Author's response to reviews

Title: Using clinical trial data and linked administrative health data to reduce adverse drug events associated with the uptake of newly released drugs by older Australians: a model process

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Title: Using clinical trial data and linked administrative health data to reduce adverse drug events associated with the uptake of newly released drugs by older Australians: a model process

Version: 1 Date: 29 October 2010

Reviewer: Professor Graziano Onder

Thank you for your suggestions. We will address them in two sections. Responses to your Recommendation 1 will be addressed in Section 1, and Recommendations 2, 3 & 4 will be addressed in Section 2.

Section 1. Recommendations concerning reducing the length of the paper, and combining medications data for the Year 1999 and Year 2000 cohorts.

We have considered combining the 1999 and 2000 medications data, but this is infeasible. The extraction process was based on annual cohorts (even though we also asked for one year of back data for any patient whose details were extracted based on the their fulfilment of the selection criteria applied). We asked for both cohorts because we wanted to have two annual snapshots of Western Australian arthritis patients aged 65 and over in order to avoid the criticism that the findings for only year only happened to be a one-off.

The extraction criteria for each of the years 1999 and 2000 cohorts did not disallow common membership in each of the two years. The problem will not exist in future. The Australian Commonwealth Department of Health and Ageing, which administers the national subsidised Pharmaceutical Benefits Scheme (PBS), introduced mandatory enhanced identification processes in July 2002 that would be better able to support the future success of the model for prospective identification of patient groups at risk of an adverse event associated with a new drug. We benefited from these improved identification in the better data we received for the shorter 2003-2004 data analysis.

As noted in the paper, we had to drop the Year 1999 hospital morbidity data because the 1999 data showed inconsistencies between the first and second six months which we could only attribute to changes in the application of secondary arthritis codes between ICD-9-CM and ICD-10-AM. ICD-10-AM was introduced in July 1999. We have made the decision to include only the Year 2000 medications data and the year 2000 hospital morbidity data.

Section 2. Recommendations concerning exclusion criteria most commonly used in the RCTs assessing the efficacy of rofecoxib (and related tables)

We have followed your suggestion regarding the value of expanding on the distribution of exclusion criteria listed in Table 1 in the 1999 and 2000 (combined) cohorts. We have deleted the original Table 1 and replaced it with two Figures:

Figure 1: Main comorbidity exclusion protocols applied in the efficacy clinical trials of rofecoxib (VIOXX®), by arthritis type, and
In preparing the tables, we differentiated between those exclusions related to the indication that was the subject of the clinical trial, and those exclusions related to other body systems. We have included an explanation in par 3, Section 2.1 as follows:

“The examination of reports of clinical trials of new drugs should take into consideration the scope of the research questions posed, what data were sought, from whom they were sought, what endpoints were adjudicated, and what were the bases for outcome analyses. In this process, it is important to differentiate between those exclusions which are specifically related to the research questions being asked, and those exclusions which relate to other body systems. For example, a clinical trial of a new drug which is being evaluated for its specific effects on gastric mucosa may have a protocol that excludes persons already suffering from gastric morbidities such as ulceration or bleeding. The exclusion of patients with such gastric morbidities relates specifically to the research question which seeks to evaluate the new drug in relation to its effects on gastric mucosa. However, exclusion protocols relating to morbidities in other body systems are applied for different reasons, and can reduce the availability of important knowledge about the action of the new drug in patients who have those excluded morbidities.”

We believe that the case you spoke of concerning walking capacity is in this category. We have inserted some extra explanation of the exclusions relating to research questions in Section 3.1.

“Persons of both genders aged 65 years and over, the age group of interest to us, were represented in the RCTs analysed. We took into account that the COX-2-selective NSAID rofecoxib was developed specifically to relieve the pain and inflammation of arthritis without the gastrointestinal morbidity associated with the use of non-selective NSAIDs to treat arthritis inflammation. As expected, there were consistent applications of gastric morbidity exclusion protocols specifically related to enabling the research questions to be asked. There were also applications of exclusion protocols related to enabling assessment of whether use of rofecoxib resulted in improvement in arthritis symptoms. For example, in an RCT evaluating rofecoxib for its specific effects on improving pain on walking, exclusion protocols required the capacity to walk for some measurable distance in order to be able to evaluate improvement.”

We tried to exercise judgement in assessing which of the common exclusion protocols related to the research question/s in the RCTs we looked at. We also did not include exclusion protocols relating to other body systems when these exclusions were not common.

We have followed your recommendation concerning inclusion of percentage values in the tables, and have added some content in the text for some of the tables. We hope this is useful.

Data from the subsidised national pharmaceutical benefits scheme (which covers all Australians) indicate that the 60-and-over age group in Australia are taking a wider range of medications [1], and a recent study using linked Australian administrative health data confirms that medication-related hospitalisations of patients 60 years and over have increased five-fold between 1981
and 2002. [1,2]. Estimates based on Australian statistics note that by 2002, there were 80,000 hospital admissions that were recorded as medication-related, at an annual cost of $350 million [1]; the estimates for 2008 record 190,000 hospital admissions that were medication-related, at an annual cost of $660 million [3]. Older patients with comorbidities and taking multiple medications were the group disproportionately represented in these statistics. People aged over 65 comprise only about 14% of the population in most industrialised countries, yet they consume nearly a third of all drugs [4].

The intent of our process is to have a relatively rapid means of establishing the potential for adverse drug events for any new drugs that target chronic diseases or diseases that are particularly experienced by older people, who typically have multiple morbidities and/or take multiple medications. The model process we have outlined should be able to carried out quickly, before the drug is listed in the subsidised national pharmaceutical benefits scheme, so that we can buy time for older patients until more is known about a new drug. There are regular publications by the National Prescribing Service which could carry the circulate the output of the model, including Australian Prescriber, Nurses Update, NPS News, Prescribing Practice Review, and RADAR (Rational Assessment of Drugs and Research).

Data in our paper show that, right up until its safety withdrawal in September 2004, Australian patients over 65 years were still being co-prescribed rofecoxib and cardiovascular drugs, despite the fact that adverse cardiovascular events (mostly MIs, and many fatal) were becoming increasingly associated with use of rofecoxib. If our model process had been undertaken before rofecoxib was subsidised through the national pharmaceutical benefits scheme in 2001, there would have been a warning that significant cardiovascular, cerebrovascular and renal exclusions were applied in the clinical trials for which there was published information, and that almost 70% of Australian arthritis patients suffered from one or more of the excluded morbidities, so prescribing rofecoxib to arthritis patients with these comorbidities should be on hold. All we are saying to the drug manufacturer is that we don’t have any hard evidence available as to how a new drug will act in the presence of comorbidities experienced by many of our patients, but excluded by the manufacturers in the clinical trials. It is inarguable.

Perhaps manufacturers will consider the advice given in a letter from the Netherlands agency Expertisecentrum LEEFtijd to the European Union. This advice recommended that proposals for clinical research studies in EU countries should be considered and approved by the EU before they are started. The agency recommended that it should be a prerequisite that the subjects are representatives of the target population. Such recommendations are usually dismissed, but more medical experts, both in practice and in academe, are considering how this might be done, and publishing their ideas in the medical literature.

References:


Title: Using clinical trial data and linked administrative health data to reduce adverse drug events associated with the uptake of newly released drugs by older Australians: a model process

Version: 1 Date: 23 December 2010

Reviewer: Professor Ugo Moretti

A number of revisions have been made to the paper, and Version 2 may answer some of the criticisms made by Professor Moretti. In the meantime, it is difficult to reply to a major compulsory revision requirement when there is no requirement specified and the review basically says that the whole exercise is pointless. We will therefore take the opportunity in this response to counter the views of Prof Moretti and explain why we do not agree with his ideas relating to the clinical trials and safety of new drugs. We will present our arguments in two sections.

Section 1 contains the response to the Major compulsory revision statement, and includes one sub-section on the effects of exclusion protocols in the RCT study design, and a second sub-section on pharmacovigilance and the safety of new drugs. References are provided for Section 1. Section 2 contains the response to the Minor essential revision requirement.

Section 1. Major compulsory revision

(i) The effects of exclusion protocols in the RCT study design

Prof Moretti comments that the authors may not have understood the role of exclusion criteria in the RCT study design. We have now included new paragraph (pars. 1 & 2, Section 2.1) which notes that we are aware that the RCT study design relies on the exercise of a range of controls to minimise bias, and that this is done in order to achieve the internal validity that is seen as a scientific gold standard. However, as we note, this internal validity is often achieved at the expense of external validity.

We do not believe that an excluded morbidity will necessarily cause an adverse event in the presence of the new drug, and we realise that there may be good reasons for not including patients with some morbidities. What we are saying, however, is that once exclusion protocols are applied, for whatever reasons, the findings of the RCT cannot be applied with certainty to persons with the comorbidities and/or the co-medications that were subject to exclusion protocols. There is no certain knowledge of the action of the new drug in these persons. We can surmise how the trialled intervention will act in the context of the exclusions, but we do not know for sure.

Our special concern is for new drugs that target chronic diseases, or diseases that are particularly experienced by older people who typically have multiple morbidities and/or take multiple medications. These are the people who are excluded from the RCTs, yet it is patients in older age groups who are most frequently being prescribed new drugs as soon as they are approved. People
aged over 65 comprise only about 14% of the population in most industrialised countries, yet they consume nearly a third of all drugs [1].

Data from the national pharmaceutical scheme indicate that the 60-and-over age group in Australia are making increasing use of a wider range of medications [2]. The effects of this increased exposure are exacerbated by increasing age and worsened by polypharmacy, and a study using linked Australian administrative health data, confirms that medication-related hospitalisations have consistently increased in older Australians [3].

Prof Moretti says that it is the responsibility of prescribers to pay attention to age, polytherapy and comorbidities in their patients, as these are well known risk factors for all adverse reactions. This is true. But we are not succeeding. Estimates based on Australian statistics note that by 2002, there were 80,000 hospital admissions that were recorded as medication-related, at an annual cost of $350 million [2]; the estimates for 2008 record 190,000 hospital admissions that were medication-related, at an annual cost of $660 million [4].

Data in our paper show that, right up until its safety withdrawal, Australian patients over 65 years were still being co-prescribed cardiovascular drugs and rofecoxib, despite the fact that adverse cardiovascular events (mostly MIs, and many fatal) were becoming increasingly associated with use of rofecoxib. At the hearings in the Australian VIOXX® class action, doctors who were called to give evidence said that when they queried drug company representatives about the possibility of cardiovascular safety issues they were told that there was no problem, and that their concerns were merely concerns put about by companies making rival COX-2-selective NSAIDS [5]. Prescribers do not get access to data that manufacturers of a drug do not wish prescribers to know.

However, as noted in our paper, this is changing following regulatory requirements in major drug safety legislation in the U.S. [H. R. 3580: Food and Drug Administration Amendments Act of 2007]. The regulations under this Act will significantly change the availability of data on clinical trials of new drugs. The U.S. has become the major single country for the development and launching of new drugs [6], and 50% of the world’s new drugs are trialled and first marketed in that country [7].

The FDAAA 2007 Act requires that, within 50 days of the enrolment of the first patient in a clinical trial, data on that trial are to be made available on the U.S. National Institutes of Health (NIH) website. Data are to include the purpose of the trial, the study design, the disease or condition being studied, the name of the intervention, primary and secondary outcome measures, eligibility criteria, including exclusion protocols, and the trial protocol identifier. Within 30 days of the approval of the new drug by the FDA, full details of all the clinical trials of that drug that were submitted to the FDA as part of the application for approval to market. Required data also included data on trial arms undertaken in other national jurisdictions, and data on clinical trials sponsored in other jurisdictions when those trials have U.S. trial arms.

(ii) Pharmacovigilance and the safety of new drugs

Prof Moretti argues that the post-marketing risk profile of a drug will be established via spontaneous reporting of adverse events, and that these reports will be the cornerstone of a pharmacoepidemiological risk assessment. The authors contend that this is not so, and indeed the point of our research is to make a case against relying on this method for signalling safety
concerns, in particular when the newly approved drug is to be prescribed for older patients, the focus of our model process (pars. 5 & 6, Section 1). We present below some of the evidence that points to the ineffectiveness of current pharmacovigilance systems in ensuring patient safety.

In 2004, the Deputy Director of the FDA Office of Surveillance and Epidemiology considered that as little as 1% of adverse drug events are actually reported [8]. Two years later, a group of senior US medical professionals agreed with that estimate [9]. In 2007, the former chief counsel at the FDA, commented that “the FDA generally assumes that only 1 in 10 adverse events is reported” [10]. The lack of systematic collection of post-marketing data on the use of drugs has delayed the discovery of serious problems until after very large numbers of people have been exposed [11]. Underreporting and variable data quality have been recognised as issues with the US MedWatch system, and one of the problems identified is that “spontaneous reports are a particularly poor instrument for detecting increased risks of common conditions, such as cardiac disease” [11].

An expert witness in a US Government Senate hearing following the safety withdrawal of rofecoxib notes that “it would not have been possible to use the MedWatch system to detect reliably, for instance, the increased risk of cardiovascular events associated with the COX-2 inhibitors” [12].

Morbidities such as cardiovascular disease are often those diseases which become chronic in older age groups, and increases in cardiac morbidity or mortality in older patients are not easily identified as being associated with a reportable medication-related adverse event. Patients in older age groups are increasingly suffering the effects of the impact of new drugs in the context of already existing morbidities, morbidities that were excluded from clinical trials.

Quite apart from the data collection issues discussed above, adverse drug event reporting has an in-built epistemological problem as it is subject to Type I and Type II errors of underascertainment and overascertainment respectively [13].

There are other safety issues associated with new drugs and the FDA pre-marketing evaluation process. These include issues with the role of pharmaceutical manufacturers as substantial funders of the FDA regulatory process, and the use by pharmaceutical manufacturers of the Priority Review option to expedite FDA approval. The impact of U.S. drug safety regulatory performance extends beyond its borders to countries importing pharmaceuticals developed and approved in the U.S.

The situation in Australia regarding pharmacovigilance is similarly insecure. In a context of continuing increases in the number of new drugs approved for marketing, reporting rates by GPs to the Adverse Drug Reactions Advisory Committee actually fell from 3,314 in 2002 to 2,075 in 2004 [14], and this lack of information was noted as particularly conspicuous in the area of medication safety incidents, which constituted half of all the incidents reported in that general practice monitoring study [14].

All in all, prescribers cannot rely on pharmacovigilance to provide timely warning of risks associated with new drugs, and the evidence is that this risk is much greater for their patients in older age groups. The warnings will have to be found elsewhere. Our model for identifying those older patient groups who have been excluded from the clinical trials of a new drug is a start, because we do know that we don’t yet know how these patients will respond to the new drug.
Patient waiting until more is known about a new drug will save patients from unexpected morbidity or mortality.

References:


Section 2. Minor essential revision

Professor Moretti considers that there is a problem with the authors’ use of the term ‘adverse drug event’, and requires that instances of ‘adverse drug event’ be altered throughout the text to read ‘adverse drug reaction’.

The authors have noted that in the current literature ‘adverse drug reaction’ and adverse drug event are often used interchangeably (see [14] & [15]). They also note that there are definitions
which present the term ‘adverse drug event’ as encompassing ‘adverse drug reaction’, but also allowing for medication-related adverse events when the causal pathway is not clear. In the end, we were guided by the US Institute of Medicine definition: An adverse drug event is an injury resulting from medical intervention related to a drug.

We have removed the word ‘drug’ on the title page and the abstract, so that the term now reads ‘adverse event’. We have included a note after the abstract to say that we will be using the wider term ‘adverse drug event in the rest of the paper for the sake of consistency.


These editorials appeared one year apart, and both focused on community-based medication-related incidents that cause patient harm, yet in 2005 the term used was ‘adverse drug reaction’, and in 2006, the term used was ‘adverse drug event’.