PROTECT: key results and recommendations

Good Signal Detection Practices

When a new medicine enters the market, it is important to detect as early as possible new safety issues that may be experienced by patients and were not known at the time of marketing authorisation. This detection is generally based on the spontaneous notification of adverse reactions by patients, pharmacists and physicians to national health authorities or pharmaceutical companies. These notifications are stored in large databases which are screened regularly to detect new safety signals. Adverse reactions to drugs may also be detected by analysing patients' electronic health records and data from clinical trials.

Over a period of 5 years, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project has addressed key research questions relevant to the science of safety signal detection. In an article in the journal Drug Safety, PROTECT reported 39 recommendations that can be converted into meaningful and implementable outputs, as well as 25 recommendations for further research.

Detection of adverse drug reactions from spontaneous reports often involves calculating statistical measures of association between each drug and each adverse event. Further investigation follows when these reach a chosen threshold. The choice of the threshold value is fundamental to the success of the signal detection system because it influences the balance between earliness and number of detected signals and the amount of resources needed for the task. Many statistical measures were tested in PROTECT and found to be equally effective. Thus the choice should be based on ease of implementation, interpretation and optimisation of resources. The performance of a signal detection system should also always be assessed in the database where it will be applied. PROTECT also recommends that a list of terms should be created and systematically used to avoid missing medical events that are serious or have a high probability to be related to a medicine. The performance of signal detection in subgroups defined by various variables has been examined and subgrouping of the data by age, country and continent of origin showed the highest improvement of precision.

Regarding use of electronic health records for signal detection, they were found potentially useful but their limitations in terms of both their size and scope (which drugs and diagnoses they capture) and the results of clinical, pharmacological and epidemiological review of the identified medical events

should be taken into account for the interpretation of safety signal detection. Further research is needed in this field.

Several methods for signal detection from clinical trials were explored and found potentially useful, but the selection of the most appropriate methods must consider the size of the available clinical trial database and computational requirements.

Recommendations for observational studies on drug safety

In many cases, safety signals detected from spontaneous reports need to be further investigated and electronic health records are increasingly used for this purpose as they may provide rapid response and permit the study of rare adverse events due to their large size and breath of data collection. However, there is continued scepticism about the reliability of their findings due to the diversity and discrepancy of their results even when different studies investigate a same safety issue.

To evaluate and mitigate the effects of these differences due to the choice of the data source and study design, PROTECT applied different designs and analytic methodologies for six drug-adverse event pairs across several electronic healthcare databases and registries. Common protocols and analytic specifications were used by research teams located throughout Europe and the United-States. A special issue of the journal Pharmacoepidemiology and Drug Safety with 16 articles reports on the results of these individual studies and provides lessons learnt for multi-centre, multi-database studies with common protocols.

PROTECT recommends that conducting multi-centre database studies requires very detailed common protocols and data specifications that reduce variability in interpretations by researchers. It was found that a priori pooling data from several databases may disguise heterogeneity that may provide useful information on the safety issue under investigation, and it should be avoided. PROTECT rather advocates to analyse databases in parallel and explore reasons for heterogeneity through extensive sensitivity analyses. This approach will eventually increase consistency in findings from observational drug effect studies, or reveal causes of differential drug effects. The design and analysis of studies should also be tailored to the specific drug-adverse event association of interest with a consideration to case-only designs that were found to add insight into associations because of the different assumptions. Furthermore, no universal recommendations on which method to control for confounding variables could be made from the findings: this should be assessed on a case-by-case basis.

Other results from PROTECT (available on the website www.imi-protect.eu) have emphasised the importance of access to drug utilisation data and national drug consumption databases and provided examples of their use in public health. Registering protocols of drug-adverse event studies in an electronic public register is also recommended to improve transparency.

Direct-to-patient pharmacovigilance

PROTECT investigated direct reporting of drug exposures from treated subjects to study the safety of medicines. Medication use in pregnancy was selected as a test case for evaluation, since the use of medication during pregnancy may be essential for the health of the mother but some have potential to cause harm to the foetus.

Currently the majority of data available on medications used during pregnancy and lifestyle factors are usually collected either from health care professionals, through direct patient questioning or by making use of prescription or dispensing records. These methods have limitations since they do not allow collecting data early in pregnancy, they may be time-consuming or expensive or they can only be performed infrequently during pregnancy which may lead to loss of information. In addition, women

may be reluctant to provide information on lifestyle behaviours. PROTECT therefore piloted a study designed to explore use of the Internet to overcome these issues and assess whether information collected through the Internet was complete and accurate enough to be used for pharmacovigilance.

The results of the study were recently published in the journal JMIR Public Health and Surveillance. PROTECT concluded that direct to patient is a useful method for learning about use of prescription and nonprescription medication use, including medications that may be administered in hospitals, emergency room or as outpatients, or used on an as-needed basis, and in some cases these data are more complete than data from prescription registers and electronic health records. Further, using the Internet makes it easier to collect data regularly during pregnancy, to provide information on drug exposure during the early weeks of pregnancy and to provide a picture of factors which may contribute to an adverse outcome of pregnancy. Nonetheless, clinical input may be needed to fully understand patients' medical histories and capture birth outcomes.

Recommendations for methods and visual representations of benefit–risk assessment

The decision to authorise drugs to be launched on the market and further evaluations during their life-cycle require carefully weighing of their benefits and their risks. Judgements by individuals or committees have traditionally been the main approach for benefit-risk assessment but explicit, quantitative approaches are useful to improve transparency and consistency of decisions. However, although various structured approaches to decision-making have been developed in other fields, a thorough appraisal of methodologies and their practical applications in different real-life studies were missing and no agreed method existed for the benefit-risk assessment of medicines.

A comprehensive review of benefit-risk methods and how to represent them visually has been performed by PROTECT and published in the journal Pharmacoepidemiology and Drug Safety. The research consisted of the identification and testing of methods of assembling data on benefits and risks from various data sources and of integrating them with regulators' decision criteria and values expressed by patients, health care providers and regulators on the favourable and unfavourable effects of drugs; the identification and testing of methods to support decision-making along the lifecycle of the products; and the development of methods of graphical expressions of the benefits and risks of the medicinal product for use by the patients, health care providers and regulators. Researchers selected 13 methodologies for investigation in case studies.

The resulting recommendations provide guidance on the available tools to integrate and visualise data on favourable and unfavourable drug effects and on a more harmonised approach for benefit-risk assessment. This ground work is being used in subsequent research projects and recommended methods are being tested for their applicability in regulatory practice.