

Regulatory Approaches for a Retrospective Multicentre Multinational Study on Data: An Example Conducted in France, Ireland and England

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Abstract: Retrospective studies are studies that easily provide data on a population. As the data are already available in the medical records, the collection and analysis of the results is faster. These studies are particularly valuable in the post-marketing clinical follow-up of medical devices. They allow manufacturers to easily and proactively obtain safety and performance data. The regulatory procedures associated with this type of study also appear to be much less burdensome than a prospective study. We propose to illustrate the procedures through a multinational retrospective study conducted in France, England and Ireland.

1 INTRODUCTION

A retrospective study is a study that “investigates outcomes specified at the beginning of a study by looking backwards at data collected from previous patients. Patients are enrolled after the clinical event of interest or exposure has occurred: this is usually conducted by review of the medical notes. Retrospective studies may be either cohort or case-control studies and have four primary purposes: (1) either as an audit tool for comparison of the historical data with current or future practice, (2) to test a potential hypothesis regarding suspected risk factors in relation to an outcome, (3) to ascertain the sample

size and data required for a prospective study or trial, or (4) to investigate uncommon or rare events (e.g. graft infection), where the size of a prospective study would be prohibitively large and take too long to conduct” (Powell & Sweeting, 2015). The data in retrospective studies comes from data that has been entered into a clinical database, medical records and not collected for the purpose of the research, resulting in possible missing data and poor data collection. The level of quality of the information and data collected could then be criticized and considered as lower than in a prospective study. In contrast, these studies are easier to set up in regulatory terms and in practice and normally quicker in getting the results than prospective study.

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Here we present the regulatory approaches of a retrospective study conducted in France, Ireland and England.

2 RETROSPECTIVE STUDY INTEREST

Retrospective study can be conducted to define characteristics of a population before developing or introducing a procedure, a device, a drug etc. as an “historical” cohort to replace a control group in a controlled trial. This could be a real opportunity to do without a prospective control group in study where the risks/benefits with the current care are already known, or in cases where standards of care could differ from centres, doctors, patients in order to get the actual data for each centre; so to complete the possible lack in knowledge of the practices

Retrospective studies are also conducted in the framework of post marketing investigations for drugs and post market clinical follow-up for devices (PMCF), when a new scientific question occurs, and when data could be available in the medical records. PMCF studies are studies carried out following the CE marking of a device and intended to answer specific questions regarding the safety or clinical performance (e.g. residual risks) of a device when used in accordance with its approved use in accordance with its approved CE labelling. The European Medical Device Regulation (EU MDR) 2017/745 strengthens studies post CE mark. Manufacturers have to evaluate their device during the whole life cycle of the product, i.e. even after the CE marked product in accordance with the EU MDR 2017/745. The number of retrospective studies could therefore multiply in the next few years, since they make it possible to easily obtain data on the device, provided that these data are well transcribed in the patients' medical records. We can also add the development of data science, big data, and of the medical records access for the use in research purposes, all in that in the general framework of General Data Protection Regulation (<https://eur-lex.europa.eu/eli/reg/2016/679/oj>).

We will use the example of a retrospective study conducted to better describe a population with iatrogenic pneumothorax. This population will then be used as a historical cohort for a study with a new device on the same targeted population. As the literature is not sufficiently developed on the subject and recommendations diverge, we decided to conduct this study in 3 different countries in order to consolidate the literature. This study aims to describe current practices through retrospective data collection, not focus on the evaluation of one device

or another. We will define how this retrospective study is handled in each of the countries concerned. On another side we well noticed that EU MDR 2017/745 is the regulation under which any investigation on a medical device will apply from May 2021.

3 FRANCE

In France, this research, evaluating current practices, is classified as research outside the Jardé law. It corresponds to the research cited in paragraph II 3° of article R1121-1 of the public health code (Legifrance, 2021): “*Not considered to be research involving the human person within the meaning of this title is research with a public interest objective of research, study or evaluation in the field of health conducted exclusively on the basis of the use of personal data processing mentioned in I of Article 54 of Act No. 78-17 of 6 January 1978 as amended relating to information technology, files and freedoms and which falls within the competence of the ethical and scientific committee for research, studies and evaluations provided for in 2° of II of the same article.*”

Retrospective studies must be conducted under the responsibility of a data controller. The regulatory approaches in France for retrospective study appear to be very light. These studies do not require the authorisation of the competent authority and the opinion of the “Comité de Protection des Personnes”, the committee responsible for evaluating studies under the Jardé law. On the other hand, the favourable opinion of a local ethics committee (institution or region) is recommended and may be indispensable for the publication of articles about the said research. The documents to be prepared and the time needed for the evaluation of local ethics committees depend on the organisation of the committee. In our recent example, the study was submitted to the research ethics committee of the University of Burgundy Franche Comté (<https://www.ubfc.fr/recherche/cer-ubfc/>). The time to obtain a first opinion was 3 months including a period of holidays. Some hospitals also have their own research ethics committees.

The General Data Protection Regulation (GDPR) provides a framework for data processing (EUR-lex, 2016). The GDPR has been implemented in French law by the law of 20 June 2018 on the protection of personal data. The main development of the law of 20 June 2018 is the expansion of the powers of the Commission Nationale de l'Informatique et des Libertés (CNIL) (<https://www.cnil.fr/>), which is now the authority responsible for the application of the GDPR in France. The CNIL has adopted five

reference methodologies (RM) to simplify the procedures for accessing health data. These methodologies provide a framework for the processing of personal data in the context of health research. When setting up a study, the sponsor must certify to the CNIL that the study complies with one of the corresponding reference methodologies. In the opposite case, the sponsor must file an application for authorisation with the CNIL.

If studies do not respect a reference methodology, the data processor must declare the study to CNIL for authorisation. Submission to CNIL is through the Health Data Hub (<https://www.health-data-hub.fr/depot>) who will transmit file to the “Comité d’Expertise pour les Recherches, les Études et les Évaluations dans le domaine de la Santé” for assessment of:

- The purpose and methodology of the research
- The need for the use of personal health data
- The ethical relevance
- The scientific quality of the project
- If applicable, the public interest character of the project.

And then the file will be transmitted to CNIL for final approval.

Retrospective study respects RM004 (Legifrance, 2018) when data collected are the only required for the research purpose and are scientifically justified. This is the principle of relevance, adequacy and limited in conformity with GDPR. Data on geocode, social security number, religious views, and data relating to offences must not be collected and analysed. The storage and archiving of data must respect the legal delay and lastly patients must be informed according to article 13 and 14 of GDPR and the patient have the right to object to the use of his data at any time.

Patient information can be:

- (1) In some institutions, when patients are admitted at the hospital (both inpatient and outpatient), they are directly informed that their data may be re-used for research purposes, unless they object: systematic patient information. When a new study emerges that requires the re-use of these patients' data, the institution should publish information of the study as for example on the institution's webpage and information on their rights in accordance with the GDPR. In this way, the patient can object to the re-use of their data.

- (2) Sending an information note and opposition form to the patient's home. The patient information note must contain all information according to article 13 and 14 of GDPR. This is based on the “silence means assent” principle. If patient contacts investigator or sends the opposition form he cannot be included in the study as he objects to the reuse of its data. In the opposite case, patient data can be reused.

For this second option, the vital status of the patient must be identified to ensure that they are still alive before the documents are sent home. For this, the initiator is responsible for ensuring the vital status of each patient. The information can be found in the patient's medical record, but this is not always updated when the patient dies and even more so when the patient dies elsewhere.

A simple way to find the vital status of a person is to use the MatchID application for France (<https://deces.matchid.io/>). MatchID is a project initiated at the Ministry of the Interior which uses the nominative files of deceased persons (deceased since 1970) collected by INSEE, the national statistics office. The INSEE files of deceased persons are established from information received from the municipalities: death certificates. MatchID does have some limitations:

- INSEE cannot guarantee that the files of deceased persons are free of errors or omissions. The information reported in MatchID are deaths of which INSEE is aware.
- Persons without an NIR number (born abroad and without affiliation to a Social Security organisation) and some persons who died abroad will not be identified in MatchID.
- Recently deceased persons may not be found in MatchID (delay in transmission of information by the family to the town hall, then from the town hall to INSEE, then import of data by MatchID).

On the other hand, the use of anonymised personal data makes it possible to evade data protection regulations and thus to use the data freely, since it is impossible to trace the identity of the person through anonymization.

4 IRELAND

In January 2021, the Health Research Regulation was amended by the Minister of Health (Irish Statute

Book, 2021). This amendment deals with the consent challenge for retrospective chart reviews studies. Retrospective chart reviews are defined by:

- low risk study carried out by a controller
- on personal data only
- where that personal data has already been obtained by that controller for the purposes of the provision of health care to an individual by the controller.

Explicit consent will not furthermore apply for studies when:

- it has been approved by a Research Ethics Committee (REC)
- where the REC, as part of that approval, is satisfied and states in writing that the required data protection risk assessment carried out by the controller indicates a low risk to the rights and freedoms of the data subjects whose data will be accessed and used in the study.

In order to be coherent with GDPR, notices and posters must be displayed in public areas of the controller's organisation where patients attend for the provision of health care.

This means that retrospective study needs to be submitted to local or Joint RECs which is different from the National Research Ethics committee – NREC (<https://www.nrecoffice.ie/>). Research Ethics Committees are local committees attached to hospitals or universities. Whereas NREC is the national committee involved in study on medicinal products or medical devices. Last experience for our study, we submitted to the research ethics committee of Saint James hospital and Tallaght University Hospital (<https://www.tuh.ie/Departments/TUH-Research-and-Ethics-/>). The evaluation time for this study was approximately 2 months. This low risk retrospective study was associated to an "expedited review".

It is also possible to apply for an exemption from consent where explicit patient consent is required. This must be fully justified, it must be demonstrated that the public interest in health research significantly outweighs the public interest in requiring the explicit consent of the research participant. A strong argument will be required in order for the consent exemption to be granted. This application must be submitted to the Health Research Consent Declaration Committee (HRCDC) (<https://hrcdc.ie/apply>). For that, the HRCDC form must be completed and accompanied by a Data Protection Impact Assessment. HRCDC meets each month to review project and can except a formal

decision letter within 5 working days after the meeting.

Based on our experience with the retrospective study on pneumothorax, we had to submit to Saint James Hospital, in addition to the Research Ethics Committee:

- a research application form to the research and innovation office
- a form to the Clinical Research Facilities Department, as the study will be conducted through this department.

The patient data in our example study will be anonymised for Ireland. Thus no patient consent is required and no application to the HRCDC was necessary.

5 ENGLAND

Studies limited to working with retrospective data may be classified as research if the results are deemed generalisable. If classified as research, the study must apply for approval from the Health Research Authority (HRA). The following tool allows to define whether the project is classed as research or not: <http://www.hra-decisiontools.org.uk/research/>.

The decision is based on whether participants are randomised to different groups, whether the study requires a change to patient care or whether the findings are generalisable or transferable. Following the answers selected, the tool can advise whether it is necessary to apply for HRA approval. In the case of our study, we completed the tool and did not find the project to be classified as research however the organisation's R&D office felt the results could be considered generalisable. We were then able to contact the HRA Queries Line to seek further clarification - queries@hra.nhs.uk.

In order to obtain approval from the HRA, the applicant must register and fill in the Project Filter form on the Integrated Research Application System (IRAS) (<https://www.myresearchproject.org.uk/>). This initial form determines which other authorities your study needs to be reviewed by based on your answers to the project filter questions. The IRAS system allows a study to be submitted to both the ethics committee (where applicable), the competent authority and the HRA for approval.

Where explicit patient consent is not being sought and the information required for the study is deemed to meet the definition of personal data, an application must be made to the Confidentiality Advisory Group (CAG) through IRAS. This application is considered alongside the application to the HRA.

Where the study is not classified as research, the impact and level of risk of sharing the data must be assessed by the organisation who will complete a form called a Data Protection Impact Assessment (DPIA). A DPIA is an important tool for negating risk and demonstrating compliance with GDPR; as there is no standard document template for a DPIA, the questions posted in the DPIA are unique to each organisation. Following completion of the DPIA, this document is then reviewed by the Caldicott Guardian, a senior person responsible for protecting the confidentiality of people's health and care information and making sure it is used properly. The Caldicott Guardian will check that all processes described within the DPIA are in-line with the Caldicott Guardian Principles.

A Privacy Notice is in place on the Oxford University Hospitals NHSFT website outlining the how a health record is used and in what circumstances it may be shared and with whom. New guidance is also emerging which advises organisations to publish a Data Access Register (DAR) to allow patients to view how data has been used by the organisation and for what purpose under more specific terms.

6 CONCLUSION

As we can see from the example of these three countries, there is no harmonised regulatory approach for retrospective studies. Although the opinion of an ethics committee seems to be required to start the research, the additional procedures remain specific to each country, or even to each health organisation (case of the Saint James Hospital).

It is therefore important to have a point of contact in each of the countries where the study will be undertaken in order to carry out the correct regulatory procedures and to comply with national and/or local regulations.

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