

Observational studies: an opportunity for scientific communication

(Part 2)

Observational studies play an important role in finding out whether the efficacy of a pharmaceutical product under controlled conditions translates into efficient treatment in day-to-day medical practice

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In contrast to the approach used in clinical trials ... an observational study should select "the average doctor" in order to build a representative sample

The role and value of observational studies has long been discussed and debated. This is the second in a series of two articles that aim to show the potential and opportunities offered by observational studies in scientific communication. In this second article, the authors discuss the main rules for the development and conduct of scientifically sound, high quality and well-performed observational studies.

The conduct of studies

In conducting medically and scientifically sound, high-quality and well-performed observational studies, five points are crucial and constitute the core of a well-conducted observational study protocol:

A relevant scientific context An adequate scientific committee brings a guarantee of seriousness to the study and ensures its relevance. This means choosing not only leaders in the studied pathological field (including an epidemiologist) but also doctors from the investigator's target area.

High quality standard data record forms In observational studies, data collection support must meet the study's objectives, while at the same time remaining close to usual medical practice. Doctors

participating in a study are not selected for their specific competencies in data collection – as they are in randomised controlled clinical trials. Consequently, a pilot phase to ensure the validation of tools is crucial; this includes the conduct of in-depth face-to-face interviews with a number of study target doctors prior to questionnaire writing. This procedure makes it possible to obtain a reliable tool that integrates elements from the usual medical practice, without ambiguous items, and is adapted to a self-completion questionnaire. The purpose is to create a logical, practical tool that respects the need to avoid modifying the relationship of doctor and patient.

Rigorous selection of doctors Observing usual medical practice requires a random selection of participating doctors (or a quota method); this will also be the case for the patients included. In contrast to the approach used in clinical trials (where one seeks the "good investigator"), an observational study should select "the average doctor" in order to build a representative sample. In addition, this "representativeness" is checked at the time of the analysis, on the basis of those criteria considered to be relevant with regard to the study objectives.

“Average doctors” will have to include “average patients” in chronological order, starting from the implementation of the study and usually with very “light” selection criteria. Thus, the representativeness of the sample will be ensured by the representativeness of the investigators’ sample, and by the absence of more controlled selection of patients.

Statistical assessment of subjects and participating doctors In order to take into account all the practice habits and/or use of a therapeutic class or product, the statistical calculation in observational studies will involve vast samples of patients – often up to several thousands. The statistical laws to establish the number of subjects are generally different from those used in clinical trials – but the same rigour of calculation is essential.

Data and quality assurance With data being recorded according to usual medical practice, without modification of the relationship between the doctor and patient, quality monitoring is less complicated than in randomised controlled clinical trials. Three types of quality control are used:

- *Prior to the study* Feasibility is assessed prior to the study; the pilot phase (filling tests) and naturalistic conditions of the study reduce investigator constraints and so optimise the quality of the data.
- *During the study* Written queries are generally limited to key data relating to the primary objective. Controls by phone can supplement these queries; without requiring the doctors to respond, they ensure a faster response time during the study period and allow the participating doctors to be made aware of the need for the consecutive selection of patients for inclusion.

- *At the end of the data collection period* More and more often, monitoring/quality assurance visits are carried out at the end of the data collection period. The objective is to control randomly drawn centres and in particular to check out the existence of those patients included and compare key data with source-files.

Specificity within the method

Two particular problems, certainly found in all types of studies, have an added significance within the framework of the observational study: the degree of confidence in diagnosis and the checking of drop-out patients in a cohort follow-up.

Confidence in the diagnosis As in a market survey, there are generally no methods of diagnosis imposed on participating doctors (biological or radiological examination, for example). However, study of the care management of a certain illness or disease would require data centred on this target disease. As a result, it is generally recommended that the Scientific Committee be involved in an individual review of the returned data record forms. If the number of returned files is too large for this to be practical, the definition prior to the study of a set of criteria (generally founded on clinical elements) allows for the differentiation of “certain diagnoses” from “probable diagnoses” at the time of analysis.

Drop-out patients The specificity of the collected data, the modification of the doctor/patient relationship and the patient’s agreement – prior to the trial – of the constraints related to the protocol for some reason tend to limit the potential number of drop-outs. However, within the strict framework of an observational study with cohort follow-up, it

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Table 1. Main differences between observational studies, clinical trials and market research studies.

Clinical trials	Observational studies	Quantitative market research studies
Function is to demonstrate	Function is to describe/explain	Function is to know
Important regulatory requirements (ethics committee and regulatory authorities' approval)	Regulatory requirements depending on the country but usually just regulatory information	—
Patient's written consent	Patient's information	—
"Good" investigators	Representative "average" doctors	Representative "average" doctors
Selected patients	Representative "average" patients	Representative "average" patients (diaries)
Site monitoring	Site monitoring rare	—
Written queries	Written queries (key data), occasional phone-monitoring	Occasional phone-monitoring on key data (diaries)
Scientific reliability of data depending on the quality of project and monitoring	Scientific reliability of data depending on the relevance of the project	Scientific reliability of data depending on the quality of the methodology

This is why authorities are increasingly initiating observational studies – in particular to analyse the “good use” of a specific drug

is not possible, for example, to impose follow-up visit dates on included patients; the number of drop-outs is logically increased in comparison with a clinical trial – which can harm the quality of the final data. To help address this problem, it is generally recommended that – with the patient’s consent – contact details, including an address, be collected at the time of inclusion. Drop-out patients can then be contacted for important key data at the end of the study – even if this data does not exactly fit the data collected by the participating doctors.

A communication tool

The results and conclusions of observational studies can help familiarise pharmaceutical companies with the care management of a specific disease area and the modalities of use for a product. This helps companies to rationalise and optimise the use of those drugs for which they are responsible.

Beyond this prime objective, for several reasons, observational studies also constitute a communication tool in other ways:

At the beginning of study As already mentioned, observational studies must integrate and take account of the whole of medical practice and the modes of use of a therapeutic class or product. Consequently, the necessary “representativeness” of samples requires the selection of large populations and thus, for the pharmaceutical company, collaboration with a large number of clinicians.

The implementation of such studies can be carried out using selection via telephone, followed by the sending of study documents, or individual visits, or regional and even national meetings. In a very concrete way, the sales representatives of pharmaceutical companies often take part in the start-up visits or meetings. Indeed, the significant number of doctors to be selected (from random lists segmented by visit sector) and the reliance on usual medical practice support the integration of these medical representatives into the study process.

During the study In addition, a pharmaceutical company can provide invaluable help in making follow-up contacts and motivating the study clinicians

Table 2. A schematic characterisation

Clinical studies	Observational studies	Market research studies
Methodology is to prove	Methodology is to observe	Methodology is to observe
Selected centres	Scientific representatively	Usual medical practice
Exclusion criteria	Inclusion criteria	No criteria
Arbitrary variables	Usual medical practice	Usual medical practice
Modification of the patient/doctor relationship	No modification	No modification
Coordinator	Scientific board	Nobody
Ethics & regulatory requirements	Minimal regulatory requirements	None
Protocol	Protocol	Nothing
Tracking (+++)	Tracking (+)	Nothing
100 patients	1,000 - 10,000 patients	100 - 1,000 patients
On-site monitoring	Audit visits	Nothing
Double entry + data clarifications	Scanner + key data clarifications	One entry
Quality control (+++)	Quality control (+)	Quality control (+/-)
Statistics test	Quantitative analysis/statistical test	Quantitative analysis / statistical test
End-result is approval dossier and scientific communication on the drug	End-result is multiple communication: relationship with the participants (during the study reps implication), communication on the pathology or therapeutic class or habits, drug positioning thoughts (internal communication)	End-result is drug positioning (internal communication)

on a daily basis. Marketing and sales management within pharmaceutical companies are usually interested in furthering this use of representatives, as the studies provide an opportunity to develop the relationship with a doctor through contacts that aren't based on a direct product-related promotion.

After a detailed briefing on the study objectives and methods, and with the active support of the research centre, marketing and sales representatives can often be a real asset in the regular management of observational studies. However, we do not recommend including them in the scientific follow-up of the study – and in particular in the data control – because it is important to dissociate the scientific controls from the commercial objective of marketing/sales visits.

At the end of the study The results included in scientific publications and oral communications at meetings and symposia form part of the supportive documentation of the pharmaceutical representative's visit. An observational study is designed to describe usual medical practice; it is not intended to test an assumption, or to prove equivalence or the superiority of one product over another. Thus, the results of the observational study are always 'communicable'.

Clinicians generally prove to be very interested in this type of data. There are two reasons for this. On the one hand, they are sensitive to data relating directly to their own medical practice – rather than the intrinsic characteristics of a molecule or active ingredient in a specific product. In addition, they are *a priori* interested in comparing their own practice with that of their fellow clinicians.

The regulatory authorities are in favour of the development of such studies. Indeed, the study of drugs in a real-life situation represents an opportunity to understand the real use of reimbursed drugs, apart from the strict framework defined by their SPC or (package) insert. This is why authorities are increasingly initiating observational studies – in particular to analyse the "good use" of a specific drug.

Constraints and limits

Relevant and recognised constraints of observational studies include:

- *The regulatory framework* Although they respect usual medical practice, observational studies are subjected to constraining local authorisations (medical data confidentiality, respect of the patient, regulation of the investigator's fees and so on).
- *The selection of patients* Taking into account the necessary representativeness of the sample, investigators are randomly drawn rather than selected on the basis of criteria such as "quality of investigator" or "relationship with the sponsor".

Limits of observational studies are generally recognised as:

- *Drug efficacy* The objective of observation and description excludes the aim of demonstrating the efficacy of a given molecule, active ingredient or pharmaceutical product – since the purpose is not to study intrinsic characteristics of specific products but their modalities of use.
- *Transience of the information* Observational studies look at care management or modalities of use of a therapeutic class or drug at a given time. The results are therefore "time-bound" since they are established within an environment likely to evolve constantly. By comparison, the data from a clinical trial will usually remain unchanged, regardless of the evolution of a therapeutic field.

Conclusion: a real opportunity

Observational studies play an important role in finding out whether the efficacy of a pharmaceutical product under controlled conditions in a randomised controlled clinical trial in specialised centres translates into efficient treatment in day-to-day medical practice. These studies are not a replacement but a useful adjunct. Hence, randomised controlled clinical trials and observational studies should not be considered as mutually exclusive. As we've discussed, they each have specific advantages and disadvantages: randomised controlled clinical trials have high internal but lower external validity, whereas real life practice studies have less internal and more external validity (1).

Observational studies have made considerable strides forward. Unlike randomised controlled clinical studies, they represent an opportunity for all participants in the pharmaceutical marketplace:

- *For pharmaceutical companies*, they enable an operational collaboration with broad samples of clinicians and communication of the results through all the stages of the project.
- *For investigators*, they permit a new perspective on medical practices. Doctors naturally tend to be isolated in their practise of medicine, and the data resulting from observational studies can provide an opportunity for the real exchange of information with peers.
- *For regulatory authorities*, they provide another source of information for answers to public health questions.

Well-conducted observational studies offer a great opportunity for developing a true synergy between scientific objectives, and marketing and communications issues. Often they are cheaper, quicker and less difficult to carry out than traditional randomised controlled clinical trials. And as an

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The importance of guidelines and procedures

In conducting observational studies and randomised controlled clinical trials (RCCTs), two types of data error may occur (2). The first is deliberate falsification, and the second results from human or measurement errors (such as inaccurate data entries, faulty transfer of data, misinterpretation and inherent limitations of the instruments of measurement). Naturally, errors caused by deliberately falsifying data are very serious and must be dealt with accordingly. Human or measurement errors may be serious or trivial; for this reason, observational studies and RCCTs must include procedures to avoid or minimise data errors.

It is essential for the quality, credibility and validity of observational studies to promote and develop a rigorous set of guidelines which

will be instrumental in reducing important errors such as phantom participants, fabrication of data, entry of participants with major ineligibility criteria, and outcome measurement mistakes. RCCTs require protocols. In ensuring that important data are collected in observational studies, written protocols – called critical pathways (3) – have emerged as a new initiative that promises to reduce costs and improve study outcomes. These ‘protocol-like’ critical pathways are crucial to the results of observational studies. Only if observational studies are conducted in compliance with such pre-designed and structural methods can they contribute to health care – offering doctors and patients the necessary reliable information that they deserve.



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adjunct to such research, well conducted observational studies can provide a significant contribution to evidence-based medicine. Consequently, these studies can be expected to advance the standard of medical communication, and contribute to a better understanding of the effects of medicines and the validity of therapies in real-life settings.



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