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A Pathway to Improved Prospective Observational Post-Authorization Safety Studies

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Abstract

Randomized controlled trials (RCTs) are the gold standard for assessing the efficacy of drugs but not necessarily so for drug safety where inadequate power to detect either multiple or rare adverse events is a major handicap. Furthermore, the conditions under which drugs are approved for market use are often different from the settings in actual use. Indeed, with their control mechanisms, trials are by design largely inadequate for the identification of potential safety signals, especially of the rare type, hence the value of post-marketing surveillance and risk management plan-based activities.

Today, clinical trials constitute only a part of the research that goes into assessing the safety of drugs. Observational studies, where the investigators merely collect data on treatments received by patients and their health status in routine clinical practice are increasing in uptake because they reflect the real-life utility of drugs, despite the absence of random treatment assignment. Although such studies generally provide less compelling evidence than RCTs, they can be far more useful to drug safety assessment activities than generally acknowledged.

An increasing number of post-authorization safety studies (PASS) within the European Medicines Agency's jurisdiction are of the observational type – considered perhaps as more appropriate vehicles for exploring and documenting how products perform in the real world. A similar trend is emerging in the US following the FDA Amendments Act of 2007; since early 2010, an increasing number of post-approval commitments mandated by the FDA include observational studies. However, despite this pattern, not much is known about ongoing efforts to address many of the recognized inadequacies associated with existing methodologies and practices currently adopted in observational PASS. This current opinion presents an overview of some of the main challenges we face in prospective observational PASS, mainly from practical experience, and proposes certain steps for improvement.

The randomized controlled trial (RCT) is considered the gold standard in drug research, primarily because it is capable of providing the most compelling evidence on the efficacy of a healthcare intervention.[1] However, sample size considerations for a trial routinely take into account the cost aspect, and features such as short duration and restricted populations, especially in drug

safety assessments, often make trials inadequate for determining rates of adverse effects because of low frequencies. Experience has acknowledged this problem in the form of the so-called 'rule of three' – namely, that for an adverse event with an assumed background incidence of zero, approximately 3-fold the number of patients would need to be treated and observed for the adverse effect to become manifest and reliably linked with the drug.

Indeed, trials are particularly inadequate for detecting multiple rare adverse effects and, not surprisingly, in terms of proportion, the vast amount of adverse effects is caused by those drugs that have been on the market a long time.[2] Today, regulatory agencies and other stakeholders consider the postmarketing phase as the richest source of safety data and clinical trials constitute only a part of the research. Observational studies (of the non-interventional type) are becoming increasingly popular mainly because they reflect real-life utility of drugs, although evidence from these studies is often dismissed because of the absence of randomization and the likely consequences of selection bias. However, despite their inherent inadequacies, there is sustained growth in the utility of these studies for safety surveillance, as alternative post-authorization safety studies (PASS). Part of the reason may be because in some situations a trial may be either inappropriate or inadequate or even impossible to conduct, making the observational study an acceptable alternative to doing nothing. The other reason is because when properly conducted, these studies are capable of providing compelling safety data which in certain circumstances may be as valid as evidence from RCTs.[3-7] For instance, for certain treatments, it might be reasonable to consider the physician as possibly unaware of the risk to the patient of developing an adverse effect for the drug at the time of prescription, especially if that effect is unpredictable. In such situations, the physician can correctly be considered as blind to the prognosis when prescribing (i.e. prescribing is thus independent of prognosis). Indeed, this possibility has made some researchers question the role of randomization for the assessment of 'unintended treatment effects' in the post-approval phase where a large proportion of adverse effects is unpredictable and unexpected.[8-11]

The usefulness of certain observational studies can also be enhanced by the appropriate application of analytical tools to break the link between prescription and prognosis by the use of derived indicator variables such as propensity scores and instrumental variables. Considered as independent of the prognosis, these variables are used to either define the treatment groups for comparison or conduct stratified or adjusted analysis.[10]

We present an overview of some of the main challenges posed by prospective observational PASS and propose certain steps for improvement.

1. The Current State of Post-Authorization Safety Studies

Where the primary objective is to assess whether or not a specific drug of interest causes a particular common adverse effect, there is no better design than an RCT. However, at the post-approval phase where a number of adverse effects are not so common, causality is not so easy to determine. Indeed, a vast majority of safety studies are only aimed at assessing associations between exposure and events. Thus, the problem is not that observational studies fail to match results from RCTs. It is mainly our inability to design appropriate observational studies that sufficiently control for the important biases in such studies. For example, in the practical world of rare adverse effects, trials do not necessarily provide the gold standard, although, at least in theory, they do possess that potential.

Of note, there have been recent examples that highlight the value of observational studies in the post-approval phase of prescription drugs. The cardiovascular risk associated with Vioxx (marketed in the US since 1999) was first reported in studies in 2002 by the US Medicare and Tennessee Medicaid cohorts, and later replicated in many others, including a US FDA-sponsored study,[12-23] although the WHO Uppsala Monitoring Centre (UMC) had, by 2001, already detected the signal in their spontaneous reporting system and presented it as a drug of special interest at the annual meeting of centres in Tunis, Tunisia. Similarly,

other observational studies have also helped to trigger further studies which eventually provided evidence on risks associated with the drugs of interest that are different from those previously reported.[24,25]

Currently, PASS that are conducted within the EU countries can be either interventional (i.e. RCT) or observational by design.[25-27] Similar developments are also evolving in the US, notably the creation of the Quantitative Safety and Pharmacoepidemiology Group (QSPB) by the FDA in 2006 and the agency's recent draft guidance document on implementation of the FDA Amendments Act of 2007.[28,29] Indeed, in Europe an increasing number of PASS are of the observational type, involving prospective data collection strategies similar to what is obtained in clinical trials. The result is that activities in such PASS (i.e. those involving prospective data collection) have remained largely within the confines of secondary care use of prescription drugs because of cost and logistical problems associated with prospective data collection at primary care. Consequently, a large number may fail to provide adequate context data for spontaneous reports from the primary care setting. Although several safety studies are also conducted with routinely collected retrospective data in primary care, these are generally considered inferior to their prospective counterparts and hence their potential remains largely untapped. However, there are compelling reasons why retrospective data-based studies are not so warmly received – the literature is awash with studies whose findings have attracted numerous controversies and counter findings.[30-52] Thus, for the rest of this current opinion, our focus will be restricted to prospective observational PASS.

Prospective observational safety studies also pose their own challenges, some of which are not adequately addressed by current guidelines. Although they require a lot more resources to conduct compared with their retrospective counterparts, many of their critics consider prospective observational safety studies as nothing more than activities for collecting additional data on adverse events. Consequently, many of these studies lack internal comparators by design, a deliberate act to circumvent comparative assessments. Indeed, an overwhelming majority of observational PASS protocols are restricted to descriptive methodologies, hence unwittingly exposing their findings to the risk of comparisons with unsuitable external data (i.e. data lacking in comparability on key factors). However, there is anecdotal evidence of a wider recognition of this potential danger as we observe a sudden increase in the proportion of study protocols with objectives that invite comparative assessments and robust statistical analysis.

Interestingly, many observational PASS involving prospective data collection are erroneously still being referred to as 'registry' studies and almost all are initiated and managed by the same personnel responsible for the conduct of trials. Indeed, most are based on the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines, which are primarily for trials and also lack adequate epidemiological input. As a consequence, it is not uncommon to find, in a typical PASS, that a number of the likely sources of bias in observational studies have been largely ignored both at study design and at data analysis because of misplaced reliance on the assumptions that underpin clinical trials. However, with the emergence of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the recently passed EU legislation on pharmacovigilance that came into effect in July 2012 along with Directive 2010/84/EU,[53] we can expect to see significant improvements in this area. The new law will establish the Pharmacovigilance Risk Assessment Committee within the European Medicines Agency (EMA), with a mandate to review and approve all PASS protocols to be implemented in the EU. Indeed, ENCePP is currently finalizing work on methodological standards for pharmacoepidemiological studies which will provide guidance on study design, data sources and analysis. Today, studies that comply with the ENCePP checklist of activities can apply for registration and their associated protocols granted the ENCePP seal of approval.

However, things are not all plain sailing in the EU as researchers are often confronted by problems resulting from the fragmentation of regulations in

terms of central versus national requirements. EU regulators often ponder over the need for representative data and the associated pragmatic challenges across the region as well as the actual use of the product in the EU compared with the US. Nevertheless, it is reasonable to expect some progress in these areas as a result of the new pharmacovigilance legislation and actualization of a number of the ENCePP planned programme of activities under development.

2. Areas for Improvement

Industry awareness of the value of safety data from sources other than RCTs and spontaneous reports for effective assessment of pharmaceutical products is indeed a welcome development. It is also good for patients that this awareness is resulting in a number of regulatory-led activities aimed at achieving tangible progress on drug safety. However, although the evolving environment is offering more opportunities for observational safety studies, it is also posing challenges which if not adequately addressed may ultimately undermine the relevance of these studies. In the current climate of increased prospective observational research in drug safety, the engagement of subject-matter experts with sufficient experience of active involvement in the design and conduct of these studies will be particularly vital to any effort aimed at drawing attention to those challenges in need of viable improvements. In this regard, the main focus should be on protocol development,[54] with emphasis on the feasibility of its implementation, whilst bearing in mind the following properties:

- *Ecological validity:* the dual challenges of recruiting the right population to ensure adequate capture/reflection of the real-life setting and fulfilling vital risk management plan (RMP) obligations.
- *Achievable study objectives:* the challenge of ensuring the best possible study design and analysis for each critical objective. The cohort design is not necessarily always suitable, we can achieve better with other types in certain situations.
- *Tailored operational processes:* the challenge of ensuring effective conversion of each study design into the best possible operational model and adequate collection of follow-up data.

2.1 Study Population

Ecological validity, a measure of how accurately the study reflects real-life in terms of the methods, materials and setting, is vital to an observational safety study. A notable common practice in observational PASS is the exclusion of patients currently engaged in any ongoing trials, a necessary condition since the primary interest of such studies is exclusively about the safety of the drug of interest in its real-life usage. However, many of these studies have no process for handling or even identifying patients who subsequently enrol in interventional studies (i.e. trials) initiated during the course of the PASS. Being observational, patients involved in PASS cannot be prevented from participating in interventional studies, but the resulting data on such patients may lack some of the vital real-life quality. Consequently, although these studies do not actually compete with trials for patients, they can still suffer the effect of decline in eligible patients as a result of large numbers of ongoing or initiated trials during the periods involved. This is particularly important in light of the growth in the variety and number of observational studies being initiated, resulting in rapidly increasing competition between such studies for suitable sites and patients.

It is also common to find in many observational PASS the adoption of exclusion criteria similar to those used in the preceding trials of the associated drugs, a practice that may result in an inadequate reflection of real-life clinical practice. Reflection of real-life drug use is a major strength of properly conducted observational safety studies. Experience suggests the exclusion of certain patients in observational PASS is often the result of simplistic adoption of the corresponding trial protocol without adequate consideration for the consequences. Failure to consent and collect data on all patients exposed to the drug of interest in an observational study can be a missed opportunity to proactively and promptly respond to regulatory concerns about possible off-label usage of the drug. Indeed, the RMP template of the EMA

does require such data. For example, section 1.4.2 ''Actual post-authorization usage data'' of the EU-RMP, requests information on how the realized pattern of exposures to the drug has differed from what has been predicted, including off label use.[55]

Data on off-label usage, where possible to collect, may also complement proactive risk minimization efforts as they can facilitate the design of appropriate interventional tools targeted at the prevention of such practices deemed as undesirable because of possible risk implications. Indeed, such data may also provide suitable context for certain spontaneous reports. For instance, evidence of no such unauthorized usage of the drug in a real-life setting may, in certain circumstances, provide compelling supportive information on prescribing compliance, a likely valuable guide to any risk mitigation effort. It is therefore reasonable to reflect on the relative merit of each exclusion criterion, as part of the planning process of an observational PASS, involving proper assessment of the potential benefits to be gained from data on unauthorized usages within the framework of the likelihood of such practice. Furthermore, an assessment of the level of completeness and quality of the available data on post-authorization usage of the drug, in cognizance of its RMP requirements, may be a useful step in the planning process of such a study.

Therefore, for a typical observational safety study, it may be useful to seek the consent of patients eligible to use the drug of interest as well as any off-label users during the course of the study, the latter, primarily to serve the broader objectives of the associated RMP, without necessarily including such in the analyses for the specific study objectives. In this regard, the following checklist, along with both the authorized product information and RMP, may provide a useful guide on decisions about suitable study population.

- Can we identify any gaps on actual post-authorization usage?
- Is the drug prescribed also in primary care, a likely rich source of off-label usage?
- Is off-label prescription possible/likely?
- If yes, can we collect such data without seemingly encouraging such practice?
- With the RMP in mind, do we have acceptable rationale for each of the exclusion criteria?

For any PASS designed to include collection of off-label data, it is vital to ensure the operational study processes avoid steps that may encourage off-label prescriptions. Indeed, it may be prudent to use a separate case report form (CRF) to collect data from off-label users and, in any case, for the study team to specifically seek prior approval from the Committee for Medicinal Products for Human Use for the proposed off-label data collection so as to avoid the risk of disqualification of the study as non-interventional for reason of usage outside the 'terms of a marketing authorization'.

2.2 Achievable Study Objectives

Many observational PASS are conducted to achieve multiple objectives, based on protocols that typically involve simple, descriptive, statistical approaches that largely ignore the possible influences of bias from a number of sources. However, this practice, although still common, is changing as a result of the emerging dynamic regulatory environment in which PASS are being conducted.

One of the principal reasons for this dynamism is the increasing employment of comparative assessment strategies by regulatory agencies and other stakeholders to challenge the safety of prescription medicines using data from diverse sources, often times without regard to whether or not such data are suitably comparable. Consequently, PASS results face the risk of unfavourable interpretations arising from the involvement of unsuitable comparators external to the study, a risk that, ideally, can be minimized by the involvement of suitable internal comparators. In other words, we may be able to avoid unsuitable comparisons by designing the PASS in such a way as to provide the most viable data for each of its objectives. One such approach could be to consider the complete study data as a cohort within which to implement the most appropriate design for each objective, by aligning each objective with the best possible design and analysis.

For certain objectives, such a process may also involve prior identification of the possible sources of bias and confounding problems and the

application of appropriate minimization steps. In strictly epidemiological terminology, bias refers to error in the measurement of a variable whereas confounding refers to error in the interpretation of what may be an accurate measurement. However, in general usage both problems are commonly referred to as biases, and experience suggests an adequate understanding of their possible sources in any planned observational study, as described in the following subsections, may be vital.

2.2.1 Case Misclassification Bias

This is an important source of bias in observational studies, although more so in the retrospective setting, usually resulting from the use of non-uniform diagnostic criteria or associated missing diagnostic data. However, rigorous case detection activities (including careful screening) at data collection can greatly minimize its influence in the prospective setting.[56]

One such activity can be the use of clinical events committees similar to those routinely used in clinical endpoints trials for independent case adjudication. For a PASS, the setup can take the form of case identification committees whose processes of adjudications can be described in both the study protocol and final report. Indeed, in some situations the case validation process may even take the form of simple validation conducted in a random sample of the study population, as commonly employed in retrospective observational studies.[57-59] In many cases, however, case validation can be conducted by an examination of the patient records in the period leading up to the event.

2.2.2 Exposure Misclassification Bias

This is an exposure-related measurement error with an impact that is generally similar to that of case misclassification. Common sources include poor measurement, latent event period, treatment compliance and intermittent exposure. It can also be induced from inappropriate use of time windows for exposure classification. Indeed, time is chiefly responsible for much of the exposure misclassifications we encounter in observational cohort studies – actual versus intended duration of treatment, number of times the drug was used and when the drug was last used. Intermittent exposure is more common in real-life medical practice than generally acknowledged in observational studies, and some of the problems associated with simplistic assumptions about the influence of time in these studies have already been described elsewhere.[60,61]

Yet, as is common with efficacy trials, these studies are usually based on the intention-to-treat (ITT) assumption for exposure classification. Whilst ITT may be suitable in an efficacy trial setting where randomization and control mechanisms on exposure ensure its validity, the assumption may not be appropriate in the observational setting because of the need to reflect real-life (i.e. actual) drug use. Reflection of real-life clinical practice is no doubt the most compelling strength of these studies. Failure to properly reflect reality in an observational PASS may result in biased effect estimates and false conclusions. Indeed, inappropriate adoption of the ITT approach can result in non-differential exposure misclassification (i.e. similar error in both patients with and without the event) leading to bias towards the null. In other words, we may end up with exposure effect estimates suggesting little or no association when in fact an association exists.[62-68]

To identify and reduce this form of bias, the appropriateness of the ITT assumption ought to be tested as part of the data exploratory process. Indeed, there are alternatives to the cohort design as well as analytical options for addressing time-varying exposure, although the appropriateness of each option may depend largely on its own set of assumptions, notably the nested case-control, case-time-control, case-crossover and case-cohort designs. There are also varied forms of time-dependent survival modelling available as possible options as well as the conditional logistic regressional approach, which have been comprehensively described elsewhere.[69] However, even in such settings, we will still need to guide against the problem of differential misclassification, which is likely to result in measures of association that are biased either towards or away from the null and hence obscure any association.[65]

2.2.3 The Influence of Comorbidity and Comedication

In most studies, the influence of comorbidity is modelled as constant (i.e. remaining the same over time) with the inherent assumption that the duration of the condition does not influence prognosis. This assumption was recently challenged in a study that demonstrated the time-dependent nature of the influence of certain comorbidities on survival among COPD patients in the UK GPRD.[70] Another common practice is the modelling of comorbidity influence additively, either as the number of comorbidities present or by an index (such as the Charlson Comorbidity Index),[71] often without regard to the outcome of interest. These approaches were also recently challenged in two other studies with the conclusions that (i) outcome might not be associated linearly with the comorbidity count; (ii) the weights combining a set of binary comorbidities needed not be positive (i.e. the null hypothesis that outcome worsens with increasing comorbidity might be false); and (iii) we might lose the ability to identify specific interactions influencing prognosis by such practices.[72,73] The suitability of the assumptions that underpin these approaches should be assessed.

Although comorbidities can influence effect estimates and hence need to be properly handled, so also can comedications. For instance, we know that myocardial infarction risk is higher in hypertensive patients when compared with those free of the disease, and that among patients with the disease the risk is even greater in those who do not receive treatment. Indeed, the related issue of non-compliance with treatment is a recognized source of bias in studies involving real-life data, which, because of difficulty with adequate handling, is often ignored. There is little doubt that such influences may be time-dependent and that aspects of the resulting biases can be reduced through adequate classifications following proper examination of the historical medical/prescription records of the study patients.

2.2.4 Confounding by Indication, Severity and Prescription Channelling

These issues are summarized in table I and rank among the most common sources of bias in observational studies.

Table I. Common bias/confounding problems in observational studies

Type	Description
Selection bias	The sampled population is sufficiently different from the target population
Channelling bias	A form of selection bias that occurs when the drug is preferentially prescribed to patients at high risk of suffering the outcome of interest. In other words, the clinical condition that determined the drug selection is linked to the adverse effect (such as where sicker patients are channelled to new treatments or higher doses of the treatment)
Confounding	The measure of association between treatment and outcome is distorted by the effect of one or more variables that are also risk factors for the outcome of interest (e.g. not properly accounting for age effect resulting in mixing the effect with that of treatment)
Confounding by indication	The condition (i.e. the disease) that determines drug selection is linked to the outcome of interest – a type of selection bias called protopathic bias – is more commonly identified as such when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed[74]
Confounding by disease severity	Occurs where the severity of the disease acts as a confounder[75]

There have been a number of suggestions on approaches for controlling these biases:[76-79] at the design stage – matching and exclusions such as limiting study patients to idiopathic adverse effects (i.e. patients with no risk factor for the adverse effect who could have guided treatment); and at data analysis – modelling, matching and stratification of patients along treatment groups on relevant factors (including balancing tools such as propensity scores, instrumental variables and disease risk scores).[80-87] There are also methods for minimizing the effect of unmeasured confounding, other than by study designs where each patient serves as his/her control. They include use of the Heckman models and extensions of the propensity score methodology.[88-90]

To handle these biases, the team responsible for planning such an observational study should ensure it possesses adequate understanding of the factors likely to influence treatment choices and the other relevant aspects of clinical practice. In

terms of improvement to current practice, we think there is scope for improvement in the design of the CRFs used to collect the relevant study data. For example, in observational PASS involving comparative analyses, balancing tools such as instrumental variables or propensity scores derived from data on relevant clinical indicators of the disease condition, collected directly from the study physicians via the CRFs, may be more informative than those based solely on routinely collected baseline data.

2.3 Tailored Operational Processes

Observational safety studies generally pose a unique set of operational challenges, and as they are not governed by the requirements of any strict universal directive they do not need to be run to the standards of ICH-GCP. However, PASS studies fall under Directive 2001/83 of the EU[26] where they must comply with the requirements of Volume 9A of the Rules Governing Medicinal Products in the EU.[91] The Good Pharmacoepidemiology Practice (GPP) guidelines,[92] although acceptable in a number of regions of the world, are generally considered as weak for prospective data collection activities in terms of operational guidelines. Table II provides a list of a number of guideline documents that may be useful in the planning and conduct of observational studies. While this lack of specific guidelines may offer a level of freedom when it comes to implementing an operational solution, it can also create an inconsistency of approach to operational standards and quality of study conduct. Thus, PASS operational processes ought to be flexible and practicable enough to meet the varying requirements of their stakeholders, including an end-product of acceptable scientific standard. Two vital areas in need of much improvement and innovative thinking deserve special mention: (i) site as well as patient recruitment; and (ii) data quality.

Table II. Guidelines for observational studies

1. International Society of Pharmacoepidemiology guidelines for good pharmacoepidemiology practices (GPP)[92]
2. Agency for Healthcare Research and Quality registries handbook[93]
3. Good ReseArch for Comparative Effectiveness (GRACE) principles: recognizing high-quality observational studies of comparative effectiveness[94]
4. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good research practices for CER I, II, III[95]
5. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration[96]
6. Volume 9a of the rules governing medicinal products in the EU (2007)[91]
7. International Conference on Harmonisation (ICH) E2D post approval safety data management[97]
8. European Federation of Pharmaceutical Industries and Associations (EFPIA) code of conduct and national adaptations (2008)[98]
9. Oviedo convention on human rights and biomedicine (2007)[99]
10. CIOMS/WHO ethical guidance for epidemiological studies (2008)[100]

2.3.1 Site and Patient Recruitment

Representative study population is generally the key to enhancing external validity and scientific merit for an observational study; generalizability of the study findings for the stated objectives may depend on the extent to which this desired quality is secured. In this regard, study processes ought to involve appropriate strategies for adopting the most appropriate, flexible technology for the conduct of the PASS. For those that involve countries with profound variations in clinical practice, country-specific strategies appropriately tailored to the varied requirements would be desirable.

Study processes should also include strategies for reducing the proportions of sites and patients who decline to participate; both are vital if study results are to command a measure of external validity and scientific merit. The factors that motivate physicians to agree to participate and recruit patients into non-interventional PASS are often very different from those of clinical trials; the latter are usually more scientifically robust and offer significant financial remuneration. Thus, site as well as patient recruitment efforts can pose major challenges to an observational study and other appropriate motivational drivers will be needed to attract and maintain interest among sites and patients. Another major challenge is the retention of initial site motivation levels over the study duration so as to minimize patient dropout rates, increase participation and ensure accurate data collection – even more important for PASS

with long follow-ups, bearing in mind that unlike trials where protocols determine the schedules for patient visits, patient follow-up is not guaranteed in observational studies.

Experience suggests some of the most useful tools for motivating sites and patients involved in routine clinical practice-based studies include adequate promotion of the study rationale and its scientific merit, particularly with regard to improvement of patient management, monitoring of the safety of treatment and evaluation of appropriate treatment practices. Other incentives that have also served well as effective motivators include the provision of access to patient summary data, formation of a research community and commensurable financial compensation.

The involvement of a Steering Committee (SC; ideally constituted by key opinion leaders) in a PASS has also been identified as a useful tool for facilitating recruitment and motivational efforts. Experience suggests much leverage can be gained through the SC; study promotional activities are generally more favourably received when conducted by an independent SC. Credibility is vital for an observational study. As such, the independent SC should be given sufficient leverage to play an active role in the key decisions of the PASS. Indeed, the SC should be constituted by enthusiastic members, with a leadership that is committed to successful implementation of the study.

2.3.2 Data Quality

Missing or poor quality data is a potential source of bias that can compromise the power to detect significant differences in PASS. In general, the quality of data collected in observational studies will not be as complete or as accurate as that derived from strict protocol-driven trials, largely due to the vagaries of clinical practice. For example, the complete absence of some data elements may be a consequence of variations in clinical practices at local, regional or country levels. Indeed, some data elements may not be routinely collected. To minimize potential issues about data quality, the strategies that inform the operational processes may also need to include the following monitoring steps in addition to those summarized in table III and the user guide for registries by the Agency for Healthcare Research and Quality (AHRQ):[93]

- Identification of the key data items at an early stage.
- Development of a data quality assurance plan at the commencement of the study when the various risks to achieving the data completeness and accuracy goals can be identified and mitigation steps planned in advance.
- Early assessment of the content and quality of data entry within specific (ideally, randomly selected) sites to determine if it is likely to be of a high enough standard for the planned study.
- The setting up of a 'for cause monitoring' system, one based upon prior agreed target 'triggers' for ensuring an acceptable data quality level. Such 'triggers' may include, but are not limited to, a disproportionately high query rate or significant delinquency in CRF completion by site staff, such that checks can then be focused on the event that triggered the action.

As the value of observational study to drug safety monitoring continues to gain wide recognition amongst healthcare evaluation agencies, so also is the degree of importance being attached to the quality by which these studies are conducted.

Table III. Some key steps on data quality and internal validity

1. A specific approach to data collection – describing the most appropriate, reliable method of collecting data of good quality for the study purpose(s)
2. The outcomes of interest are clinically relevant and are clearly defined
3. All necessary information is collected on all relevant factors – exposures, risk factors and other mitigating factors at baseline and at indicated times during follow-up
4. Exposure data are as specific as possible
5. A set of quality metrics for documentation and reporting of adverse effects
6. Contingency plan for improving overall data quality
7. Pragmatic action plan for minimizing loss to follow-up
8. Follow-up period is reasonably sufficient enough for assessment of the key effects of interest
9. Data quality is assessed on at least a random sample of patients. Where specified standards are not met, then implement contingency plan, which may include:
   - re-training of sites
   - re-emphasizing of study requirements across all sites
   - re-sampling and reassessment of quality

One of the evaluation processes that is becoming a feature of prospective observational studies is source document verification, although its role is not necessarily to verify every data item but to take a representative sample of patients to measure data quality to be documented in the study report. In this regard, it is vital that the adopted process is designed in a way that avoids discriminatory monitoring – a likely bias from patient selection, such as when only the records of patients with the events of interest are targeted.[101]

In general, however, the backbone to any effective quality control operation is often a combination of the level of robustness and flexibility of the processes put in place to support the quality and regulatory requirements that are critical to successful conduct of the study. Our experience suggests such processes should be designed in such a way that they are easy to implement in any location. They should primarily be comprised of the systematic set of activities for collecting and maintaining data of excellent quality at a minimum cost, with emphasis on quality assurance and quality control, thus also incorporating the corrective and preventive contingency actions to be followed when necessary.

As part of such processes, we also recommend the conduct of feasibility assessment based on protocol-specific questionnaires aimed at identifying the best sites for successful patient enrolment of the target sample size. Such a site assessment, involving investigators who have expressed interest in study participation, can inform on local acceptability of the proposed protocol and provide useful data on the levels of site interest, resources, potential subjects and availability. Indeed, if planned and conducted well in advance, the resulting data can also assist the study site distribution as well as country allocation and selection processes, bearing in mind the need for a representative study population as necessary.

3. Conclusions

Observational PASS may be just as valid as and perhaps even more appropriate than trials for the monitoring of unintended treatment effects since treatment allocation is usually not related to the prognosis with respect to the specific unintended effect.[10] Indeed, adverse events are generally unintended treatment effects – outcomes that are usually rare (i.e. approximately less than 1 per 200 person-years) or take quite a considerable time to develop (i.e. more than 1 year on average).[8]

However, observational studies possess certain drawbacks primarily because of the absence of random treatment assignment. They also generally offer unique operational challenges because of the absence of study-driven interventional steps. One of these is the difficulty of separating treatment effect from the competing temporal effects of risk factors, which similarly increase with time, such as age, duration of illness, duration of follow-up and observation calendar period in these studies. Indeed, the problem is more critical in those studies that aim to evaluate the relationship between cumulative exposure to treatment for a chronic disease and the risk of an adverse event.[102] Disentanglement of true associations from induced associations between collinear or strongly related predictor variables is a major challenge of observational PASS, one that becomes even more daunting as the number of such temporal factors increases. This is a challenge we should address when designing such studies. Indeed, there are many other important problems associated with the design of PASS protocols that have not been highlighted in this current opinion. They include the lack of clear roles and responsibilities among investigators, sites and study team members; the lack of a clear research question; the lack of a well defined study population, study time period, adequate information on the disease (including its seasonality, indications, comorbidity, etc.) and supportive data on sample size or statistical power considerations. These are all challenges that need similar attention in the planning process of an observational PASS and some may be better handled with approaches either in combination with those described in this current opinion or as alternatives on their own merit. Among these, two deserve special mention on the grounds of value; notably, drug utilization studies and large simple trials, the latter being particularly more appropriate in certain situations such as evaluation of the safety of vaccines.

This current opinion has highlighted some of the biases and challenges of note that we encounter in PASS and proposed possible solutions. It has also drawn attention to some of the current practices in need of improvement. Uppermost, among these is the common practice of adopting the phase III protocol of a given prescription drug, with minimal modifications for the conduct of the corresponding observational PASS of the same indication, often at the risk of contravening aspects of the observational property of the study. Another questionable practice is the utilization of traditional statistical techniques borrowed from clinical statistics without much regard to the peculiarities and circumstances of the observational data or the assumptions that underpin correct application of such methods in the real-life setting. For example, the commonly used ITT assumption that is generally valid in efficacy trial settings may not be tenable in a long-term observational PASS where analysis based on actual exposure may be more appropriate. For certain PASS, the consequence of exposure misclassification bias due to simplistic adoption of the ITT principle may be an attenuation of treatment effect to the extent of false conclusions, an unacceptable error in the current environment.

Many who criticize the relevance of observational studies often forget the profound inadequacies of trials for the assessment of rare adverse effects. By taking a broader view on drug safety evaluation, particularly over a longer period of time than may be possible with trials, we can easily recognize the potential benefits that observational PASS offer. In this context, we should consider the growth in these studies as good for patients, regulatory agencies, researchers and other stakeholders, granted that they are being conducted appropriately. The main task then is for researchers involved in such studies to accept their associated challenges and rise up to them.[103] Observational PASS are usually conducted in environments where partial understanding of the study settings can result in inappropriate designs, data analyses and false conclusions, which in turn can cause untold damage to the health of patients or confer negative publicity and reactions to otherwise safe drugs unnecessarily. These are compelling reasons why we must continue to strive for improvements in the conduct of observational PASS.

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