in appropriate cases. The commitment to comply with a RM avoids the need to apply for authorisation from the CNIL prior to the research.

(9) Update HAS guidelines document with the following title "Post-registration studies on health technologies (medicinal products, medical devices and procedures). Principles and methods" dated November 2011 [22] to take into account the recent changes in the PRS and the recommendations previously stated.

The profile of the PRS conducted since 2011 has changed, following in the footsteps of recent regulatory changes applicable to the operation of medical/administrative databases and the expansion of the latter over time. Hence, the proportion of PRS conducted using databases is tending to increase. The methodological changes arising from new data processing techniques and the changes in ways of accessing these data are paving the way for innovative approaches (e.g. propensity scores, hybrid studies). HAS guide from November 2011 concerning "post-registration studies on health technologies (medicinal products, medical devices and procedures). Principles and methods", the reference on the subject, must reflect these changes and will require updating in the near future.

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Disclosure of interest

The authors declare that they have no competing interest.

References


