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Open-Label Extension Studies

Do They Provide Meaningful Information on the Safety of New Drugs?

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Abstract

The number of open-label extension studies being performed has increased enormously in recent years. Often it is difficult to differentiate between these extension studies and the double-blind, controlled studies that preceded them. If undertaken primarily to gather more patient-years of exposure to the new drug in order to understand and gain confidence in its safety profile, open-label extension studies can play a useful and legitimate role in drug development and therapeutics. However, this can only occur if the open-label extension study is designed, executed, analysed and reported competently. Most of the value accrued in open-label extension studies is gained from a refinement in the perception of the expected incidence of adverse effects that have most likely already been identified as part of the preclinical and clinical trial programme. We still have to rely heavily on post-marketing safety surveillance systems to alert us to type B (unpredictable) adverse reactions because open-label extension studies are unlikely to provide useful information about these types of often serious and relatively rare adverse reactions.

Random allocation into test and control groups is needed to produce precise incidence data on pharmacologically expected, or type A, adverse effects. Some increased confidence about incidence rates might result from the open-label extension study; however, as these studies are essentially uncontrolled and biased, the data are not of great value.

Other benefits have been proposed to be gained from open-label extension studies. These include ongoing access to an effective but otherwise unobtainable medicine by the volunteers who participated in the phase III pivotal trials. However, there are unappreciated ethical issues about the appropriateness of enrolling patients whose response to previous treatment is uncertain, largely because treatment allocation in the preceding randomised, double-blind, controlled trial has not been revealed at the time of entry into the open-label extension study.

Negative aspects of open-label extension studies revolve around their use as a marketing tool, as they build a market for the drug and generate pressure for subsidised access to the drug from consumers and their physicians. Consumers, institutions where these studies are conducted and research ethics committees need to be convinced of the motives, as well as the quality, of the open-label extension study and its execution before supporting such studies.

Open-label extension studies do have a legitimate but limited place in the clinical development of new medicines. The negative perceptions about these studies have arisen because of perversion of acceptable rationales for this type of study and a failure to recognise (or disclose) the limitations resulting from the inherent weaknesses in their design. Increased human exposure to a new medicine under reasonably controlled circumstances to increase confidence in the safety of the medicine is an acceptable rationale for an open-label extension study, and a useful activity to increase the knowledge of the safety profile of a new medicine. However, this goal is increasingly being achieved by means other than open-label extension studies.

1. Open-Label Extension Studies

As the name implies, an open-label extension study is an 'appendage' to a randomised controlled clinical trial, usually of an unregistered medicine or intervention. Often the drug is being studied under an investigational new drug (IND) licence or equivalent legislation. The open-label extension study is identified formally as a study. Depending on the jurisdiction(s) in which the study will be performed, approval will be required, at minimum, from a research ethics committee, and the study must be registered with a regulatory agency. A protocol describing the open-label extension study and the consent of participating volunteers will be required. It is intended that all participants in the open-label extension study will take the trial medicine and will know they are taking it. Most commonly, the open-label extension study follows a phase III, pivotal (for registration) study of the new medicine and is incorporated into the protocol for the phase III study; herein lie some of the problems with interpreting the results of open-label extension studies (see section 2). Open-label extension studies have been described as "case series [studies] of the survivors of the [double-blind] trials",[1,2] inferring a range of deficiencies and potential biases in their design and interpretation, issues which will be discussed in this article.

The most commonly imputed rationale for undertaking an open-label extension study is to increase the knowledge about the safety profile of a new drug. Knowledge about efficacy is less likely to be the motive for the open-label extension study. Terms such as 'long-term safety', 'safety and tolerability' and 'safety and efficacy', and 'efficacy and tolerability' are commonly employed. However, other possible motives, whether overt or not, include: collecting data for pharmacoeconomic analyses; familiarising prescribers and patients with the use of the product and, thereby, achieving marketing objectives; allowing compassionate provision of medicines to the patients who are most in need; and generating pressure on funding providers (e.g. government and hospitals) to purchase the drug (a further marketing objective).

Research ethics committees spend much effort identifying the motives behind extension studies, because open-label extension studies commonly lack clear aims and objectives and raise a number of ethical questions. For example, arrangements for the continuing supply of the medicine being investigated following an open-label extension study can be a very difficult issue for public facilities and sponsors, both ethically and financially. Most importantly, is the proposed open-label extension study true research and, if so, is it of sufficient quality to generate meaningful information on the safety and possible efficacy of the drug to warrant approval of the study?

There are many questions that can asked about open-label extension studies, only some of which can be addressed in this paper because the answers are often unavailable. If an open-label extension study is conducted to provide more useful information regarding the safety of a new medicine, what evidence is there to suggest that these types of study do actually deliver this information? Furthermore,

what standing does this information have with regulatory agencies and what is the likelihood that the information will appear in the approved product information or 'label'? Is there regulatory guidance concerning open-label extension studies? Is this consistent across the International Conference on Harmonisation (ICH) regions (USA, Europe, Japan)? What is the view of national umbrella organisations for biomedical research and research ethics committees about these studies and what guidance is offered to ethics committees? This paper attempts to review the practice(s), the evidence for improvement of knowledge about the safety of examined drugs, the particular advantages or disadvantages and the trends associated with these types of studies. The questions a researcher or ethics committee might ask when contemplating participating in or approving an open-label extension study are also considered throughout the paper.

2. How Common Are Open-Label Extension Studies?

There are factors that are predictive of whether open-label extension studies will be undertaken. Phase III studies in chronic diseases where inadequate response to conventional, available medications is a criterion for entry into the study are likely to be followed by an open-label extension study.

As alluded to earlier, one difficulty in gaining detailed information on open-label extension studies is that they are frequently reported as a 'footnote' to the phase III trial. That is to say, although a publication may give a comprehensive summary of the aims, methodologies, selection criteria and so forth for the phase III trial, details are often largely overlooked for the associated open-label extension studies. Furthermore, it can be difficult to determine what open-label extension studies are being conducted. A search of databases (e.g. MEDLINE or the NIH Clinical Trial Registry) for open-label extension studies undoubtedly understates the number of open-label extension studies being conducted because the registered title of the study or publication does not necessarily mention that an open-label extension study is incorporated into the design of the phase III study.

3. Reasons for Performing Open-Label Extension Studies

3.1 Supply of Unregistered Medicines

Often a drug will not be registered for some time following the pivotal phase III studies; therefore, open-label extension studies are one way to continue to provide medicine to patients who have volunteered in the pre-registration clinical trials until registration or subsidised funding of the medicine occurs. Typical funding agencies include private health funds, health maintenance organisations (HMOs) or government funding agencies, including public hospitals. However, the practice of undertaking an open-label extension study is sometimes more focussed on generating a market for the drug than on altruistic reasons. It can be difficult to be sure whether the motive is more related to marketing or to providing genuine help for patients; however, ethics committees and funding institutions seem to be increasingly aware of this issue. How long the new medicine's supply will continue can also be a vexing question because predicting when registration or subsidised funding will occur is not possible. Will the sponsor agree to continue supply until registration? What if the drug is not registered but is effective in a trial participant? What if the drug is registered but expensive and the funding organisations do not subsidise it or there is a substantial delay? What obligation does a hospital that approves the open-label extension study have to the trial participants if the sponsor withdraws provision of the drug prior to other funding sources agreeing to subsidise the drug? These situations have become more frequent and all participant 'stakeholders' have become more aware of the potential hazards.

Tensions are increased when the drug has a role in treating a serious illness and important benefits are perceived to be accrued. An example is the tumour necrosis factor (TNF) inhibitors (etanercept, infliximab, adalimumab) that have revolutionised the treatment of rheumatoid arthritis, a serious,

debilitating and chronic illness, along with other serious inflammatory arthropathies. These medicines showed remarkable efficacy in pre-registration trials and this efficacy was largely seen in individuals who had not responded to all other options.[3] Open-label extension studies commonly followed the pre-registration clinical trials for the TNF inhibitors. These drugs were entirely new in their mechanism and potential adverse effects; thus, performing open-label extension studies to gain further safety information was justifiable. However, the drugs are very expensive – within the order of $US16 000 per person per annum for long-term therapy. Therefore, an ongoing supply becomes a critical issue for all stakeholders: the patient, particularly if they have responded well to treatment; the sponsor who wishes to continue to sell the drug and expand their market; the funding agency that wishes to control its expenditure but provide the required drugs responsibly; the regulatory agency that wishes to be reasonably confident about long-term adverse effects; the politicians who are pressured by sponsors and patient groups that are sometimes funded by the drug manufacturers; prescribers who wish to continue to prescribe effective medicines to their patients; and institutions and their research ethics committees that have the responsibility for allowing their patients to enter open-label extension studies and do not wish to possibly be encumbered with ongoing financial commitments if external sources of funding for the drug are not available when the sponsor ceases to supply the drug for the study participants. Generally, the stakeholders are aware of these issues and endeavour to avoid problems with the ongoing supply and funding of new medicines by paying careful attention to the proposed arrangements for these in association with open-label extension studies.

Ethics committees find it difficult to approve a study where continued access to a medicine that benefited a patient cannot be provided at least until the medicine is registered. Additionally, access to an otherwise unobtainable medicine might be a powerful motive for participation by a patient and for a physician to recommend a study to a patient. However, important ethical concerns have been raised about the potential coercive effects of open-label extension studies for inducing participation in double-blind studies with the 'carrot' of access to the new medicine at the end of the double-blind phase.[4] Taylor and Wainwright[4] further suggest that a patient cannot give properly informed consent regarding participation in an open-label extension study unless the treatment they were taking in the preceding phase III study is known. It is unusual for this to happen as trialists, sponsors and regulatory agencies are uncomfortable about potential biases introduced into the ongoing phase III study when any unblinding occurs. The ethical concern that informed consent cannot be given is clear: response while receiving placebo or lack of response to the new medicine by the patient in the 'active' arm of the phase III study would not provide a sensible basis for participation in an open-label extension study. Taylor and Wainwright[4] also argue that unblinding for an individual participant could be accomplished without jeopardising the overall double-blinding of the phase III study, although this would take effort and care. Unfortunately, this practice is not widespread or often discussed. Given the upsurge in open-label extension studies, this ethical issue needs urgent attention by the clinical trial community.

If the primary motive for an open-label extension study is continuation of supply, Taylor and Wainwright[4] recommend that the decision of whether to proceed should not be made by a research ethics committee because research is not the rationale for the 'study'. They recommend that other parts of the institution responsible for the care of patients should fill this role; for example, the drug and therapeutics committee, which is responsible for the supply of appropriate medicines to patients in the hospital.

3.2 Disguised Marketing

A new drug entering a competitive 'field' of alternatives upon registration might be more likely to be the subject of an open-label extension study under the 'guise' of a safety study. As mentioned in section 3.1, the sponsor can use the open-label extension study to influence prescribers such that they

will pressure funding agencies into providing the new medicine. The reputation of open-label extension study has been damaged by studies for which this has been the motivation. They have commonly been distinguished by rudimentary data collection and quality, revealing the true motive, namely market expansion. The motive of collecting useful information about the drug is hard to fault; however, even if the collection of data is meticulous (which is not always the case), the value of these data is much diminished because of the lack of randomisation and a contemporary control group.

Ethics committees and host institutions, which may be under pressure to continue to supply the medicine after the open-label extension study has terminated, need to be alert to the marketing motivation that can be exerted via, not only prescribers, but also patients and patient organisations. Similarly, investigators and potential volunteers should investigate the study rigorously to ensure the rationale for its performance is to increase the knowledge of the safety of the medicine before agreeing to participate.

3.3 Familiarisation

Physicians can use the opportunity of an open-label extension study to increase their experience with the new drug beyond that obtained during the double-blind clinical trial. However, this could also be questioned ethically because the choice of the drug appropriate for a patient would depend on full knowledge of their response to either the placebo, the comparator drug or test medicine in the double-blind phase, which – as discussed in section 3.1 – is rarely available for participants entering open-label extension studies. Again, to many sponsors the marketing benefit of having clinician researchers who are often 'opinion leaders' continuing to use the new drug is a compelling motive for performing an open-label extension study.

3.4 Adverse Drug Reactions

The commonly stated aim of an open-label extension study is to examine the safety of the new drug. It is increasingly understood at the time of registration of a new drug, especially if it is a member or index agent of a novel class, that there is a risk of unidentified, potentially serious, adverse reactions classified as type B,[5] such as aplastic anaemia, hepatic failure or Stevens-Johnson syndrome, which can be unacceptably high (table I). This is because only hundreds or, at most, 1000–3000 patients have been exposed to the medicine at the time of registration; therefore, serious adverse effects that occur at rates of the order of one per 1000 prescriptions or less frequently cannot be identified. Thus, despite there being a big increase in the number of patients studied in phase III, pivotal trials and studies being generally longer in duration over the last two decades, our total experience with newly registered drugs in humans is miniscule, particularly for drugs that will have long-term use. Regarding rare, type B adverse reactions, a useful guide is the 'rule of three': if the risk of a serious adverse drug reaction (the reaction being exclusive to the drug and not one that happens spontaneously) is 1 in 10 000, then there is 95% confidence that this reaction will be observed if 30 000 patients are exposed.[6] There have been many drugs withdrawn because of serious type B reactions that have occurred at approximately this incidence rate.[7] Clearly, no pre-registration trial will ever include 30 000 patients and no open-label extension study will identify such reactions that, although rare, have an incidence that might lead withdrawal of the drug from the market.

There is even greater difficulty when the observed adverse reaction also occurs spontaneously in the absence of a drug and is a reasonably common form of morbidity, such as a myocardial infarction or a gastrointestinal bleed. A drug-induced 'increment' in the risk of a commonly seen clinical entity, such as a myocardial infarction, is extremely difficult to detect, as has been observed with rofecoxib,

Table I. Classification of adverse drug reactions[6]

Characteristics	Type A	Type B
Pharmacology	Augmented	Bizarre
Predictability	Yes	No
Dose relationship	Yes	No
Relative morbidity	High	Low
Relative mortality	Low	High

other cyclo-oxygenase (COX)-2 inhibitors and perhaps NSAIDs in general.[8]

The duration of open-label extension studies is very variable. The additional period of exposure of an individual to the medication beyond that encountered in the primary study can be from weeks to years – typically the exposure is 2–3 times the duration of the original trial. Interpreting the risk of a specific and particularly uncommon adverse effect from experience gained through open-label extension studies, particularly in the absence of a control group, is highly tenuous.

One needs also to consider the effect of non-adherence with the medication upon the open-label extension study safety data. The longer the duration of therapy, particularly for a 'silent' disease such as hypertension, the poorer the adherence.[9] In addition, the potential for confounding of the data, due to the under-reporting of drug-emergent adverse events, is large.

3.4.1 The VIGOR Study: Would an Open-Label Extension Study Have Helped?

An open-label extension study could also be used to extend a phase IV study. By definition, phase IV studies follow registration of the medicine. A phase IV study might examine the efficacy and safety of a registered medication for a new indication, explore unregistered dosages or try to establish an improved safety profile that regulatory authorities will accept so that the product information or label can be amended. An example of this type of study was the controversial VIGOR (Vioxx GI Outcomes Research) study that compared rofecoxib, the selective COX-2 inhibitor, with naproxen in >8000 patients with active rheumatoid arthritis.[10] The drug had already been registered to treat osteoarthritis, but the product information or label did not distinguish between NSAIDs and rofecoxib regarding the risk of serious gastrointestinal bleeding or perforation. The US FDA required that improved actual outcomes, in terms of decreased rates of peptic ulcer and gastrointestinal complications, not those based on surrogate endoscopic data, be shown before the label could be altered to indicate lesser risks of these adverse events with rofecoxib compared with naproxen. This study did show a significantly reduced risk of serious gastrointestinal adverse effects with rofecoxib versus naproxen during the double-blind study phase. The FDA approved a change in the product information indicating this advantage. However, controversy emerged because the trial also showed an increased risk of thrombotic disease associated with rofecoxib compared with naproxen.

There was no incentive for the sponsor to contemplate an open-label extension study following the VIGOR study because the drug was already registered, and the altered product information allowed promotion of the gastrointestinal advantage. Furthermore, an open-label extension study following the phase III pivotal registration studies would not have been able to prove greater gastrointestinal safety versus naproxen to the satisfaction of the regulatory authorities, so the sponsor opted for a large, randomised controlled, phase IV study, namely the VIGOR study.

The rofecoxib example indicates one of the key deficiencies associated with the use of open-label extension studies as a possible mechanism to contribute to knowledge about the safety profile of a new drug or device. Considering the thrombotic risk associated with rofecoxib, as noted, it is extremely unlikely that an open-label extension study following the original pivotal studies that led to the registration of rofecoxib could have produced definitive information about this adverse effect. This is because the absolute risk posed was low, the relative risk for myocardial infarction with rofecoxib versus naproxen was 2- to 3-fold and also because of the lack of a parallel, matched control group.[11] Thus, an important limitation with open-label extension studies is 'power'. That is, the statistical power to detect significant risks of important adverse effects that are not apparent from the pivotal studies because their incidence is insufficient to be detected given the limited numbers of patients that have been studied by the end of phase III.

It is now clear that rofecoxib increases the risk of myocardial infarction in a dose-dependent manner and that this adverse effect is more likely in those patients with prevalent risk factors for myocardial

infarction.[12] This 'risk' was not recognised at registration, although it was thought to be theoretically possible, and then epidemiological studies began to emerge following the publication of the VIGOR study that suggested this might be the case.[13]

The inclusion criteria for participants in the phase III and other pre-registration studies for rofecoxib selected generally 'healthier', younger patients than the demographic that was prescribed the medicine following registration.[14,15] Although there are increasing efforts to recruit older individuals into clinical trials, patients included in pivotal studies generally have fewer comorbidities and are younger than the eventual target population for the medicine. Adverse reactions will be more likely in patients with comorbidities who are receiving multiple medications, a situation that is most commonly encountered in the elderly population. The numbers of patients that need to be included in a controlled trial in order to demonstrate an incremental effect, such as a 2- to 3-fold increase in the risk of myocardial infarction, can be much greater than the numbers required for a phase III efficacy study, and this was the case with rofecoxib. The fact that rofecoxib was compared with various NSAIDs in pivotal trials in rheumatic disorders and no signal of increased risk of myocardial infarction emerged,[16] in retrospect made determination of the actual risk even more difficult, as it appears likely that the NSAIDs themselves might confer some level of risk.[8]

It took a phase IV, randomised controlled trial comparing rofecoxib with placebo in another indication, namely the chemoprevention of colon cancer, to finally prove the relationship between rofecoxib and myocardial infarction.[12] This cancer prevention study was also considerably longer than the efficacy studies that led to the registration of rofecoxib. A long-term study comparing rofecoxib with placebo in patients with rheumatic disorders that are painful and debilitating, although clearly desirable to understand the risks associated with this drug in the target population for anti-inflammatory medicines, would also not be ethical, presenting another dilemma.

Will open-label extension studies contribute to the safety information concerning rare but serious adverse reactions? This is unlikely unless the adverse reaction has a considerable incidence, i.e. greater than a few percent, because the numbers of patients studied in such studies can only approach those entered into the phase III studies that are being extended. Patient-years of exposure to a new medicine will accrue in open-label extension studies but this is only likely to confirm or refine the rates and types of common adverse reactions associated with the medicine. These are the expected reactions from the pharmacological properties of the medicine known as type A adverse drug reactions,[6] which can usually be predicted from the preclinical studies and have been identified in phase I and II studies. As there will not be a parallel, randomised control group for the drug-exposed group in the open-label extension study, reliable treatment-specific incidence figures will not be obtained. This raises serious doubts about the value of these types of studies.[2]

3.4.2 Usefulness for Detection of Adverse Drug Reactions

Open-label extension studies might be most effective in improving the knowledge of adverse reactions associated with a new medicine when the pivotal studies have included relatively few patients, as might be the case in the treatment of malignant diseases or serious infections. Even if the open-label extension study includes few patients, important adverse reactions that have a reasonably high incidence could emerge, particularly if time is a factor in their emergence; however, rare adverse reactions will remain undetected.

3.5 Efficacy Assessment

In most cases, the optimal situation would be for the randomised, double-blind, pivotal phase III study to continue long enough that all the key efficacy questions could be answered. However, this is usually not the case, and although pivotal studies are longer now than they used to be, many commentators continue to believe that they should be longer still, especially for medicines that will be adminis-

tered over long periods, e.g. drugs to treat schizophrenia, osteoarthritis, hypertension and diabetes mellitus. A trend has developed to obtain more efficacy information by the mechanism of open-label extension studies. As can be seen from the product information sheets for haloperidol and olanzapine, the pivotal studies undertaken for the registration of haloperidol compared with olanzapine for schizophrenia were varied vastly in duration, illustrating the rapid change in requirements and practice to satisfy safety and efficacy standards for registration over recent years. Thus, the product information for olanzapine refers to about 2500 patients given the drug in the pre-registration clinical trials for a total of >1000 patient-years of treatment with the drug. The product information for haloperidol contains no clinical trial information. Interestingly, the pivotal studies for olanzapine were only of 6 weeks' duration, but three were followed with 'blinded', extension studies for responders that compared continued response at 1 year versus placebo or an active comparator, haloperidol. These extension studies are not 'open-label' and therefore not strictly the subject of this paper. Open-label extension studies have the potential to provide more information concerning efficacy or at least hypotheses about efficacy that could be pursued further. The danger is that open-label extension studies might substitute for double-blind studies of appropriate length.

4. Attitudes of Regulatory Agencies

It is useful to explore the websites of the major regulatory agencies to gauge their attitude to open-label extension studies. Searching for 'open-label extension studies' or 'extension studies' does not produce any specific 'guidance document' on the FDA website. However, perusal of 'Guidance of Industry: Pre-marketing Risk Assessment' written in March 2005[17] is helpful in its discussion of the appropriate size for the database of patients exposed, and the appropriate duration of exposure, to new medicines, which depends on the severity and seriousness of the condition being targeted as well as characteristics and signals that have emerged in preclinical and early-phase clinical studies of the test drug. However, the bias in favour of data in the safety database being derived from controlled studies seems clear from the statement "In general, efforts to ensure the quality and completeness of a safety database should be comparable to those made to support efficacy".[17] Some guidance has come from the OMERACT (Outcome Measures in Rheumatology Clinical Trials) organisation about the conduct of long-term studies in arthritis.[2,18,19]

Perusal of any of the very large number of open-label extension studies that have been published reveals great variability in their analytic approaches. Questions to be dealt with when planning the data collection and analyses include: what to compare efficacy outcomes with, e.g. comparison of the efficacy outcomes with those at baseline prior to the double-blind phase; what to do about patients who withdraw from the open-label extension study, e.g. is imputing last observations carried forward in the open-label extension study acceptable; how to deal with individuals who withdraw during the double-blind phase, i.e. should they be allowed into open-label extension study and under what circumstances (e.g. after how many doses or over what time period of participation in the double-blind phase); and what statistical tests, if any, can legitimately be applied. Transparency with respect to the disposition of all patients who entered the double-blind phase and then tracking them through the open-label extension study, as is shown in the CONsolidated Standards Of Reporting Trials (CONSORT) diagram in a recent open-label extension study of topiramate in painful diabetic peripheral neuropathy,[20] would seem to be a minimal requirement.[4]

5. Value to Prescribers and Patients

The value of an open-label extension study to consumers and prescribers is very sensitive to the indication that the drug is intended to treat. Open-label extension studies involving short-term therapy for serious, life-threatening diseases, such as various cancers, will be considered very differently to those concerning chronic disorders that might not be associated with substantial reductions in life expectancy,

such as well controlled asthma. In this latter group, the goal of therapy with the medicine will be influential in understanding the significance of the open-label extension study. A therapy that reduces symptoms associated with the disorder is in a different category with respect to 'acceptable' levels of risk than is a medicine that is used to prevent an illness reoccurring (secondary prevention) or occurring for the first time (primary prevention). Thus, with a drug that reduces plasma cholesterol levels and is therefore used for secondary or primary prevention of cardiovascular disorders, only an extremely low incidence of serious type B adverse drug reactions would be acceptable. The withdrawal of cerivastatin after marketing approval due to a rate of rhabdomyositis that was 20–80 times greater than that for other registered HMG-CoA reductase inhibitors (or 'statins') 'set the bar high' for rosuvastatin, which was the first statin approved by FDA following that withdrawal. Rosuvastatin had the largest preregistration patient experience of any statin.[21] However, the bulk of the data was sourced from the large number of randomised controlled studies performed. Again, neither these studies, nor the open-label extension studies associated with them, exposed the highest risk patients for this serious adverse drug reaction, namely elderly, renally impaired women who might be taking concomitant interacting medicines, to rosuvastatin treatment.

How data from open-label extension studies are analysed and reported is critical for interpreting the significance of the results. As noted, it is difficult to produce reliable data on the absolute risk of adverse reactions with the new medicine from open-label extension studies. Those patients allocated the medicine during the double-blind phase III study and who enter the extension study are already a select group who can tolerate the medicine. Any report from the open-label extension study must present the 'disposition' of all participants from the phase III study in the report so that this effect is understood, otherwise the bias is towards apparent greater tolerability than in reality – even in the usually highly selected patients eligible for the double-blind study.

6. Best Practices

There is little easily accessed guidance from regulatory agencies (e.g. the FDA, the European Agency for the Evaluation of Medicinal Products, the National Health and Medical Research Council of Australia) or the ICH on how to conduct open-label extension studies. For example, the ICH guidelines General Consideration for Clinical Trials (E8)[22] and Guideline for Good Clinical Practice (E6)[23] do not mention open-label extension studies.

Although linked to a phase III efficacy study, a separate protocol for the open-label extension study should be prepared and constructed with a protocol template that is broadly similar in construction to that of the phase III study (table II). Particular attention needs to be paid to the inclusion criteria and the methods of analysis proposed, taking into account the entry criteria for the phase III protocol and the withdrawal rates and reasons for patient withdrawal during the phase III protocol. Finally, the ethical implications of including patients from each of the treatment arms of the phase III study when the treatment that the potential participant in the open-label extension study has received in the double-blind phase of the study is unknown needs to be dealt with clearly for potential patients, ethics committees and clinical researchers.

Ultimately, a good test of the value and quality of an open-label extension study proposal might be that it is published. Few such documents are published,

Table II. Issues to be addressed in study protocols for open-label extension studies

Separate protocol to the randomised, double-blind, controlled study phase
Strong rationale for the study
Hypothesis
Inclusion and exclusion criteria
Data-collection plan including frequency of visits and contacts with patients
Instruments used to collect data
Methods of analysis
Adverse event reporting procedures and data safety monitoring
Consent forms and patient information documents
Ethical analysis focussing on the effect of original treatment allocation on the advisability of the patient entering the open-label extension study

and an even smaller proportion are reported as stand-alone studies. Furthermore, the requirement for registration of clinical trials is increasing internationally.[24] The statement by the *International Committee of Medical Journal* editors does not address the matter of open-label extension studies and registration of these studies, but it would seem to be an important concept for exploration.

All research studies sponsored by a pharmaceutical company should be the responsibility of the medical department of the company and not the marketing arm. The rationale for the open-label extension study should be clear and ethically acceptable. The methods should be sound and the data should be carefully analysed and a report written. Careful attention should be given to the inclusion and exclusion criteria, and to addressing the effect of not knowing the patient's previous treatment. Efforts should be made to explore the possibility of unblinding the potential participants' previous treatment in the double-blind phase and their response. This would need to be carried out in a manner that does not jeopardise the conduct or analysis of the phase III study by introducing bias. There should be a commitment to publish the results of the open-label extension study for the benefit of patients and clinicians. Preferably, the open-label extension study should be published separately from the blinded study. This would give the study a specific focus. Currently, the methodologies for open-label extension studies are often obscure and 'buried' within the primary study. Separate publication of the open-label extension study would also allow for a clear description of the aims of the open-label extension study, and an adequate description of details of the study, notably, the manner in which the safety data were collected, how adherence was monitored and the power of the study to detect significant drug-emergent adverse events. Having hypotheses about safety based on preclinical and phase I and phase II studies would add to the rigor and relevance of open-label extension studies and their ability to truly contribute to the safety profile of the studied medicine.

Put simply, the investigator should be very clear about the rationale and motivation for the open-label extension study. If marketing is the motive, then the investigator should not participate. If the open-label extension study is a mechanism to provide an ongoing supply of the drug, then the investigator should recommend that the ethics committee refer this study to the drug committee or another group in the hospital or institution responsible for the supply of medicines. Investigators should think carefully about their responsibility to recommend the best treatment options to a potential participant and whether this will be possible if the patient's treatment and response in the preceding blinded study are not available. The publication of the open-label extension study should be an expectation of potential investigators.

Taylor and Wainwright[4] point out that it is difficult for a patient involved in the controlled trial to make a decision about and/or their usual physician to advise them regarding entry to an open-label extension study. If the patient responded well, they might be inclined to continue; however, if they were previously receiving the placebo they will therefore be embarking on their first exposure to the test drug, with all that it entails. If they had not responded, there is still uncertainty, i.e. they may have been receiving the active comparator, a placebo or the test drug, and clearly the decision to continue into the open-label extension study would be strongly influenced by information on their original treatment allocation, which is not generally available. On the other hand, the controlled trial may ultimately indicate that the medicine is ineffective or less effective than current therapies. However, in practical terms, it is not possible to delay the commencement of the extension study until the randomised controlled trial is analysed.[4] Therefore, it is important that these uncertainties and their implications are presented to potential participants in open-label extension studies to help them make a decision. The quality of information presented to patients and consent forms for open-label extension studies have not received due attention and these are matters that require attention.

Research ethics committees have had concerns about a proportion of open-label extension studies being motivated by marketing imperatives more than scientific enquiry.[4] Coercion to enter either the phase III study, the extension study, or both is a real possibility. It might be implied that the only way to access the medicine long-term is to participate in the phase III study. Ethics committees must examine this possibility carefully.

A motivation for proposing an open-label extension study might be to allow compassionate access for patients with a serious disease who do not have other treatment options. In fact, ethics committees may feel it unethical if compassionate access is not possible upon completion of the trial and before the drug is registered and marketed. However, if that were the only motivation for the study, it is not appropriate to label this mechanism of access a research study. There are usually other mechanisms for access to unregistered medicines available, depending on the jurisdiction where the phase III study has been undertaken. The ethics committee should consider the matter of compassionate access when evaluating the phase III trial application, and notify other parts of the organisation, such as the drug committee, to this possibility, so that seamless access to the drug between the end of the phase III trial and the registration of the drug can occur when clinically appropriate.

7. Alternatives

An increased appreciation by all stakeholders that there is insufficient information about the safety of a medicine at the time that it achieves registration has led to the emergence of concepts such as 'provisional registration'.

The goal of education about the safe use of newly registered medicines is to indicate to stakeholders that care should be taken before prescribing or taking this medicine given the small numbers of humans exposed at the time of registration of a drug. An increase in such an attitude would increase pressure on sponsors to undertake soundly designed studies with sufficient power and quality to increase the knowledge about possible, as yet undetected, adverse reactions. Controlled cohort and case control studies would be examples of the types of studies that might be mandated by regulatory agencies.[25] Some studies might mandate particular inclusion and exclusion criteria. National and other electronic databases of prescribing and medical services will be used to undertake post-marketing studies of good quality. Pharmacovigilance plans for a new medicine already receive substantially more attention and are mandatory in the European Union. More emphasis is placed on post-registration studies as part of these plans. Although agencies have requested post-marketing studies in the past, often these have simply not been done. Compliance with agreed to post-marketing studies will be required for registration to be confirmed. Penalties that are effective but do not interfere with the required treatment of patients need to be carefully considered and established – ideas such as continuation of temporary licence beyond the planned date and monetary penalties could be considered. As the use of pharmacovigilance plans and the possibility of performing high-quality clinical studies in patients in more realistic clinical situations than possible in phase III pivotal registration studies increase, the rationale for open-label extension studies is likely to decrease. Perhaps this will be welcome given the difficulties and low value of open-label extension studies.

8. Conclusions

If undertaken primarily to gather more patient-years of exposure to a new drug to understand and gain more confidence in its safety profile, open-label extension studies can sometimes play a useful and legitimate, albeit limited, role in drug development. However, this can only occur if the open-label extension study is designed, executed, analysed and reported competently. Most of the value accrued in open-label extension studies comes from a refinement in the perception of the expected incidence of adverse effects that have most likely already been identified as part of the preclinical and clinical trial programme. Although unlikely, it is possible that the occurrence of type B adverse drug reactions in open-

label extension studies would inform ongoing pharmacovigilance plans for the drug. Large numbers of patients need to be included in open-label extension studies to develop confidence about the incidence rate for type B reactions. This means that large numbers of patients are also needed in the pivotal phase III studies. There is a limit to the numbers of patients that can be included in pivotal studies; therefore, open-label extension studies can only contribute to the safety picture of a drug in a small way. Currently, we rely heavily on post-marketing safety surveillance systems to alert us to type B reactions that may lead to the withdrawal of a medicine. Further caveats concerning open-label extension studies are that only limited value is obtained from the increased experience of type A adverse effects because random allocation to test and control groups is needed to produce meaningful incidence data on these pharmacologically expected effects. Some increased confidence about incidence rates might result from the open-label extension study, but as the data are essentially uncontrolled and biased they are not of great value.

It has been argued that other benefits accrue from open-label extension studies. These include ongoing access to an effective but otherwise unobtainable medicine by the volunteers who participated in the phase III pivotal trials. However, there are unappreciated ethical issues about the appropriateness of entering patients whose response to previous treatment is largely uncertain into open-label extension studies, because treatment allocation has not been revealed at the time of entry into the open-label extension study.

Negative aspects of open-label extension studies revolve around their use as a significant marketing tool – building a market for the drug and generating pressure from consumers and their physicians for subsidised access to the drug. Consumers, institutions where these studies are carried out and research ethics committees need to be convinced of the motives as well as the quality of the open-label extension study and its execution before supporting such studies.

Open-label extension studies have a legitimate place in the pantheon of approaches to the clinical development of a new medicine, but these may be replaced by other approaches. The negative perceptions about these studies have arisen because of the perversion of acceptable rationales and a failure to recognise (or disclose) the limitations and inherent weaknesses in their design. Increased human exposure to a new medicine under reasonably controlled circumstances to increase confidence in its safety is an acceptable rationale for an open-label extension study. Increasingly, this goal can be achieved by means other than open-label extension studies.

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